12èmes

Journées Cancéropôle Grand Sud-Ouest

23 au 25 Novembre 2016

Montpellier/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,
le SIRIC Montpellier Cancer,
pour leur participation et leur implication dans l'élaboration du programme de ces 12èmes Journées.

Comité de pilotage Scientifique

JP. Bleuse, P. Cordelier, P. Denèfle, M. Djavaheri-Mergny, A. Evrard, D. Fisher, A.M Gué, U. Hibner, N. Houede, B. Jacques, S. Krouri, F. Lalloué, G. Laurent, M. Mathonnet, M. Molimard, S. Pyronnet, P. Rochaix, P. Soubeyran

Comités de pilotage des Axes

Axe 1 - Signalisation cellulaire et Cibles thérapeutiques
O. Coux, F. Dalenc, F. Delom, Y. Denizot, K. Durand, G. Guichard, JP Hugnot, C. Laurent, J. Pannequin, J.-M. Pasquet, **S. Pyronnet**, D. Tosi

Axe 2 - Dynamique du Génome et Cancer
K. Bystricky, F. Chibon, J. Dejardin, L. Delpy, E. Espinos, **D. Fisher**, E. Julien, M. Lutzmann, M. Teichmann

Axe 3 - Innovation thérapeutique, de la biologie à la recherche clinique
E. Assenat, N. Bakalara, P. Barthélémy, JP Brouillet, L. Casteilla, T. Chardes, E. Chatelut, M. Dufresne, A. Evrard, V. Gigoux, **N. Houédé**, F. Lalloué, MA Poul, J. Robert, I. Soubeyran, N. Tubiana-Mathieu

Axe 4 - Cancers : enjeux individuels et collectifs
D. Alabarracin, C. Bellera, F. Cousson-Gélie, P. Gorry, S. Gourgou-Bourgade, **B. Jacques**, M. Kelly-Irving, N. Léone, A. Sasco, F. Sordes

Axe 5 - Technologies pour la santé
A. Bancaud, M. Bardiès, S. Begu, M. Busson, L. Cognet, T. Colin, P. Cordelier, V. Couderc, P. Fernandez, R. Ferrand, J. Feugeas, M. Gary-Bobo, **AM. Gué**, G. Kantor, D. Kouamé, S. Lecommandoux, A. Pothier, MP. Rols, O. Sandre, H. Seznec, V. Sol

Bienvenue à cette 12ème édition des Journées Annuelles du Cancéropôle Grand Sud-Ouest.

Depuis plus de 10 ans, notre communauté a créé un tissu dense de relations, de collaborations et de projets dont ces Journées sont le reflet. Elles témoignent également de l'évolution de l'organisation de la cancérologie, avec l'intégration, depuis la précédente édition, des SIRIC à la construction du programme. Une session est cette année pleinement organisée par le SIRIC Montpellier Cancer.

Nous avons également souhaité faire évoluer le format de ces Journées, en laissant un large rôle aux Axes scientifiques du Cancéropôle GSO dans leur construction. Ils contribuent fortement à la structuration du Cancéropôle GSO, sans induire de cloisonnement de la recherche, comme les sessions interaxes ou les interventions croisées le soulignent.

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 permettre 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

LES PROGRAMMES DE SOUTIEN DU CANCEROPOLE GRAND-SUD-OUEST

MOBILITE

OBJECTIF Maîtriser 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

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)

AAP OUVERT AU 1ER TRIMESTRE

Programme de soutien à l'émergence de collaborations (uniquement Axe 4 Cancers : enjeux individuels et collectifs)
Financement **d'un montant de 3k€** pour faciliter la mise en place **de partenariats scientifiques** afin de **construire un projet.**

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

Le **Cancéropôle GSO** et le **GIRCI SOOM** organisent annuellement un AAP Inter-régional Cancer

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

FINANCEMENT **40k€** par projet (maximum)

LES NOUVEAUTES

SYNERGIE, SOUTIEN A LA PREMATURATION DE PROJETS

OBJECTIF Accélérer les projets en phase de prématuration en facilitant l'accès aux expertises industrielles

THEMATIQUES Seront précisées dans l'AAP

CRITERES Projets à fort potentiel pour lesquels les chercheurs ont besoin de lever des verrous ou de valider les étapes à réaliser

RESULTATS Accès à des expertises industrielles ou à des plateaux techniques, mises en place de collaborations scientifiques, financement ou cofinancement de prestations …

LANCEMENT DE L'AAP FIN 2016, EN PARTENARIAT AVEC L'INSTITUT ROCHE

AAP STRUCTURANT INTER-REGIONAL

OBJECTIF Structurer la dynamique inter-régionale autour de grands programmes qui amélioreraient la lisibilité du Grand Sud-Ouest au niveau national voire international.

THEMATIQUES Oncogériatrie, pesticides (de la biologie à la gestion du risque), signalisation / cycle cellulaire / épigénétique

CRITERES Projets innovants, originaux et pluridisciplinaires, intégrant des approches technologiques

Implication d'équipes des 2 régions Occitanie et Nouvelle-Aquitaine (3 à 4 équipes maximum par projet)

DUREE Projets de 2 à 3 ans

FINANCEMENT 200 à 300 K€ par projet (financement de 2 ou 3 projets)

LANCEMENT FIN 2016 OU DEBUT 2017

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

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.

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.

En format résidentiel, l'école alterne cours et ateliers pratiques sur les plateformes d'imagerie. Elle a lieu tous les 2 ans (prochaine édition, mai 2017).

DEVELOPPEMENT D'UN MEDICAMENT

Le **Cancéropôle Grand Sud-Ouest** organise, avec le soutien institutionnel de plusieurs laboratoires pharmaceutiques, une formation sur les **différents aspects du développement d'un médicament en cancérologie.**

Organisée en alternant cours et d'ateliers, cette formation a pour objectif de former ensemble des jeunes médecins (internes, chefs de clinique), pharmaciens (internes) et chercheurs (fin de thèse et post-doctorants) afin de favoriser les échanges transversaux autour de cette thématique.

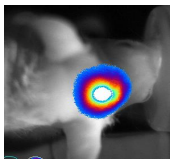
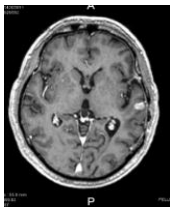
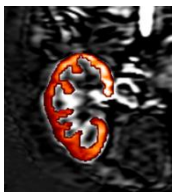
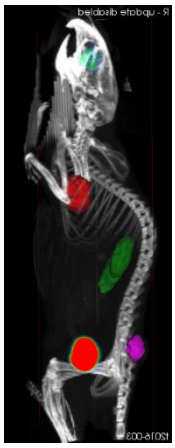
Elle a lieu tous les 2ans (prochaine édition septembre ou octobre 2017).

WORKSHOP JEUNES CHERCHEURS :

Un Workshop Jeunes Chercheurs est mis en place chaque année avec pour 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 chefs d'équipe) 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. La thématique de ce workshop annuel est décidée par le Comité de Pilotage Scientifique du Cancéropôle sur proposition des comités de pilotage des Axes.

- 2017: Nanomedecine in cancer
- 2015: Signaling in Cancer
- 2014: Genomic instability in Cancer

5EME ECOLE D'IMAGERIE
DU PETIT ANIMAL APPLIQUEE AU CANCER
28 mai – 1 juin 2017, Bordeaux

Organisée par le club Imagerie clinique et *in vivo* du Cancéropôle Grand Sud-Ouest

Lieu : Bordeaux (Inter-Hôtel Alton Mériadeck, Campus Carreire, IHU Pessac)

Objectifs :
L'imagerie préclinique *in vivo* permet de mettre en évidence de nouvelles cibles thérapeutiques et d'évaluer rapidement de nouvelles stratégies médicales. Ces techniques sont mises à la disposition de la communauté scientifique sous forme de plateformes ouvertes aux académiques comme aux industriels. La 5ème édition de cette école, organisée par le Cancéropôle Grand Sud-Ouest et la plateforme IMOTION (Imagerie moléculaire et thérapies innovantes en oncologie) de l'Université de Bordeaux abordera toutes les modalités d'imagerie in vivo (anatomique, fonctionnelle et moléculaire) ainsi que le suivi des animaux. Les principes théoriques des différentes modalités seront présentés par des chercheurs et médecins experts dans le domaine. En complément, des ateliers d'imagerie en situation réelle au sein des plateaux techniques permettront une analyse exhaustive des potentialités et champs d'applications de chaque technique

Responsables scientifiques et intervenants : Franck COUILLAUD, Muriel BUSSON, Coralie GENEVOIS, Muriel GOLZIO, Camille MENARD, Carine PESTOURIE, Tim DEVLING, Philippe FERNANDEZ, Nicolas GRENIER, Arnaud HOCQUELET, Renaud LEBRUN, Bruno QUESSON, Gilles RENAULT, Guillaume REVEILLON, Justin TEISSIE

Pré-requis : Avoir un projet d'imagerie *in vivo*

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

Programme :

- **Formation théorique** : Optique, IRM, Imagerie Nucléaire, Echographie, Microtomographie Rayons-X et analyse d'images 3D, Anesthésies et Analgésies en Expérimentation Animale.
  Tables rondes et visite du cyclotron.
- **Formation pratique** : des ateliers par petits groupes sur toutes les modalités d'imagerie avec des modèles murins.

Nombre de participants : 20

Tarifs (avec/sans hébergement) :

Académique : 900€ HT / 700€ HT
Privé : 1200€ HT / 1000€ HT

*Prise en charge possible dans le cadre de la **formation professionnelle continue***
Validation d'unité de formation continue en expérimentation animale

Inscription avant le 15 avril 2017

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

LES NOUVEAUX CLUB MIS EN PLACE

CLUB SMAC

Le Club SMAC rassemble les statisticiens et mathématiciens du Cancéropôle GSO par la recherche sur le cancer. Le club est **ouvert à tous les chercheurs travaillant sur des données populationnelles**, quels que soient leurs domaines d'application (**épidémiologie, psychologie, sciences sociales, recherche clinique**, etc.).

OBJECTIFS

- Renforcer les liens entre les équipes de biostatistique, statistique et mathématique, ainsi qu'avec les équipes qui, en sciences humaines et sociales et épidémiologie, utilisent les statistiques. Il vise à renforcer les compétences des équipes de statistique, et leur lisibilité.
- Organiser un colloque annuel sur une thématique choisie par le club

ANIMATIONS DU CLUB SMAC

2016 - Modélisation biostatistique et biomathématique des données d'imagerie (Bordeaux)
2015 - Modélisation et simulation d'essais cliniques (Toulouse)
2014 - Évaluation et analyse de la qualité de vie, nouveaux développements méthodologiques (Montpellier)
2013 - Dynamic predictions for repeated markers and repeated events (Bordeaux)
2012 - Modèles de Markov cachés mixtes et traitement des données de cohortes de cancer (Toulouse)

LE CLUB INVITE TOUS LES CHERCHEURS STATISTICIENS ET MATHEMATICIENS DU GSO
A SE FAIRE CONNAITRE AFIN DE PARTICIPER A SES ACTIVITES

Contact GSO: Olivier Claverie

CLUB METABO CANCER GSO

OBJECTIFS

- Favoriser les développements métabolomiques et fluxomiques spécifiques à la recherche en cancérologie (notamment via le financement d'un ingénieur de recherche au sein de la plateforme METATOUL de Toulouse)
- Mettre en place une animation et des actions de formation spécifiques
- Promouvoir les expertises et l'offre technologique disponibles au sein du GSO et favoriser les collaborations

ANIMATIONS

2016 et 2014 - Symposiums "Metabolism & Cancer", co-organisés avec le Cancéropôle PACA (Palavas-les-Flots et Nice)
2015 - 1ère journée du Club Métabo-Cancer GSO (Toulouse)
2012 - Symposium "Cancer Cell metabolism: beyond Warburg" (Toulouse)

Contact GSO: Karine Marendziak

RÉSEAU SUNRISE

Le Réseau SUNRiSE (SUd CaNceR Stem cEll network) vise à rassembler les chercheurs du GSO et de PACA travaillant dans le domaine des cellules souches cancéreuses (CSC) des tumeurs solides (www.sunrise-network.fr)

OBJECTIFS

- Rassembler les expertises et les ressources
- Faciliter les approches pluridisciplinaires et les collaborations pour des soumissions aux AAP nationaux et européens

RENFORCER LES COMPETENCES ET ACCELERER LES DECOUVERTES ET LEUR TRANSFERT VERS DES APPLICATIONS CLINIQUES.

ANIMATIONS CO-ORGANISEES AVEC LE CANCEROPOLE PACA

2017 - SAVE THE DATE : 2nd SUNRiSE Meeting « Stem Cells and Cancer », 26th and 27th of June (Montpellier)
2015 - 1st SUNRiSE meeting (Marseille)
2014 - Structuration du réseau SUNRISE (Montpellier)

Contact GSO: Karine Marendziak

6EMES JOURNEES ANNUELLES DU CLUB SMAC

les 4 et 5 mai 2017
Montpellier

- **ACTUALITÉ DES CRITÈRES DE JUGEMENT EN ONCOLOGIE**

Durant deux jours, ce workshop sera l'occasion pour les épidémiologistes, biostatisticiens et mathématiciens, acteurs et chercheurs dans le domaine de la santé de suivre l'actualité des **nouveaux critères de jugements utilisés en oncologie pour évaluer les traitements actuels**. Il permettra également d'appréhender les développements méthodologiques inhérents à ces évolutions.

Les nouvelles thérapeutiques proposées, comme l'immunothérapie, modifient les hypothèses des relations dose-toxicité / dose-efficacité connues pour les agents cytotoxiques classiques. Elles posent le problème des **méthodologies non-adaptées** dans ce contexte pour démontrer l'efficacité de tels traitements dès l'initiation du développement médicamenteux en phase précoce. L'amélioration des survies actuelles nous amène également à **utiliser des critères de jugement composites ou des co-critères comme critères principaux** pour le calibrage des essais cliniques. Ces problématiques ont également contribué à **faire évoluer les critères de jugements** utilisés par la **recherche de critères de substitution**. La **planification des essais et l'adaptation des critères de jugement** dans ces situations, où les **limites méthodologiques sont avérées**, sont donc d'actualité et nécessitent une **réflexion autour de ces méthodes et critères** au sein de la communauté.

Dans ce contexte il nous semble important de **faire état de la recherche méthodologique** et de l'utilisation de ces **méthodes complexes pour la planification** des futurs essais cliniques en oncologie.

PROGRAMME :

- Les critères de jugement en oncologie (jeudi 4 mai - après-midi)
- Les critères de substitution (vendredi 5 mai - matin)
- Les critères de jugement en immunothérapie (vendredi 5 mai - après-midi)

Avec la participation de : Franck Bonnetain (CHU Besançon), Xavier Paoletti (IGR), Emilie Lanoy (IGR), Christophe Borg (Besançon)…

APPEL A POSTER

Comme chaque année, **un appel à poster** sera lancé, le comité scientifique attendant tout particulièrement des propositions de jeunes chercheurs.

Le programme complet sera bientôt diffusé. Pensez à bloquer la date !

Program

Wednesday 23rd November

14:00 – 16:00

Session 1A - New therapeutic targets of signaling pathways p. 1

Chairs: Karine Durand & Stéphane Pyronnet

LECTURE: RNA binding proteins in the resistance to anti-cancer targeted therapies
Stephan VAGNER

Targeting post-translational modifications in live cells using intrabodies - **Pierre MARTINEAU**

The medullary adipocytes contribute to the bone metastasis of prostate cancer and this effect is regulated by obesity - **Adrien GUERARD**

Overexpressed flotillins, new markers of metastatic development, promote cellular invasion by disrupting cadherin-mediated adhesion and stimulating extracellular matrix degradation - **Damien PLANCHON**

How the identification of an off-target of the antitumor drug tamoxifen led to the discovery of dendrogenin A: a tumor suppressor metabolite - **Marc POIROT**

Deciphering and targeting YAP/TAZ activity in human gastric adenocarcinomas - **Julie GIRAUD**

Session 1B – Genomic instability and cancer p. 9

Chairs: Kerstin Bystricky & Eric Julien

LECTURE: Targeting histone H3K36me3-deficient cancers: lessons from yeast
Chen-Chun PAI

Towards chromosome replication profiling of tumour cells - **Etienne SCHWOB**

Deciphering the chromatin landscape at DNA double strand breaks - **Thomas CLOUAIRE**

Recurrent TRIO fusion in non-translocation-related sarcomas - **Lucile DELESPAUL**

"Bench-to-Bed" development of microRNAs for the treatment of adult and pediatric liver cancers - **Christophe GROSSET**

Session 1C - Evolution du système de santé: Dynamiques globales et spécificités de la cancérologie p. 15

Modération: Béatrice Jacques

Conférence: Evolutions des organisations de santé en France
Daniel BENAMOUZIG

Table ronde avec Jérôme VIGUIER, Institut national du Cancer (Paris), Jean-Marie BRUGERON directeur adjoint de l'ICM (Montpellier)

Session 1D - Micro devices for cancer p. 17

Chair: Anne-Marie Gué

LECTURE: Digital diagnosis of cancer cells
Andrew GRIFFITHS

The Cellular Technology: a route towards realistic tumor models - **Pierre NASSOY**

A new look at blood shear-thinning - **Manouk ABKARIAN**

Circulating microRNA detection using fluorescence-based nanofluidic platform for the early diagnosis of pancreatic cancer - **Jean CACHEUX**

Polarimetric imaging technique through an optical fiber: towards an endoscopic tool for the diagnosis of cancers of inner cells - **Dominique PAGNOUX**

16:00 – 16:30 Coffee break

16:30 - 18:30

Session 2A - SUNRiSE : Tools and models to study cancer stem cells p. 23

Chairs: Lucie Karayan-Tapon & Julie Pannequin

LECTURE: Building cancer in organoids
Marc VAN DE WETERING

Mouse models for the characterization and targeting of cancer stem cells in gastric adenocarcinoma - **Christine VARON**

Lineage tracing to study cancer stem cells in hepatocellular carcinoma - **Damien GREGOIRE**

PDX models to drive CSC personalized medicine -**Emmanuelle CHARAFE-JAUFFRET**

Session 2B - Chromatin dynamics and cancer p. 29

Chairs: Jérôme Dejardin & Martin Teichmann

LECTURE: Coactivator complexes and PIC components have two dynamic populations defined by active transcription and H3K4me3-ion
Laszlo TORA

The role of LSD1 demethylating complexes in vivo - **Luisa DI STEFANO**

Chromatin dynamics of estrogen-regulated genes associated with transcription - **Thomas GERMIER**

DNA Methylation Dynamics and its functional impact during the early stages of intestinal tumorigenesis - **Marco BRUSCHI**

Role of the 3' regulatory region (3'RR) in the epigenetic control of the IgH locus during class switch recombination - **Nour GHAZZAUI**

Session 2C - Plan cancer et évaluation des politiques de santé p. 35

Modération: Pascale Grosclaude

Table ronde avec Hélène GRANDJEAN, Nadine HASCHAR NOE, Audrey VEZIAN

Session 2D - Technology transfer and innovation p. 37

Chair: Guy Kantor

NanoMedSyn: a new platform for therapeutic targeting: Glyco-Nano-Vectors - **Marie MAYNADIER**

High sensitivity detection of DNA with microfluidics: transfer of a technology dedicated to the profiling of circulating DNA - **Aurélien BANCAUD**

ChromaLys and its Tumor-Track Project - **Marc VERELST**

How to facilitate the clinical validation of medical devices and biomarkers in the era of e-health ? **Sabrina SERPILLON**

LECTURE: Une sociologie de la recherche translationnelle? Esquisse d'un programme
Pascal RAGOUET

Thrusday 24th November

8:00 **-** Welcome coffee

8:30 - 10:00

Session 3A - Transcriptional control in cancer p. 43

Chairs: Daniel Fisher & Martin Teichmann

LECTURE: Transcriptional control and transformation by MYC proteins
Martin EILERS

The histone demethylase JMJD2A/KDM4A links ribosomal RNA transcription to nutrients and growth factors availability - **Didier TROUCHE**

The RNA-binding protein LIX1 controls the proliferation of stomach mesenchymal progenitors and GastroIntestinal Stromal Tumor (GIST) cells - **Pascal DE SANTA BARBARA**

Interplays between RIP140 and LCoR transcription factors in breast cancer cells - **Stéphan JALAGUIER**

Session 3B - Translational research : Emerging projects p. 49

Chair: Nadine Houédé

In vivo imaging of gene expression induced by magnetic hyperthermia - **Franck COUILLAUD**

Characterisation of chemotherapy effect on colorectal cancer cell phosphokinome - **Diego TOSI**

Blockade of the Neuregulin/HER3 axis to inhibit the crosstalk between CAF and tumor cells : a promising therapeutic option in pancreatic cancer - **Charline OGIER**

Design and self-assembly of CXCR3-targeting block copolymer nanoparticles - **Laura RODRIGUES**

Session 3C - Les soins de support p. 55

Modération: Eric Bauvin

Les soins de support en oncologie: une révolution en marche
Pierre SENESSE

DISSPO pour les soins de support? L'évolution organisationnelle des soins de support en département au sein de l'IUCT - **Nathalie CAUNES**

Impliquer des patients dans la co-construction d'un programme d'éducation thérapeutique au sein d'ateliers coordonnés par une unité de soins de support : Quelle(s) expertise(s) d'usage mobiliser ? - **Philippe TERRAL**

Sortir de l'ambiguïté sur l'activité physique dans les soins de support - **Grégory NINOT**

Session 3D - Nanotools for therapy and diagnosis p. 61

Chair: Jean-Pierre Pouget

LECTURE: Theranostic, How to couple diagnosis by imaging with treatment
Marc JANIER

The sweet imaging of cancer - **Frédéric FRISCOURT**

Nanoparticles for cancer theranostic: targeting, imaging and photodynamic therapy - **Nadir BETTACHE**

177Lu-lilotomab versus 177Lu-rituximab in antibody radioneclide conjugate therapy of Non-Hodgkin lymphoma: a radiobiological approach - **Alexandre PICHARD**

10:00 - 10:30 - Coffee break

10:30 - 12:00

Chair: Stéphane Pyronnet

LECTURE: mRNA capping in transcription and translation
Victoria COWLING

Epitranscriptome plasticity in colorectal cancer - **Alexandre DAVID**

The role of non-coding transcription in regulation of rDNA chromatin state - **Marta KWAPISZ**

HBZ-mediated shift of JunD from growth suppressor to tumor promoter by inhibition of ribosomal protein S25 expression - **Jean-Marie PELOPONESE**

Chair: Marc Ychou

LECTURE: The immune system, a double edge sword during colon cancer oncogenesis
Christophe BORG

BIOCOLON : translational research assay in metastatic colon cancer, from clinic to basic research - **Nicole TUBIANA , Litaty MBATCHI, Maguy DEL RIO**

Immune microenvironment drives colorectal cancer fate - **Christel DEVAUD**

Virtual ligand screening identifies the proprotein convertase small molecule inhibitors as new potential colorectal liver metastases therapy - **Abdel-Majid KHATIB**

Modération: Philippe Gorry

Conférence: Le fonctionnement d'un réseau dans son contexte. L'exemple d'Oncolor
Isabelle KLEIN

Table ronde avec Philippe VAGNER, Eric BAUVIN

Chair: Olivier Sandre

LECTURE: MRI and Nanoparticles: A tandem business
Claire BILLOTEY

Coordination polymers nanoparticles as contrast agents for MRI and SPECT - **Yannick GUARI**

Design of a nanostructured MRI contrast agent - **Paul MATHIEU**

Entropic Boltzmann closure for radiotherapy - **Jonathan PAGE**

12:00 – 13:00 - Posters sessions

14:00 - 16:00

Chairs: Estelle Espinos & Julie Pannequin

LECTURE: Translational control of colorectal cancer
Owen SANSOM

Mechanisms of translational control by RNA structures and RNA binding proteins in cancer - **Anne CAMMAS**

Active mRNA translation into invadosomes revealed by combination of laser capture and proteomic analysis - **Frédéric SALTEL**

Loss of 4E-BP1-mediated translational control favors aberrant replication in pancreatic cancer - **David MULLER**

Primary transcripts of microRNAs encode regulatory peptide - **Jean-Philippe COMBIER**

Chair: Alexandre Evrard

LECTURE: Molecular oncology and personalized medicine: the exemple of colorectal cancer
Pierre LAURENT-PUIG

The RAS-related GTPase RHOB confers resistance to EGFR-tyrosine kinase inhibitors in NSCLC via an AKT-dependant mechanism - **Olivier CALVAYRAC**

Clinical utility of longitudinal plasma analysis in examining clonal evolution and tracking secondary acquired resistance in mCRC patients refractory to targeted therapy - **Brice PASTOR**

Patient Stratification and Precision Medicine in Pancreatic cancer: a gene blood-signature for gemcitabine treatment - **David PIQUEMAL**

The mammary ducts create a favourable microenvironment for xenografting of luminal and molecular apocrine breast tumours - **Richard IGGO**

Présentations flash de posters sur toutes les thématiques de l'axe 4

Chair: Muriel Golzio

LECTURE: Defining remotely activatable nanovectors and instrumentations for cancer diagnostics and therapy
Jean-Luc COLL

Multimodal nanoparticles for tumor detection and tracking during radiotherapy - **Audrey FERRAND**

Involvement of targeted and non-targeted effects during alpha or Auger RIT of small volume peritoneal carcinomatosis - **Riad LADJOHOUNLOU**

Confocal Raman microscopy for tracing oxaphosphinanes (phostines) in glioblastom, non epithelial (SNB75) - **Hamideh SALEHI**

16:00 - 17:00 - Posters session & coffee break

17:00 - 18:00

Transparent Publishing, Preprints & Open Science: how to share reproducible data
Bernd PULVERER

Friday 25th November

8:00 – 8:30 - Welcome coffee

8:30 – 10:30

Session 7 - Making sense of (big) data p. 121

Chairs: Jacques Colinge & Daniel Fisher

LECTURE: Humanizing the mouse immune repertoire for Therapeutic antibody discovery
Allan BRADLEY

Large, complex, and rich data sets: the need for "coordinate systems" and imagination - **Jacques COLINGE**

The MARS (Matrix of RNA-Seq) viewer project - **Fabien PIERRAT**

Stratifying Patients for Immune Checkpoint Blockade Cancer Therapies - **Jean-Jacques FOURNIE**

Personal medical data linking: Development and validation of a reliable and easy-to-use software tool - **Sébastien ORAZIO**

10:30 – 11:15 - Coffee break

11:15 - 12:45

Session 8 - Pre-clinical models / Le Grand Défi Vivez Bougez p. 127

Pre-clinical models

Chairs: Claude Sardet & Charles Theillet

Tumor cell proliferation and organization dynamics in 3D - **Valérie LOBJOIS**

PDX models, why, how and for what aim? - **Charles THEILLET**

MPCC platform: preclinical models of digestive cancers - **Lucile CANTEREL-THOUENNON**

Le Grand Défi Vivez Bougez

Chair: Florence Cousson-Gélie

The Great Live and Move Challenge: Impact and mediating mechanisms of a physical activity intervention implemented among children - **Mathieu GOURLAN**

12:45 – 13:30

Bristol-Myers Squibb Sponsored Symposium **Immuno-oncology: from Research to the Clinic**

Chairs: Jean-Louis Pujol & Guillaume Cartron

Optimisation of immune activity in oncology - **Jean-Jacques FOURNIE**

Clinical practice in immuno-oncology: application in melanoma - **Olivier DEREURE**

12:45 – 14:00 - Lunch break

14:00 - 16:00

Session 1A - New therapeutic targets of signaling pathways

1A/1

RNA binding proteins in the resistance to anti-cancer targeted therapies

G. BOLDINA[1], M. VALLEJOS[1], D. ALLARD[2], I GIRAULT[2], H. MALKA-MAHIEU[1], L DÉSAUBRY[3], M. DUTERTRE[1], C. ROBERT[2], **Stephan VAGNER[1,2]**

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Recent work, including large-scale genetic and molecular analyses, identified RNA-binding proteins (RBPs) as major players in the hallmarks of cancer. Specific RBPs allow the selective regulation of cancer genes at multiple post-transcriptional levels from pre-mRNA splicing/polyadenylation to mRNA stability/translation. These multiple activities are mediated by RBP binding to mRNAs. In recent years, we have studied how the eIF4F translation initiation factor bound to the 7-methylguanosine cap structure present at the 5'-end of all cellular mRNAs contributes to tumorigenesis with a focus on its role in chemoresistance as well as the promising use of new small molecule inhibitors of the complex. We have specifically shown that, due to its location downstream of the PI(3)K/AKT/mTOR pathway and the RAS-RAF-MEK-ERK-MNK mitogen-activated protein kinase (MAPK) signal transduction pathways, eIF4F is a nexus of resistance to anti-BRAF and anti-MEK therapies in both BRAF-mutated (melanoma, colon, thyroid) and NRAS-mutated (melanoma) cancer cells. Furthermore, inhibiting the eIF4A component of the eIF4F complex, with a novel flavagline (FL3) that is insensitive to P-glycoprotein-mediated multidrug resistance, synergizes with inhibiting BRAF and MEK to kill BRAF-mutant cancer cells and synergizes with inhibiting MEK to kill NRAS-mutant cancer cells in melanoma. In parallel, while investigating a set of data based on high-throughput sequencing of polyadenylated transcripts 3'-ends (3'-Seq), we have found that a short eIF4E mRNA isoform is generated through alternative use on an intronic polyadenylation (IPA) site. The global generation of transcripts with shorter 3' untranslated region (3'UTR) is known to occur during enhanced cell proliferation and transformation into cancer cells. However, the involvement of alternative polyadenylation in the response to targeted therapies and in the spreading of cancer cells to metastatic sites is unknown. IPA site usage is known to be widely inhibited by the U1 small ribonucleoprotein particle (U1) bound to an adjacent 5' splice site (5'ss). We have found that targeting U1 with an antisense oligonucleotide (U1-ASO) leads to activation of the use of IPA sites in the eIF4E gene but also in several genes involved in the MAPK and PI(3)K-AKT-mTOR pathways. We have also demonstrated that the specificity of IPA regulation by U1 during tumour cell spreading is provided by the regulation of its binding to specific 5'ss by the RBP and U1-interacting splicing factor TIA1. The significance of these findings in tumor cell spreading and in the response to targeted therapies will be discussed.

1A/2

Targeting post-translational modifications in live cells using intrabodies

L. GUGLIELMI[1], E. RENAUD[1], V. DENIS[1], C. LARROQUE[1], L. CASSIMERIS[2], **Pierre MARTINEAU[1]**

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GFP-tagged proteins are used extensively as biosensors for protein localization and function, but this requires modification of the targeted protein and the GFP moiety can interfere with protein properties and. An alternative approach is to indirectly label endogenous proteins using intracellular recombinant antibodies (intrabodies), but most antibody fragments are insoluble in the reducing environment of the cytosol. We have designed synthetic antibody repertoires optimized for stable expression in the cell cytoplasm. Using phage-display selection it is possible to identify recombinant antibody fragments specific for any protein including their post-translational modifications. When fused to a fluorescent protein, these antibodies can be used to localize their target within a live cell. We recently exemplified the approach by isolating an anti-tubulin single-chain Fv fragment (scFv) that recognizes α-tubulin and requires tubulin's C-terminal tyrosine residue for binding. When expressed in the cell as a GFP-fusion protein, this scFv is soluble and labels microtubules in fixed and living cells. Microtubule dynamic instability, measured by tracking 2G4-GFP labeled microtubules, was nearly identical to that measured in cells expressing GFP-α-tubulin demonstrating that the intrabody does not affect microtubule dynamics. In cells, 2G4-GFP localized to most microtubules, but did not co-localize with those composed of detyrosinated α-tubulin, a post-translational modification associated with non-dynamic, more stable microtubules. This demonstrated that a recombinant antibody can be used as a specific intracellular biosensor that can differentiate between unmodified and post-translationally modified forms of a protein.

Robin G et al. (2014) J Mol Biol 426:3729; Mazuc E et al. (2014) PLoS ONE 9:e104998; Cassimeris L et al. (2013) PLoS ONE 8:e59812; Guglielmi L et al. (2011) Protein Eng Des Sel 24:873; Philibert P et al. (2007) BMC Biotechnol 7:81.

1A/3

The medullary adipocytes contribute to the bone metastasis of prostate cancer and this effect is regulated by obesity

Adrien GUERARD[1,2], Victor LAURENT[1,2], Jean-Michel LAFOSSE[2,3], Nicolas REINA[2,3], Denis CALISE[2,4], Muriel GOLZIO[1,2], Morgane LE GRAND[1,2], Sophie LE GONIDEC[2,4], Laurence NIETO[2,1], Bernard MALAVAUD[5,2], Philippe VALET[4,2], Catherine MULLER[1,2]

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Background: We have recently demonstrated that mature adipocytes of the periprostatic adipose tissue act as a driving force for the local dissemination of prostate cancer (PCa) through the secretion of the CCL7 chemokine, and that this effect was amplified by obesity. Then, PCa cells metastasize to distant site such as bone. During this dissemination, PCa cells interact with bone marrow where the main components are medullary adipocytes (MedAd)

Objective: We investigated the role of the MedAd secretions in the bone metastasis process of PCa. We also explored the amplification of this effect in obesity and aging, two known risk factor for bone metastasis in PCa.

Methods and results: Using a series of 35 samples from patients, we first showed *in vitro* (Boyden chamber assay) that conditioned mediums from human MedAd (MedAd-CM) were able to chemoattract PCa cells (by contrast to paired conditioned medium obtained from subcutaneaous adipocytes) with a strong amplification by obesity or aging. The chemoattractive potential of medAd-CM was mediated by the chemokine CCL7 which interact with one of its receptor CCR3 on tumor cells, as shown using pharmacological inhibitors, blocking antibodies and gene repression strategies. To validate this effect *in vivo*, we used the murine cell line RM1-BM able to localize to the bone after intra-cardiac injection. We observed that the loss of CCR3 in tumor cells abrogates their bone metastatic homing.

Conclusions: This study show for the first time a mechanism that could explain the increased bone metastatic dissemination of prostate cancer linked to obesity and aging. These data highlight the fact that medullary adipocytes, using the CCR3/CCL7 axis, are able to control the distant dissemination of PCa cells to the bone. In a context of obesity or aging, medullary adipocytes show a different phenotype leading to an increased secretion of CCL7 and enhanced dissemination.

1A/4

Overexpressed flotillins, new markers of metastatic development, promote cellular invasion by disrupting cadherin-mediated adhesion and stimulating extracellular matrix degradation

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Flotillins 1 and 2 are ubiquitous and highly conserved proteins associated with membrane microdomains rich in cholesterol and glycosphingolipids. They preferentially exist as heterotetramers, that oligomerize to form "flotillin-microdomains". They are involved in several cellular processes, mainly by promoting the clustering of membrane receptors and by participating in their endocytosis independently of clathrin and caveolae *(Bodin et al., 2014)*.

The overexpression of flotillins was recently reported in a wide diversity of invasive sarcomas and carcinomas (breast, lung, liver, nasopharynx, …) and is considered as a marker of poor prognosis. Overexpressed flotillins appear involved in the acquisition of a metastatic behavior. **It remains to elucidate whether this overexpression is sufficient to induce invasive properties and to characterize the downstream deregulated mechanisms**

We use a dual reciprocal approach consisting in inducing the overexpression of flotillins in non-tumoral models from epithelial (MCF10A) and mesenchymal (C2C12) origins and in down-regulating flotillins in metastatic breast carcinoma (MDA-MB-231) and sarcoma cells (rhabdomyosarcoma Rh41).

We show that ectopic overexpression of flotillins in non-tumoral cells is sufficient to induce an invasive behavior *in vitro* and *in vivo*. Reciprocally, flotillin downregulation in invasive cancer cells dramatically inhibits their invasive properties *in vitro* and *in vivo*.

Mechanistically, we provide evidence that overexpressed flotillins deregulate the vesicular trafficking leading i) to disrupt cadherin-mediated intercellular adhesion leading the cells to undergo an Epithelial to Mesenchymal Transition; ii) to favor the delivery of the matrix metalloproteinase MT1-MMP to invadopodia, hence stimulating the degradation of the extracellular matrix.

To conclude, our study indicates that overexpressed flotillins are critical for metastatic development and highlights them as new potential therapeutic targets.

1A/5

How the identification of an off-target of the antitumor drug tamoxifen led to the discovery of dendrogenin A: a tumor suppressor metabolite

Marc POIROT, Sandrine SILVENTE-POIROT

Cancer Research Center of Toulouse

Tamoxifen (Tam) is a drug used since more than 30 years in the world for the treatment of breast cancers expressing estrogen receptors (ER). Tam was initially conceived as a blocker, at the ER level, of the tumor promoting activity of 17β-estradiol. Additionnaly, Tam binds additionally with high affinity to the microsomal Anti-Estrogen Binding Site (AEBS), which is a hetero-oligomeric complex involved in cholesterol biosynthesis and which catalyzes the cholesterol-5,6-epoxide hydrolase (ChEH) activity. Tam inhibited ChEH at therapeutic doses leading to the accumulation of 5,6-epoxy-cholesterol (5,6-EC), the substrate of ChEH, which induced breast cancer cell differentiation and death. In the presence of a catalyst and a nucleophilic compound, 5,6α-EC reacted and gave a unique and chiral product of addition, suggesting the possible existence of a new metabolic pathway. To test this hypothesis, we studied the conjugation of 5,6α-EC with histamine, which gave dendrogenin A (DDA). DDA induced in vitro and in vivo cancer cell differentiation and death, suggesting that DDA could exist as an endogenous metabolite. DDA was effectively detected in several mammalian healthy tissues, while its level strongly decreased in tumors, evidencing that DDA was a metabolite and that a deregulation in DDA metabolism occurred in cancers. A complementation of this DDA deficiency in cancer cells triggered a drastic control of tumor growth and improved animal survival. DDA kills tumor cells by lethal autophagy through a dual inhibition of a ChEH subunit and of the modulation of a nuclear receptor. This original mechanism of action makes of DDA a promising drug candidate for the treatment of several refractory cancers. We established that DDA is the first steroidal alkaloid found to date in mammals. Its discovery reveals the existence of a new metabolic pathway in mammals at the crossroads of cholesterol and histamine metabolism that leads to the production of a metabolic tumor suppressor.

1A/6

Deciphering and targeting YAP/TAZ activity in human gastric adenocarcinomas

Julie GIRAUD[1], Silvia MOLINA-CASTRO[1], Cathy STAEDEL[2], Solène FERNANDEZ[1], Julien IZOTTE[1], Pierre DUBUS[1], Philippe LEHOURS[1], Francis MEGRAUD[1], Christine VARON[1]

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Gastric cancer (GC) is the fourth most common type of cancer worldwide, with 738000 deaths annually. Surgical removal of early stage GC tumors is critical to effective treatment, but because of few symptoms accompanying early GC, most GCs are found at an advanced stage.
YAP and TAZ are the key components of the Hippo pathway, a highly conserved pathway which controls organ size and tumorigenesis. YAP and TAZ are co-transcriptional factors that bind to TEAD family proteins and activate oncogenic pathways. Given the association of elevated expression and hyperactivity of YAP/TAZ in many cancers, inhibitory strategies of their nuclear activity represent rational and novel targeted approaches for the treatment of gastric cancer. Recently, a pilot screen identified Verteporfin (Vp) as a small inhibitor of TEAD-YAP interactions which prevented YAP-induced oncogenic growth.
The aim of this project was 1/ to analyze YAP/TAZ activity in gastric cancer cell lines and in Patient Derived primary tumor Xenografts (PDXs) and 2/ to target YAP/TAZ activity in those models by treating the cells with Vp to prevent tumor growth.
Preliminary results showed a nuclear expression of YAP and/or TAZ in 10-30% of GC cells in primary tumors. YAP and/or TAZ nuclear expression appears in front of migration, were the invasive cancer stem cells (CSC) have been described to reside. *In vitro,* Vp treatment decreased YAP/TEAD target genes expression in a dose-dependent manner in GC cell lines and in PDXs and led to a diminution of cellular proliferation. Vp treatment decreased the CSC pool assessed by the inhibition of tumorsphere formation and the decreased expression of the CSC marker CD44. Finally, Vp treatment decreased tumor growth *in vivo* and inhibited the ability of residual cell to initiate tumorspheres along several passages. In conclusion, targeting YAP/TAZ/TEAD could be a promising strategy in the treatment of GC.

Session 1B – Genomic instability and cancer

1B/1

Targeting histone H3K36me3-deficient cancers: lessons from yeast

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SETD2 is a tumour suppressor, which is frequently mutated in a range of different cancer types. SETD2-dependent tri-methylation of histone H3K36 performs a number of cellular functions and has been recently shown to play a key role in maintaining genome stability through facilitating checkpoint activation and DNA double-strand break (DSB) repair. Here we define a role for Set2-dependent H3K36me in promoting efficient DNA replication in fission yeast. Loss of Set2 results in inefficient dNTP synthesis and DNA replication. Moreover, loss of Set2 was synthetic lethal following Wee1 inactivation, resulting in replication arrest and subsequent mitotic catastrophe. Wee1 inactivation resulted in increased usage of inefficient DNA replication origin firing and DNA damage accumulation, which in a set2Δ background resulted in critically reduced dNTP levels, replication fork collapse, Mus81-dependent DNA damage and cell death. Accordingly, deletion of gene encoding the RNR inhibitor Spd1 suppressed this synthetic lethality. Together, these findings identify a key role for Set2 in facilitating DNA replication and viability in response to CDK1-induced replication stress. These findings are being exploited to target SETD2-deficient cancer cells.

1B/2

Towards chromosome replication profiling of tumour cells

M BIALIC, V COULON, M KOZLAK, M DRAC,**E SCHWOB**

Institut de Génétique Moléculaire Montpellier - MONTPELLIER

Every time a cell divides it has to copy its 6x109 bp genome with maximal accuracy and reasonable time. This takes place during the S phase of the cell cycle and requires the spatially- and temporally-controlled firing of ~25,000 replication origins that generate bi-directional forks moving at 1-2 kb/min. Altered DNA replication is the main source of replication stress and genome instability in cancer, and a central target of anti-cancer drugs. Properly assessing the dynamics of chromosome replication is thus key to understand the cause of cancer and to design new therapies.
We developed a method based on the successive incorporation of thymidine analogues (IdU and CldU) into DNA of proliferating cells, followed by microscopic examination of labelled replication tracts along individual DNA molecules stretched by DNA combing. Analysis of these patterns allows determination of several salient features of DNA replication in single cells, such as fork velocity (FV) and asymmetry (FA), inter-origin distance (IOD) and global instant fork density (GIFD). Comparing these parameters in normal cells, cancer cell lines and in cancer-predisposition models indicated that cancer cells have a lower density of replication forks but increased duration of S phase. Despite their potential value for tumour stratification, prognosis or therapy, little information is currently available on proliferation rates, cell cycle structure and DNA replication within solid tumours, mainly because they are heterogeneous and hard to dissociate. We will present our efforts to apply the above method on patient-derived mouse xenografts (PDX) rapidly dissociated after excision and pulse-labelled with IdU-CldU. Preliminary results suggest that replication parameters are also altered within tumours and that the method might be applicable to human samples. We will also briefly describe a novel approach for rapid replication profiling using a portable DNA sequencer that could be used in clinical settings.

1B/3

Deciphering the chromatin landscape at DNA double strand breaks

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DNA Double Strands Breaks (DSB) is the most deleterious type of DNA damage. DSB are repaired by two groups of pathways: homologous recombination (HR) and Non-Homologous End Joining (NHEJ), which vary in their mechanisms as well as their accuracy. The choice between these pathways is a critical aspect of DSB repair that is far from being understood. In eukaryotes, DNA is embedded in chromatin, which tightly regulates its accessibility and therefore impacts all aspects of DNA metabolism, including DSB repair. We recently developed a new experimental system, named DIvA for DSB Induced via AsiSI, which allows investigating the relationship between chromatin and DSB repair using chromatin immunoprecipitation (ChIP) and Next Generation Sequencing. We previously showed that DSB located in transcriptionally active, H3K36me3-rich chromatin are preferentially repaired by HR. We now want to decipher the "histone code" associated with each repair pathway, i.e. to identify the set of histone modifications that accompany repair by HR or NHEJ. We also wish to draw a more exhaustive picture of the chromatin landscape induced around DSB. For this, we are currently performing genome wide mapping of an extended set of chromatin modifications by ChIP-Seq, before and after DSB induction.

1B/4

Recurrent TRIO fusion in non-translocation-related sarcomas

Lucile DELESPAUL[1,2], Tom LESLUYES[1,2], Gaëlle PEROT[1,3], Céline BRULARD[1], Lydia LARTIGUE[1], Jessica BAUD[1,2], Pauline LAGARDE[1], Sophie LEGUELLEC[4], Agnès NEUVILLE[1,3], Philippe TERRIER[5], Dominique VINCE-RANCHERE[6], Susanne SCHMIDT[7], Anne DEBANT[7], Jean-Michel COINDRE[1,2,3], Frédéric CHIBON[1,3]

[1] Actions for onCogenesis understanding and Target Identification in Oncology

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[6] Centre Léon Bérard - Département de Pathologie - Lyon

[7] Centre de Recherche en Biologie cellulaire de Montpellier

Purpose: Despite various differences, non-translocation-related sarcomas (comprising UPS, LMS, MFS e.g.) are unified by their complex genetics. Extensive analysis of the tumor genome using molecular cytogenetic approaches showed many chromosomal gains, losses and translocations per cell. Genomic quantitative alterations and expression variations have been extensively studied by adapted high-throughput approaches, yet translocations still remained unscreened. We therefore analyzed 117 non-translocation-related sarcomas by RNA sequencing to identify fusion genes.

Experimental design: We performed RNA sequencing and applied a bioinformatics pipeline dedicated to detection of fusion transcripts. RT-PCR and Sanger sequencing were then applied to validate predictions and to search for recurrence and specificity.

Results: Among the 6,772 predicted fusion genes, 420 were in-frame. One recurrent rearrangement, consistently involving *TRIO* with various partners, was identified in 5.1% of cases. *TRIO* translocations are either intra-chromosomal with *TERT* or inter-chromosomal with *LINC01504* or *ZNF558*. Our results suggest that all translocations lead to a truncated TRIO protein either directly or indirectly by alternative splicing. *TRIO*rearrangement is associated with a modified transcriptomic program to immunity/inflammation, proliferation and migration and an increase in proliferation.

Conclusions: *TRIO* fusions have been identified in four different sarcoma histotypes likely meaning that they are not related to a primary oncogenic event but rather to a secondary one implicated in tumor progression. Moreover, they appear to be specific to non-translocation-related sarcomas since no such rearrangement was identified in sarcomas with simple genetics. More cases could lead to a significant association of these fusions to a specific clinical behavior.

1B/5

"Bench-to-Bed" development of microRNAs for the treatment of adult and pediatric liver cancers

Christophe GROSSET

INSERM U1035, Biotherapy of Genetic, Inflammatory diseases and Cancer, BORDEAUX

My team works on the regulation of genes by microRNAs (miRNAs) in hepatocellular carcinoma (HCC) and hepatoblastoma, two primary cancers of the liver in adults and in children, respectively. Currently there is no curative therapy for the patients who present an advanced liver tumor and/or metastasis. Moreover, liver tumors are molecularly heterogeneous and many gene drivers and oncogenic pathways participate in their development. For all these reasons, high-risk patients do not often respond to chemotherapy and most targeted therapies have failed to show any benefit in these cancers. Therefore, miRNA-replacement therapy is a new option for the treatment of patients with cancer as exemplified by miR-34a-5p, the first miRNA reaching the clinic in cancer. Using functional screening and molecular approaches, we selected miRNAs which down-regulate Glypican-3 (GPC3) or beta-catenin (CTNNB1), two oncogenes involved in Wnt pathway activation and liver carcinogenesis. All these miRNAs are decreased in patients' tumors and some efficiently reduced the growth and survival of liver cancer cell lines in vitro. Moreover, they impaired tumoral growth in vivo using the chick chorioallantoic membrane model. Experiments in mice are under progress. Finally, one of them sensitized tumoral hepatic cells to drugs currently used in clinic as a first-line treatment for patient with liver tumor (Sorafenib, cisplatin…). These data are of particular interest as these drugs are sometimes associated with severe toxicity and only barely increases patients' overall survival, especially in HCC. In conclusion, we identified several miRNAs acting as tumor suppressors in liver and inhibiting the key oncogenic Wnt pathway. At this stage, our goals are the development of miRNA-replacement therapy, associated or not with standard clinical drugs, using various route of administration and the transfer of the best candidate to the clinic for the treatment of adult and pediatric patients with liver cancer.

Session 1C - Evolution du système de santé: dynamiques globales et spécificités de la cancérologie

1C/1

Evolutions des organisations de santé en France

Daniel BENAMOUZIG

UMR 7116 – CSO Centre de sociologie des organisations et alliance AVIESAN

Le système de santé français est depuis longtemps l'objet de réformes, qui en modifient les caractéristiques. Différentes tendances sont à l'œuvre au niveau national et régional mais leur lisibilité n'apparaît pas toujours nettement. Tandis que le recours à des instruments économiques, en matière de tarification par exemple, laisse planer le spectre d'une « privatisation » du système de santé, le rôle de l'Etat se renforce en réalité de multiples manières. Cette contribution propose un regard sur ces transformations récentes à partir de trois types d'éléments. En premier lieu, un regard est porté sur les récentes évolutions institutionnelles. Elles permettent de caractériser un rôle plus prégnant de l'Etat et le développement de formes bureaucratiques d'organisation. Ce rôle accru coexiste cependant avec un haut niveau de pluralisme, en partie hérité de l'histoire. En deuxième lieu, le rôle de l'Etat coexiste avec un niveau élevé d'inégalités sociales de santé, en dépit de l'amélioration des conditions d'accès aux soins et d'un système de financement fortement redistributif. En troisième lieu, et de manière plus prospective, les dynamiques du système de santé sont elles-mêmes appelées à évoluer. D'importantes transformations peuvent être anticipées à partir des frontières actuelles du système de santé, dans le domaine de l'assurance maladie et en vue d'une organisation post-hospitalière du système de soins par exemple, aussi bien qu'en référence à de nouvelles frontières, en référence aux enjeux liés à l'environnement ou à la mondialisation et aux mouvements de population en particulier.

Session 1D - Micro devices for cancer

1D/1

Digital diagnosis of cancer cells

Andrew GRIFFITHS

ESPCI Paris Tech, Paris

1D/2

The Cellular Technology: a route towards realistic tumor models

Gaëlle RECHER, Kévin ALESSANDRI, Maxime FEYEUX, Dan STREHLE, **Pierre NASSOY**

LP2N, UMR 5298 CNRS/IOGS/Univ. Bordeaux, Talence

We present a simple microfluidic method based on the encapsulation and growth of cells inside permeable, elastic, hollow micro-spheres or micro-tubes. We will present and discuss how this approach may help us understand the biomechanical regulation of tumor progression and cell escape. We also describe the formation of composite capsules containing stromal and tumor cells, their relevance to tumor development and their applications for high throughput screening of drugs.

1D/3

A new look at blood shear-thinning

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Blood viscosity decreases with shear stress, a property essential for an efficient perfusion of the vascular tree. Shear-thinning
is intimately related to the dynamics and mutual interactions of red blood cells (RBCs), the major component of blood. Because of the lack of knowledge about their behavior under physiological conditions, the link between RBCs dynamics and blood rheology remains still unsettled. Performing experiments and simulations in microcirculatory flow conditions of viscosity, shear rates and volume fractions, our study reveals new RBCs dynamics, which govern shear-thinning. In contrast to the current paradigm, which assumes that RBCs align steadily around flow direction while their membrane and cytoplasm circulate, we show instead that RBCs successively tumble, roll, deform into rolling stomatocytes, and finally adopt highly-deformed poly-lobed shapes for increasing shear stresses, even for semi-dilute volume fractions of the microcirculation. Our results suggest that any pathological change in plasma composition, RBCs cytosol viscosity, or membrane mechanical properties will impact the onset of these morphological transitions, and should play a central role in pathological blood rheology and flow behavior.

1D/4

Circulating microRNA detection using fluorescence-based nanofluidic platform for the early diagnosis of pancreatic cancer

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85% of patients affected by pancreatic adenocarcinoma (PDA) are diagnosed at an advanced stage, preventing effective care and curative treatments. Therefore, it is urgent to find reliable biomarkers to manage the early detection of this disease by means of appropriate tests. MicroRNAs (miRNA) have recently emerged as candidate biomarkers due to their early alteration during pancreatic carcinogenesis. Since these molecules can be quantified in biological fluids, miRNAs provide a new class of non-invasive biomarkers for PDA diagnosis.
We are currently studying miRNA/DNA hybridization using biofunctionalized nanoslits in combination with fluorescence microscopy. Fluorescently labeled target molecules are captured in specific locations within the nanochannel. Because of the reduced depth of the channel that turns into a reduced fluorescence background, the amount of hybridized targets can be directly correlated to the fluorescence signal on the sensor. As a result, this simple fluidic platform enables studies of the miRNA interaction with probe molecules, and allows us to investigate the influence of various hybridization parameters (probe design and temperature) in order to efficiently detect SNP (single-nucleotide polymorphism) between let7-b and let7-c targets.
On the other hand, detection in complex fluids, such as plasma, is being addressed. A special care is given to the sample preparation protocol and its consequences on the detection outcome. As a proof of concept, we have shown that miRNA spiked in 10% plasma solution could be detected easily into nanochannels without extra preparation. Experiments aimed at detecting endogenous miRNA are currently ongoing. This multidisciplinay project paves the way for the simple, reliable and cost-efficient detection of candidate miRNA biomarkers for the early-diagnosis of PDA, a disease with no cure when detected too late.

1D/5

Polarimetric imaging technique through an optical fiber: towards an endoscopic tool for the diagnosis of cancers of inner tissus

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Optical polarimetry is a technique which allows determining structural characteristics of a medium at the micrometric scale, through the measurements of changes in the polarization states of light induced by its interaction with this medium. In the last 15 years, optical polarimetry has been demonstrated to be a promising tool for the characterization of biological tissues in the view of early detection of cancers. For the characterization of inner tissues, it should be associated with endoscopy, i.e. polarimetric measurements should be performed through an optical fiber terminated by a microscanner for performing remote polarimetric images. Unfortunately, optical fibers largely modify the guided polarization states on both the forward and the backward paths, on an uncontrollable and time dependent manner. This unwanted feature prevents from directly determining the polarization changes at the tissue from the proximal side of the fiber. Thus, until the recent years, polarimetry and endoscopy have long been regarded as incompatible techniques.
In this communication, we will describe a technique that we have developed in order to solve this problem. It allows performing a complete Mueller characterization of tissues through a >2m long optical fiber: simultaneous measurements of birefringence (linear and circular) and of diattenuation (linear and circular). Polarimetric images of biological tissues achieved with this technique will be presented and discussed.
The ability of a biological tissue to depolarize light is another polarimetric feature which measurement is of great interest in the view of the diagnosis of cancerous pathologies. However, because the fiber behaves as a very tight spatial filter, measuring the degree of polarization of the light reflected by the tissue from the proximal end represents a serious issue. In this communication, we will expose the research directions that we currently explore in order to reliably perform such a measurement.

Session 2A - SUNRiSE: Tools and models to study cancer stem cells

2A/1

Building Cancer in Organoids

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The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined Lgr5 as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of Lgr5 in cycling, columnar cells at the crypt base. Using lineage tracing experiments in adult mice, we found that these Lgr5+ve crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that they represent the stem cell of the small intestine and colon. Lgr5 was subsequently found to represent an exquisitely specific and almost 'generic' marker for stem cells, including in hair follicles, kidney, liver, mammary gland, inner ear tongue and stomach epithelium. Single sorted Lgr5+ve stem cells can initiate ever-expanding crypt-villus organoids, or so called 'mini-guts' in 3D culture. The technology is based on the observation that Lgr5 is the receptor for a potent stem cell growth factor, R-spondin. Similar 3D cultures systems have been developed for the Lgr5+ve stem cells of stomach, liver, pancreas and kidney. 3 Dimensional organoid cultures are derived from healthy and tumor tissue from colorectal cancer patients. Tumor organoids closely reflect their tumor with respect to copy number and mutation spectrum and are amenable to high through-put drug screens, allowing detection of gene-drug associations. Organoid technology may allow design of personalized therapy.

2A/2

Mouse models for the characterization and targeting of cancer stem cells in gastric adenocarcinoma

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INSERM U1053 Bordeaux Research in Translational Oncology

Gastric cancer is the fifth most common cancer in frequency and the third leading cause of cancer mortality in the world. Chronic infection with Helicobacter pylori, a class 1 carcinogen, is responsible for more than 90% of the cases. This cancer, mainly of the elderly, is most of the time detected at advanced and metastatic stages, and of poor prognosis. Unlike breast cancer or colon cancer that have been extensively studied, few studies have focused on cancer stem cells (CSCs) in gastric adenocarcinoma. Cancer stem cells (CSC) are defined as a sub-population of tumour cells characterized by self-renewal and asymmetrical division properties, giving rise to the more or less differentiated cells composing the tumour. CSC can stay in quiescence and resist to conventional therapies, to be later at the origin of recurrence and metastasis. Contrarily to carcinoma of others extensively studied organs such as breast and colon, CSCs have been poorly studied in gastric carcinoma. To confirm their existence in gastric carcinoma, we developed mouse xenograft models of patient's derived primary tumours, allowing to reproduce in mice tumours like those of the patients. Using these models as well as in vitro tumourspheres assays, we showed evidence of the existence of CSC within human gastric adenocarcinoma. We characterized some surface markers of enrichment of CSC, among them CD44 and ALDH. In parallel, we generated a mouse model of chronic infection with H. pylori, which reproduced within a year the sequence of histopathological events occurring in 70 years in human and leading to gastric carcinoma. In this model, we demonstrated that gastric CSC could originate from both local epithelial stem cells, or at a lower frequency from bone marrow derived stem cells. In both cases, the neoplastic lesions were composed of CD44+ cells. Using in vitro co-culture experiments of gastric epithelial cells lines with carcinogenic strains of H. pylori, we demonstrated that chronic H. pylori infection led to an epithelial to mesenchymal transition (EMT) and the emergence of CD44+ cells with CSC properties. We recently confirmed in a transgenic mouse model predisposed to EMT that H. pylori -induced dysplasia developed earlier and were more severe with age than in wild type mice. Based on these complementary in vitro and in vivo models, our current research aims to characterize EMT/CSC-specific signaling pathways driving the CSC self-renewal and tumorigenic properties, in order to specifically target them and eradicate gastric carcinoma progression.

2A/3

Lineage tracing to study cancer stem cells in hepatocellular carcinoma

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The model of cancer stem cells (CSC) postulates that a subset of tumoral cells with stem cell features dictates a hierarchical organisation of the tumour, and is responsible for relapse, metastasis and chemoresistance. If the concept of cancer stem cells has now been validated, the definition of these cells, also called Tumour Initiating Cells (TIC), their proportion inside the tumour, and even their existence in some types of cancer, is still a subject of debate. This is notably true in hepatocellular carcinoma, the main primary liver cancer, for which markers of CSC have been difficult to identify. A specificity for this cancer is that the cell of origin, the hepatocyte, shows some stemness features regarding its capacity to contribute to organ regeneration upon damage. Cancer stem cells are usually defined by functional test of xenograft experiment. Lineage tracing is increasingly used to better understand population dynamics inside organs and tumours. We have developed a murine experimental model of hepatocellular carcinoma combining intrahepatic injection and lineage tracing to study population dynamics and intercellular interactions during tumour growth and dissemination. Hepatic progenitors are transformed ex vivo by expression of different cellular oncogenes, or genome editing with CrispR/Cas9 approach. The cells also express a combination of fluorescent proteins, giving rise to distinct multi-color marking of different tumour clones or subpopulations. Injection in the liver parenchyma generates aggressive orthotopic tumours that give rise to intra- and extrahepatic metastases. I will present advantages and limitations of the tool we developed, as well as the first results we obtained using it. We believe that the use of clonal tracing within the primary tumour and metastatic outgrowths will be a useful tool to better characterize cancer stem cells in hepatocellular carcinoma.

2A/4

PDX models to drive CSC personalized medicine

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In the developing area of personalized medicine, targeted therapies are mainly based on genomic characterization of each tumor, and is currently proposed as promising strategies for resistant breast cancer (RBC). Despite the promises of advanced genome sequencing, many patients still fail therapy, resulting in disease progression, recurrence, and metastases. Cancer stem cells (CSCs) concept illustrates the non-genetic intrinsic resistance, recapitulates tumor heterogeneity that creates hierarchically organized tumor tissues where a subpopulation of self-renewing cancer stem cells (CSCs) sustains the long- term clonal maintenance of the neoplasm. Evidences indicate that CSCs survive many commonly employed cancer therapeutics. Patient-derived tumor xenograft (PDXs) models recapitulate tumor complexity and heterogeneity at cellular, and molecular level. We aimed to specifically address the therapeutic sensitivity in RBC, by using a PDX prospective collection, fully characterized for genomic alterations. In this work, we aim at defining for each tumor the best therapy to target breast cancer intratumor heterogeneity, the CSC component. For that, we defined a panel of 44 FDA-approved compounds used for cancer treatment, including breast and other types of cancer, cancer stem cell drugs, chemo or targeted therapies. For each drug, we screened the differential sensitivity of the bulk tumor cells and the CSC components for 12 PDX models using an ex vivo screening approach on short term culture. To assess intra tumor heterogeneity, we set up an original dual strategy: for the bulk cells, an ex vivo assay based on IC50, and for breast CSC component a miniaturized Aldefluor assay. First, we demonstrate that bulk cells and CSCs sensitivity may be dissociated for the same drug in the same PDX models. Then, we observed that bulk cell sensitivity is often correlated to tumor genomic abnormalities. By opposite, CSC sensitivity seems not to follow the rule and displays selectively sensitivity to specific targeted compounds belonging to Tyrosine Kinase Inhibitors family. We are exploring the pathways that sustain this selective sensitivity in the CSCs components. Then, we validated the hits predicted from ex vivo screening assays by treating different PDX models for selected drugs. As a Proof-of-concept, we have already validated one CSC targeted strategy for one PDX model. In that work, we demonstrated that CSCs and bulks cells are not sensitive to same treatment, independently to their genomic abnormalities. This result highlights the need for differential testing on the two tumor components, proposes a dual-screening strategy to evaluate the differential drugs sensitivity, validated in PDX models. After all, we emphasized the importance of integrating CSC drug sensitivity in the new area of personalized medicine currently focused on genomic-based strategies and irrespective of intra tumor heterogeneity.

Session 2B - Chromatin dynamics and cancer

2B/1

Coactivator complexes and PIC components have two dynamic populations defined by active transcription and H3K4me3-ion

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Initiation of transcription by RNA polymerase II (Pol II) according to the textbook view is believed to be the outcome of a number of sequential events beginning with the binding of specific activators to their cognate binding sites. This initial step will trigger the recruitment of coactivator complexes and general transcription factors (such as for example TFIIB and TFIID) at promoters to allow the loading of Pol II into the preinitiation complex (PIC). In this process, coactivators play multiple crucial roles through enzymatic as well as non-enzymatic functions. SAGA (Spt-Ada-Gcn5-Acetyltransferase) and the ATAC (Ada-Two-A-Containing) complexes are two functionally distinct, but related, coactivator complexes with several enzymatic activities: histone acetyl transferase (HAT, for ATAC) or HAT and deubiquitinase (for SAGA). These complexes have been shown to regulate global gene expression and chromatin architecture through their enzymatic activities. With a combination of fluorescence recovery after photobleaching (FRAP), fluorescence loss in photobleaching (FLIP) and fluorescence correlation spectroscopy (FCS) we analyzed the dynamic behavior of TFIIB, TFIID, Pol II, SAGA and ATAC in living cells. Our FRAP and FLIP measurements indicate that TFIIB, TFIID, ATAC and SAGA subunits are highly dynamic and exhibit only transient interactions with the chromatin with no detectable immobile fractions. In contrast, we found that the recovery rates of the TATA binding protein (TBP, a subunit of Pol I, II and III transcription machineries), and RPB1 (Pol II subunit) were significantly slower than that of TFIIB, or TFIID, ATAC and SAGA subunits. Furthermore, our FCS measurements indicate that ATAC and SAGA have two distinct diffusing populations in the nucleus: a 'fast' population (having the approximate size of the studied complexes) and a 'slow' population (representing chromatin interacting, but still mobile complexes). The changes of the dynamic behavior of these complexes upon inhibition of transcription, or histone H3K4me3-ion, and their relevance in transcription regulation will be discussed.

2B/2

The role of LSD1 demethylating complexes in vivo

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Aberrant activity of chromatin modifying enzymes, such as the histone demethylase LSD1, has been shown to play a role in tumor development. LSD1 is highly expressed in a plethora of tumors and there has been a growing interest in LSD1 as a drug target. However, although important progress has been made in vitro, its precise role in tumorigenesis still needs to be elucidated. Our strategy is to use an animal model system, Drosophila, as a starting point to identify genes and pathways that modulate LSD1 activity in vivo and then test their conservation in mammals and their potential implication in cancer. We found that the Drosophila ortholog of LSD1, dLsd1, plays an important role in the regulation of chromatin homeostasis and gene expression. In addition, using a genetic approach, we found interplays between dLsd1 and other histone demethylases such as Lid, components of signaling pathway such as the Notch pathway and RNA binding proteins such as Pumilio. Importantly, we showed that most of these interplays are conserved in human cells. We are now coupling our genetic approach with "omics" data, such as ChIP-sequencing, transcriptomics and mass spectrometry to better understand the multiple roles of dLsd1 in development and in cancer. We will discuss our recent data on dLsd1 function in normal development

2B/3

Chromatin dynamics of estrogen-regulated genes associated with transcription

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The spatial organization of chromatin in the nucleus is non-random and chromatin dynamics participate in regulating nuclear processes. Transcriptional activity has been correlated with relocalization of gene loci within the cell nucleus. However, we do not know whether changes in transcription per se alter motion of the underlying chromatin fiber. We developed a non-invasive method to label DNA for imaging chromatin in living cells. The ANCHOR™ method is based on insertion of a short ANCH sequence (< 1kb) recognized by OR proteins which accumulate by oligomerization. Coupled to fluorescent proteins, this system allows visualization of genomic loci in real time. Here we used estrogen-responsive genes in living human breast cancer cells as a model system to rapidly activate gene expression. We generated cells with several genomic integrations of the ANCHOR system fused to the CCND1 gene under the control of its endogenous, estrogen responsive, promoter. The MS2 system was included in the construct to enable monitoring of CCND1 mRNA production. For the first time, we are able to follow chromatin dynamics of a specific gene locus during transcription activation within 1h in single living human cells. We report here the simultaneous observation of mobility and transcription of a single gene. Addition of estradiol caused a rapid decline in chromatin motion, prior to detection of new mRNA and regardless of pre-induction mobility. Inhibition of transcription elongation did not fully restore chromatin motion, indicating that as soon as RNA polymerase II initiates transcription the CyclinD1 gene domain undergoes major conformational changes that reduce its mobility. Our observation that transcription initiation locally reduces chromatin dynamics within minutes is compatible with the idea that existing chromatin conformation reorganizes to facilitate enhancer promoter contacts and chromatin de-and reassembly.

2B/4

DNA methylation dynamics and its functional impact during the early stages of intestinal tumorigenesis

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Institut de Génomique Fonctionnelle

Cancer initiation and progression represent the outcome of the progressive accumulation of genetic and epigenetic alterations. Global changes in the epigenome are now considered as a common hallmark of malignancies. However, most of our present knowledge represents the result of the comparison between fully established malignancies and their surrounding healthy tissue. Such comparison is not informative about the epigenetic contribution to the very early steps of cancer onset. By performing DNA methylation and gene expression profiling of *Lgr5*$^{+}$ intestinal stem cells we found that part of the phenotype resulting from the constitutive activation of the Wnt pathway upon *Apc* loss is acquired via differential epigenetic regulation of key biological processes controlling the balance between self-renewal and differentiation. In particular we found that intestinal stem cells become less responsive to the pro-differentiation stimuli exerted by the surrounding microenvironment via the BMP/TGF- signaling. This altered responsiveness reduces the fate determination of intestinal stem cells toward terminal differentiation resulting in the accumulation of those cells. By using conditional genetic *ex vivo* models (intestinal organotypic cultures) we found part of these oncogenic effects to be reversible via the modulation of the machinery responsible for *de novo* methylation of the DNA.
Overall, this work confirms that the epigenetic remodeling is an early event in tumorigenesis that is necessary for cells to acquire their oncogenic potential. The functional impact of our findings on cancer initiation *in vivo* is currently under investigation.

2B/5

Role of the 3' regulatory region (3'RR) in the epigenetic control of the IgH locus during class switch recombination

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Lymphopoiesis is coupled with programmed accessibility of Ig genes to transcription and to several major transcription-dependent DNA remodelling events. Multiple cis-regulatory elements located 5' and 3' of constant (C) genes control B-cell ontogeny. Among 5' elements, the intronic Em enhancer is reported as a master control element of V(D)J recombination. The IgH 3' regulatory region (3'RR), that encompasses the four transcriptional enhancers hs3a, hs1,2, hs3b and hs4, controls mtranscription in mature B-cells and is the master element controlling class switch recombination (CSR) and somatic hypermutation (SHM) but without role on V(D)J recombination. In mature B-cells, CSR replaces the expressed constant Cm gene with a downstream CH gene. How the four transcriptional enhancers of the IgH 3'RR control CSR remains an open question. We have investigated IgG1 CSR in 3'RR-deficient mice. We show that the 3'RR enhancers target the Switch (S) g1 acceptor region (and poorly the Sm donor region) by acting on epigenetic marks, germline transcription, paused RNA Pol II recruitment, R loop formation, AID targeting and double strand break generation. Levels of H3ac, H4ac and H3K4me3 were not affected by the deletion of 3'RR enhancers in the Im-Sm-Cm region during IgG1 CSR. In contrast, H3ac, H3K4me3 and H3K9ac were dramatically lowered in the Pg1-Ig1-Sg1-C g1 region. This suggests that a reduction in histone acetylation is the most upstream defect after 3'RR deletion. In contrast, location and diversity of Sm-Sg1 junctions are not affected by deletion of the 3'RR. Thus, the 3'RR controls the first steps of CSR by priming the S acceptor region but is not implicated in the choice of the end joining pathway. Numerous mature B-cell lymphomas are marked by oncogene translocation into the IgH locus where they come under the 3'RR transcriptional control. The 3'RR might therefore represent a potential suitable target for anti-lymphoma pharmacological therapy with HDAC inhibitors.

Session 2C - Plan cancer et évaluation des politiques de santé

Table ronde

Session 2D - Technology transfer and innovation

2D/1

A New Platform for Therapeutic Targeting: Glyco-Nano-Vectors

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The spin off **NanoMedSyn** aims to develop new targeted therapeutics. Thanks to the company's proprietary synthetic derivatives (named **AMFA**), NanoMedSyn provides a compound with an high affinity for the mannose 6-phosphate receptor, the major addressing pathway to lysosomes. These AMFA compounds have the potential to target various proteins or drugs to tissues and cells expressing these receptors in order to facilitate their cellular entrance and finally lysosomal uptake.
NanoMedSyn mainly applies the **AMFA** technology to Enzyme Replacement Therapy (E.R.T.) of orphan Lysosomal Storage Disorders. Another objective of **AMFA** targeting is the treatment of cancer using multifunctional nanoparticles. These nanovectors are addressed specifically to small size solid cancers overexpressing the mannose 6-phosphate receptor.

2D/2

High sensitivity detection of DNA with microfluidics: transfer of a technology dedicated to the profiling of circulating DNA

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Circulating cell-free DNA is becoming a key biomarker for the management and follow-up of solid tumors. Various types of DNA alterations have been reported in ccfDNA, including point mutations, DNA hypermethylations, microsatellite instabilities, and in many instances, these alterations were identical to the ones found in the primary tumor tissue of the patient. Among the growing list of biomarkers extracted from ccfDNA, the concentration and DNA integrity index have been shown to provide a predictive measurement. However, modern tools to characterize ccfDNA profiles are limited in sensitivity so that ccfDNA cannot be characterized directly and PCR-based techniques, which scarcely represent the composition of ccfDNA, have to be employed. In this talk, we will describe the novel technology µLAS, which allows the characterization of minute DNA samples with cutting-edge sensitivity. With this technology, which was developed in a technology CNRS lab and transferred to Picometrics Technologies (Labège), we can measure ccfDNA size range profile with one 1 µL of purified ccfDNA from plasma or directly with 1 µL of plasma. We will show recent results obtained with patients' samples and conclude with our future lines of development toward RNA and epigenetic detection without molecular amplification.

2D/3

ChromaLys and it's Tumor-Track project

Marc VERELST

CHROMALYS SAS

ChromaLys is a young innovative company, spin off from French academic laboratories belonging to the CNRS and INSERM. ChromaLys designs, manufactures and sells new innovative luminescent and/or multimodal nano-probes for biological imaging (in vitro and in vivo) at preclinical stage [1] today and for clinical applications tomorrow.
In this communication, we will present briefly our Tumor-Track R&D project which deals with Nanotechnology for tumor detection and tracking during radiotherapy. Radiotherapy has been widely used in the treatment of cancer for many years but generates significant side effects because it is very difficult to irradiate the targeted tumor without reaching the surrounding healthy tissue. This problem is exacerbated when these tumors move with the patient's breathing (liver, prostate, lungs tumors …). Our ambition is to ensure the subjection of a radiotherapy treatment to the movements of a mobile tumor, thus greatly limiting the damages to surrounding healthy tissue. This control requires detection of tumor movements, by X- Ray radiography, simultaneously with the radiation therapy treatment [2]. This dynamic detection will be performed by tumor labelling with our nano-reagent [3] which will greatly help the tumor detection during radiotherapy treatment.
Moreover, during this presentation, we will also present the different steps leading from the fundamental research to the creation of an innovative company with the aim to market a product for medical use.

[1] http://www.chromalys.fr
[2] French patent : FR 1452111 «NANOPARTICULES POUR LEUR UTILISATION DANS LA DETECTION DE TUMEURS MOBILES»
[3] S.A. Osseni, S. Lechevallier, M. Verelst, P. Perriat, J. Dexpert-Ghys, D. Neumeyer, R. Garcia, F. Mayer, K. Djanashvili, J. A. Peters, E. Magdeleine, H. Gros-Dagnac, P. Celsis, R. Mauricot « Gadolinium oxysulfide nanoparticles as multimodal imaging agents for T_2 -weighted MR, X-ray tomography and photoluminescence » NANOSCALE, 2014, 6, 555.

2D/4

How to facilitate remote patient monitoring in the era of e-health ?

Sabrina SERPILLON, Daniel LAUNE

Kyomed - MONTPELLIER

While reducing the frequency and number of hospitalization as well as the duration of hospital stays in favor of appropriate ambulatory care is a top concern, monitoring patients outside the conventional clinical settings is one of the major challenges that clinical centers and healthcare professionals have to face. New healthcare pathways and patients' follow-up tools must be designed to maintain the same quality of care and patient safety. This is particularly important when patients have to deal with complex care processes such as in oncology with severe side effects and when medical decisions require early detection and fine biomarker monitoring. Such systems may not only facilitate medical care provided on an outpatient basis but will also provide a comforting and supportive environment to patients and their families.

E-health technologies including bedside diagnostics, sensors, devices, and personalized softwares for disease management have the potential to meet the specific needs related to ambulatory care, especially in cancer patients. They enable the collection of both objective biomarkers (e.g. weight, blood pressure, blood analysis, overall activity) and perceived patient data (e.g. pain, appetite, energy). Such systems allow the analysis and the follow-up of a wide range of information, from blood biomarkers to behavioral, and also lifestyle, dietary as well as mental health indicators, thereby providing a global picture of the patient.

Importantly, new digital care pathways will be adopted and used on a long-term basis, only if the technology is designed around the needs, requirements and aspirations of people - professionals and patients - who will use them. To go even further in this approach, the role of technology is to strengthen human aspects of healthcare. Existing methods like living lab approaches help to make a success of this challenge.

2D/5

Une sociologie de la recherche translationnelle ? Esquisse d'un programme

Pascal RAGOUET

Centre Emile Durkheim

En sociologie, les concepts que nous utilisons sont issus d'un travail de spécification de notions utilisées dans le langage courant. Ainsi en est-il des notions de « découverte » ou d'« innovation » qui, du fait de leurs usages multiples et récurrents, sont souvent chargées de représentations et d'impensé. La notion de découverte est, par exemple, souvent associée au thème de l'individu créateur qui jette un voile sur la réalité collective de toute découverte. De la même façon, la notion d'innovation technique est, d'une part, largement assimilée à un processus linéaire de maturation d'une recherche fondamentale - représentation qui persiste dans l'imaginaire collectif, mais aussi dans le discours des pouvoirs publics - et constitue, d'autre part, une injonction omniprésente dans les politiques de recherche, que l'on se situe au plan international, national ou local. Il serait sans doute possible d'en dire de même pour la notion de recherche translationnelle. Cependant, pour le sociologue, le qualificatif « translationnel » peut constituer un point de départ plus intéressant pour penser sociologiquement l'innovation dans le domaine biomédical. L'objectif de mon exposé est de proposer à la discussion, à partir d'exemple, les grands traits de ce que pourraient être une sociologie du translationnel.

Session 3A - Transcriptional control in cancer

3A/1

Transcriptional Control and Transformation by MYC Proteins

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Deregulated expression of MYC oncoproteins is a central driver of human tumorigenesis. MYC proteins are transcription factors that bind globally to virtually all promoters with an open chromatin structure as well as to many enhancers. Proof-of-principle genetic experiments show that many tumors are addicted to elevated levels of MYC and therefore argue that inhibiting MYC will have significant therapeutic effects for multiple tumor entities. I will discuss two main open questions in the field: First, while MYC proteins bind pervasively to promoters, they appear to regulate a much smaller set of genes. Several models have been proposed to explain this apparent discrepancy and the resulting question what the function of MYC proteins at promoters of "non-regulated" genes might be. Second, deregulated expression of MYC not only promotes growth and proliferation but also strongly sensitizes tumor cells towards apoptosis, yet it has been difficult to exploit the pro-apoptotic function of MYC for therapy. Recent results from my laboratory provide a potential explanation for this difficulty and suggest a strategy how to overcome it.

3A/2

The histone demethylase JMJD2A/KDM4A links ribosomal RNA transcription to nutrients and growth factors availability.

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The interplay between methylation and demethylation of histone lysine residues is an essential component of gene expression and there is considerable interest in elucidating the roles of proteins involved and how they are regulated to participate in the fine-tuning of genes expression. KDM4A/JMJD2A is a histone-demethylase of the Jumonji family that specifically demethylates tri-and di-methylated forms of Lysine 9 of histone H3 (H3K9me), a repressive mark of transcription. Pre-rRNA synthesis is the first step and a major control point of ribosome biosynthesis. It is down-regulated in response to nutrient starvation, differentiation, or inhibition of protein synthesis, and is up-regulated upon re-addition of nutrients, or growth or proliferation stimuli. We found that KDM4A localize to the nucleoli of proliferating human cells, suggesting that it may regulate Pol-I driven ribosomal RNA (rDNA) transcription. Indeed, we found that KDM4A is recruited to the promoters of active rDNA copies where it associates with Pol-I machinery. Noticeably, KDM4A accumulates in nucleoli in response to serum, demethylates H3K9me at rDNA promoters and activates their transcription, suggesting that KDM4A controls the initial stages of transition from 'poised', non-transcribed rDNA chromatin into its active form. We further demonstrate that PI3K, a major signaling transducer central for cell proliferation and survival, controls nucleolar localization of KDM4A and consequently its association with ribosomal DNA through the SGK1 downstream kinase. We propose that the interplay between PI3K/SGK1 signaling cascade and KDM4A constitutes a mechanism by which cells adapt rDNA transcription and thus ribosome biogenesis to the availability of growth factors and nutrients.

3A/3

The RNA-binding protein LIX1 controls the proliferation of stomach mesenchymal progenitors and GastroIntestinal Stromal Tumor (GIST) cells.

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During development, the digestive musculature arises from mesenchymal cells. In adults, these cells can undergo oncogenic transformation, leading to GastroIntestinal Stromal Tumors (GISTs). Because tumorigenesis often involves the reactivation of developmental processes, a better understanding of the molecular mechanisms driving digestive mesenchyme development could offer insight into altered mechanisms in gastrointestinal cancers.

Recently, we focused on the *Limb Expression 1* (*LIX1*) gene. LIX1 is a 281 amino-acid protein. Predictive in silico studies have shown that LIX1 has a double-stranded RNA-binding domain such as DICER and DROSHA (unpublished data), suggesting that it could be involved in RNA or miRNA processing. Using the avian embryo as a model organism, we demonstrated that *LIX1* specifically defines the population of mesenchymal progenitors, thus identifying *LIX1* as a marker of stomach mesenchyme immaturity. Furthermore, using *in vivo* gain- and loss-of-function approaches, we demonstrated that expression of LIX1 must be tightly regulated to allow fine-tuning of the transcript levels and state of activation of the pro-proliferative transcriptional coactivator YAP1 to regulate proliferation rates of stomach mesenchymal progenitors and their differentiation. Our data highlight dual roles for LIX1 and YAP1 and provide new insights into the regulation of cell density-dependent proliferation, which is essential for the development and homeostasis of organs (Mckey et al., *BMC Biol*, 2016).

These properties lead us to examine the possible function of LIX1 in tumorigenesis and tumour progression. We examined the level of*LIX1* transcripts in digestive mesenchymal-derived tumors and found an aberrant high level of *LIX1* expression in GIST patients. Moreover, we found that LIX1 silencing in GIST cells induces a decrease in proliferation and invasion, indicating that LIX1 has a crucial role in GIST malignancy.

3A/4

Interplays between RIP140 and LCoR transcription factors in breast cancer cells

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Breast cancer is the most common female cancer and the second most frequent cancer in the world. In the majority of mammary tumors, estrogen receptors (ERs) control cancer growth and cell proliferation. ERs are members of the nuclear receptor superfamily which are ligand-activated transcription factors. These receptors exert either a positive or negative control of gene expression by recruiting transcriptional cofactors. Among these latter, RIP140 (Receptor Interacting Protein of 140 kDa) and LCoR (Ligand-dependent CoRepressor) interact with several agonist-bound nuclear receptors, including the ERα. They mainly act as transcription corepressors by recruiting histone deacetylases and C-terminal binding proteins.
In this study, we have investigated both the expression and the biological activity of LCoR in human breast cancer cells. We highlighted the repressive role of LCoR in breast cancer cell proliferation. We identified and characterized a protein complex formed by LCoR and RIP140 as well as the role of RIP140 in the regulation of gene expression and cell proliferation by LCoR. Moreover, we uncovered the positive effect of RIP140 on the expression of the LCoR gene. Finally, we studied the expression of the two transcription factors in human breast cancer biopsies. These data highlighted the predictive role of the two nuclear receptor cofactors in breast carcinogenesis.

Session 3B - Translational research: Emerging projects

3B/1

In vivo imaging of local gene expression induced by magnetic hyperthermia

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Colloidal dispersions of maghemite nanoparticles stabilized with dextran macromolecules placed into an alternating magnetic field produced heat. The present work aims to demonstrate that these particles could be used in vivo for local and non-invasive deposition of thermal energy sufficient to trigger thermo-induced gene expression. Iron oxide nanoparticles were first characterized in vitro on a bio-inspired setup, then they were assayed in vivo using a transgenic mouse strain expressing the luciferase reporter gene under transcriptional control of a thermosensitive promoter. Iron oxide nanoparticles dispersions were applied topically on the mouse skin or injected sub-cutaneously with Matrigel™ to generate so called pseudo tumors. Temperature was monitored continuously and a feedback loop used to control the power of the magnetic field generator in order to avoid overheating. Thermo-induced luciferase expression was followed by bioluminescence imaging 6 hours after heating. We showed that maghemite nanoparticles dispersions were able to induce in vivo mild hyperthermia compatible with thermo-induced gene expression in surrounding tissues and without impairing cell viability. These data opened new therapeutic perspectives for using magnetic hyperthermia for non-invasive modulation of tumor microenvironment by local thermo-induced gene expression or drug release.

3B/2

Characterisation of chemotherapy effect on colorectal cancer cell phosphokinome

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Background: Resistance of cancer cells to targeted agent treatment is frequently associated to the reactivation of the inhibited pathway or to the activation of escape pathways, and functional adaptive responses (i.e. due to cellular machinery modulations) could contribute to targeted treatment resistance.

Aim: We evaluated phosphokinome changes induced by 5FU, irinotecan, oxaliplatin in a molecularly characterized colon cancer cell line, in order to provide a rationale for associations of chemotherapy and target agents.

Materials and methods: The CRC cell line HT29 (carrying a mutated BRAF gene and a wild type KRAS gene) was xenografted into nude mice. We separated the xenografted mice into 6 groups and treated them with vehicle, 5FU, oxaliplatin, irinotecan, 5FU plus oxaliplatin or 5FU plus irinotecan. Protein extracted from the xenografts was analyzed by profiling kinase phosphorylation with the PamGene technology, and a Z score ratio of treatment versus control values was calculated for each peptide. An increase in the phosphorylation of a peptide was declared when the Z score was > 1.

Results: We found that the INSR and EPHA4 were phosphorylated in response to treatment by 5FU. Irinotecan was associated with an increase in phosphorylation of INSR, p38, AKT, MEK1 and NFkB1 among others, while oxaliplatin induced the phosphorylation of INSR, EPHA4, p38, several TK membrane receptors (including HER-family receptors, PDGFR, VEGFR), PI3K, PRGR, SYK and LAT. With combinations of 5FU plus oxaliplatin or irinotecan, we could observe in both cases an increase in phosphorylation of INSR, Ephrin receptors, several TK membrane receptors (including HER-family receptors, PGDFR, VEGFR) and LAT.

Conclusions: These data suggest that several proteins could be phosphorylated in response to chemotherapy in colorectal cancer, and that kinome phosphorylation profiles are partially specific for different agents. These data could constitute a rationale to build treatment combinations including chemotherapy and targeted agents.

3B/3

Blockade of the Neuregulin/HER3 axis to inhibit the crosstalk between CAF and tumor cells : a promising therapeutic option in pancreatic cancer

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Pancreatic carcinoma has a dramatic outcome, due to its heterogeneity, aggressiveness, desmoblastic stroma and asymptomatic evolution. Palliative therapy remains the standard and the 5-year survival rate is lower than 5%.

In an effort to find new treatments, the molecular mechanisms involved in pancreatic cancer development are still under deep investigation, uncovering key drivers and promising therapeutic targets such as EGFR family members. Pre-clinical and clinical trials have shown a correlation between the expression of EGFR family or associated ligands such as neuregulin (NRG) and a poor prognosis. Moreover, the micro-environment plays a crucial role in pancreatic cancer development and several lines of evidence reported the ability of cancer-associated fibroblasts (CAF) to secrete growth factors. The aim of this project is to disrupt the crosstalk between CAF and tumor cells by targeting these growth factors in order to inhibit tumor growth.

Our lab generated monoclonal antibodies specific to one of these ligands by lymphocyte hybridization or phage display. Their affinity, specificity and functionality on proliferation and migration have been demonstrated in several cancer cells, some expressing the ligand, other ligand sensitive. Finally, a promising therapeutic effect of our antibody was obtained in intra-pancreatic xenograft in which a significate tumor growth inhibition was observed. The next step is to study the impact of our anti-ligand antibody on pancreatic tumor stroma by using co-culture of CAF coming from patient and pancreatic cell lines in vitro and in vivo. This project described an original targeted therapy in pancreatic tumors that could represent a major advance in improving significantly the limited and hopeless therapeutic arsenal available to treat this very aggressive pathology.

3B/4

Design and self-assembly of CXCR3-targeting block copolymer nanoparticles

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The CXCR3 chemokine receptor has attracted significant attention as a new drug target regarding its pivotal role in tumor progression.1 Qualified as a "double-edged sword", its effects are mediated directly in tumor cells and indirectly through the regulation of angiogenesis and tumor immunity.
The goal of the present project2 is to formulate polymer nanoparticles targeting the CXCR3 receptor for the specific delivery of hydrophilic and/or hydrophobic anti-cancer drugs to CXCR3-expressing tumors. To this aim, the surface of these nanoparticles is functionalized with a potent low molecular weight CXCR3 antagonist.
In this presentation, we will first describe the design, synthesis and characterization of a series of block copolymers, with different hydrophilic weight ratios, as well as their controlled self-assembly into well defined nanometer-sized nanoparticles with different morphologies (core-shell micelles and polymersomes). Synthetic and self-assembly strategies to introduce the CXCR3 antagonist onto the surface of nanoparticles will also be presented, as well as the first in vitro evaluations on CXCR3-expressing tumor cell lines.

Session 3C - Les soins de support

3C/1

Les soins de support en ambulatoire : une révolution en marche !

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Très récemment, l'inca a produit un rapport pour définir « un socle de base de prise en charge avec quatre soins de support incontournables :
- la prise en charge de la douleur
- la prise en charge diététique et nutritionnelle
- la prise en charge psychologique
- la prise en charge sociale, familiale et professionnelle (retour à l'emploi, réinsertion professionnelle pour les adultes et retour à la scolarité pour les enfants/adolescents). »

Ce rapport est en accord avec les publications récentes qui confirment que les soins de support non seulement sont indispensables à la prise en charge des patients mais peuvent modifier les trajectoires des patients. L'équipe de Temel a démontré, en étude randomisée, que des soins de support (proche du « palliative care » anglosaxon) introduits précocement dans la prise en charge de patients diagnostiqués avec un cancer du poumon non à petites cellules métastatique amélioraient leur survie. La qualité de vie était aussi améliorée, résultats confirmés par une nouvelle étude randomisée dans les cancers du poumon et les cancers digestifs en 2016. Dans certaines situations, les résultats sont tellement probants que les pratiques ont été modifiées sans étude randomisée ! Par exemple dans les cancers de la tête et du cou traités par radiochimiothérapie, dans les années 2000, les patients n'avaient pas accès aux compétences des professionnels en soins de support et étaient régulièrement hospitalisés pendant leur traitement pour toxicités aigües aux traitements, souvent associées à des soins de support inadaptés tel que la nutrition parentérale par exemple, avec pour conséquence des arrêts précoces de traitement. Depuis, l'approche multidisciplinaire par des professionnels des soins de support non seulement évite des hospitalisations inutiles, mais assure la faisabilité du traitement oncologique tout en travaillant à réduire les séquelles au long court et les coûts.

Il ne s'agit pas de proposer tel ou tel support lors d'une consultation oncologique, mais bien de dépister les besoins de façon proactive et de mettre en place de nouvelles trajectoires associant les soins de support précocement avec un suivi régulier et coordonné. Au même titre que l'ensemble des traitements oncologiques, les soins de support tiendront une place essentielle en ambulatoire, tel un pivot au service du patient et des professionnels de proximité mais avec l'aide et l'expertise des professionnels travaillant spécifiquement en cancérologie.

3C/2

DISSPO pour les soins de support ? L'évolution organisationnelle des soins de support en département au sein de l'IUCT-Oncopôle

Nathalie CAUNES-HILLARY

Département soin de support - Iuct-Oncopôle

Les thématiques de soins de support sont nombreuses : prise en charge des symptômes inconfortables en particulier la douleur, nutrition, souffrance psychologique ou sociale... Les intervenants sont multiples : oncologues ou spécialistes d'organes, équipes spécialisées (algologie, réhabilitation, soins palliatifs), service social, psychologues, diététiciennes ou encore bénévoles associatifs… Pour améliorer la coordination de ces acteurs, a été créée une Cellule de Coordination en Soins de Support (C.C.S.S), regroupant médecins et paramédicaux ; ses missions étaient de coordonner la prise en charge institutionnelle en soins de support, de favoriser une continuité extra-institutionnelle et d'assurer la formation et la recherche en soins de support.
Mais, les disparités de rattachement et la priorité laissée aux activités de leur département originel n'autorisaient pas réellement les professionnels de la CCSS à dédier du temps aux soins de support. Le déménagement de l'ICR et de certains services du CHU pour créer l'Institut Universitaire du Cancer de Toulouse-Oncopôle, a conduit à de nouvelles modalités d'organisation.
Les soins de support devant s'inscrire dans une démarche transversale à tout l'IUCT-Oncopôle et favoriser le décloisonnement des services, est né un Département Interdisciplinaire de Soins de Support pour le Patient en Onco-hématologie : D.I.S.S.P.O.
Les paramédicaux restent sous la responsabilité de la Direction des soins infirmiers ; les médecins sont partiellement ou totalement rattachés au DISSPO, sous la responsabilité fonctionnelle ou hiérarchique du chef de ce département.
Cette nouvelle organisation a permis d'améliorer la visibilité et la cohésion des professionnels. Toutefois, les ressources du DISSPO restent encore trop limitées pour des évaluations ou des prises en charge plus systématiques des besoins des patients et de leurs proches.
Nous aborderons les forces de ce modèle et les difficultés rencontrées.

3C/3

Impliquer des patients dans la co-construction d'un programme d'éducation thérapeutique au sein d'ateliers coordonnés par une unité de soins de support : Quelle(s) expertise(s) d'usage mobiliser?

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Dans le cadre du contrat de recherche REFLEXISS (séminaires de REFLEXivité sur la coordination des expertises dans la recherche interventionnelle visant la lutte contre le cancer et la réduction des Inégalités Sociales de Santé) financé par l'INCa, nous nous intéressons à la nature des savoirs portés par les usagers en santé. La notion d'expertise ou de savoir d'usage renvoie à la connaissance qu'a un individu ou un collectif de son environnement immédiat et quotidien, en s'appuyant sur l'expérience et la proximité (Nez, 2013). Nous rendons compte ici des résultats de la recherche concernant des patients engagés dans la co-construction d'un programme d'éducation thérapeutique à propos des modalités de prise d'anti-cancéreux oraux au sein d'ateliers coordonnés par l'unité de soins de support de l'oncopôle de Toulouse. Depuis une enquête par observations ethnographiques et entretiens, nous soulignons la pluralité des figures des savoirs d'usage. Plus ou moins visibles et reconnus institutionnellement, ils se construisent avec ou contre les expertises scientifico-techniques (chercheurs et professionnels de santé) instituées. Nous nous attardons sur les expertises d'usage les plus valorisées dans ces ateliers et montrons combien quatre compétences génériques fondent ces positions de « patients experts » légitimes : intéresser, fédérer, traduire, hybrider. L'usager expert le plus mobilisé dans ce dispositif, qui vise une coordination des expertises scientifico-technique et d'usage, est en effet celui capable d'intéresser les autres participants à sa « cause ». Il doit aussi savoir fédérer ses pairs et faire office de « passerelle » avec les professionnels de santé. Ces compétences impliquent une capacité à hybrider savoirs médicaux institués et savoirs d'usage et, en amont, une aptitude à assimiler et à « traduire » ces diverses connaissances à destination des différents protagonistes du dispositif.

3C/4

Sortir de l'ambiguïté sur l'activité physique dans les soins de support

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Des études encouragent l'intégration de programmes d'activité physique (AP) dans le parcours de soin des patients traités pour un cancer. Des méta-analyses soulignent leur bénéfice (Carayol et al., 2013 ; Cramp et al., 2012). Des revues listent les mécanismes supposés (Romieu et al., 2012). De grands organismes attestent de leur importance (expertises INSERM et INCa en cours). Et pourtant, des zones d'ombre subsistent. Ces connaissances sont essentiellement issues d'études observationnelles, d'études pilotes ou d'extrapolation de populations saines. Les méta-analyses restent donc prudentes sur les doses à recommander (intensité, fréquence et durée des séances), sur leur nature (individuel ou collectif), sur la période optimale pour débuter ces interventions (dès l'annonce, dès le premier traitement ou après les traitements), leur association (liens entre alimentation et AP), leur lieu de pratique (établissement, domicile, salle de fitness), leur mode d'encadrement (à distance, supervisé) et leur référentiel théorique (changement de comportements). Les études manquent encore de puissance et d'évaluation multimarqueurs. Les durées de suivi sont trop courtes pour avoir des effets sur la survie sans récidive. Ainsi, il est difficile de conclure actuellement entre une AP durant les traitements envisagée comme un vecteur de promotion de la santé (message incitatif), de prévention tertiaire (démarche recommandée visant à réduire les complications) ou de soins intégrés (intervention non médicamenteuse prescrite). De ce fait, les organisations et les pratiques actuelles sont très hétérogènes, rarement fondées sur la science et laissées au bon vouloir des établissements, des cliniciens et des patients (Zafar et al., 2012). La communication illustre cette réflexion à partir d'études menées en collaboration avec l'ICM, le CHU, l'hôpital d'Edmonton, le SIRIC et le GSO. Elle souligne les besoins de recherche interventionnelle dans le domaine.

Session 3D - Nanotools for therapy and diagnosis

3D/1

Theranostic: How to couple diagnosis by imaging to treatment

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More and more publications are emphasizing the wonderful properties of the new incredible nano-objects which will treat all the tumors or other diseases. Indeed, as I say to medical students, medical imaging has started with the discovery of the X-rays by Rontgen and of the radioactivity by Pierre and Marie Curie in 1896-8; has switched from analogic to numeric imaging modalities in the 1970s thank to the Beatles ; and is living, since 1998, a new era thanks to the tight interactions of imaging with chemistry. This new era leads to huge amount of publications describing more and more sophisticated nano-objects aimed at treating the cancer or all kind of diseases. This enthusiasm is wonderful, but I would like through this presentation, not to temper this enthusiasm, but to provide chemists, biologists and physicians involved in such developments, with some elements to better structure their future developments in order to have a chance to end-up with a useful compound for clinical practice. As a physician, specialized in Nuclear Medicine, I will present the development of news nano-objects for "theranostic" purposes and through my experience try to show you traps to avoid.

3D/2

The Sweet Imaging of Cancer

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There is a growing appreciation that complex glycans, displayed on glycoproteins and glycolipids, play key roles in numerous physiological and pathological processes. Changes in the glycome of cells have been found to be associated with the onset of cancer and have been involved in tumor proliferation, invasion, angiogenesis and metastasis. **Consequently, aberrant glycosylation of proteins, such as upregulation of sialosides, offers the possibility to target novel cancer biomarkers for early diagnosis.** Previous efforts towards glycans imaging have been relying on the use of lectins (glycan-binding proteins) and monoclonal antibodies. However, lectins typically are tissue-impermeant and often toxic, raising monoclonal antibodies to specific glycans is highly challenging due to the ubiquitous presence of glycans in mammals and their inherent poor immunogenicity.

Our group focuses on employing the **bioorthogonal chemical reporter strategy**, which elegantly combines the use of metabolically labeled azido-sugars and highly reactive cyclooctyne probes, as an emerging technology for labeling and visualizing glycans (Friscourt et al. 2013). Although, dibenzylcyclooctynes have proved to be exciting glyco-probes (Friscourt et al. JACS 2012; Friscourt et al. Chem Eur J 2015), their aromatic nature makes them highly hydrophobic, promoting their sequestration by membranes and nonspecific binding to serum proteins, ultimately limiting their application for in vivo imaging.

To address these issues, we have recently developed the first fully water-soluble glyco-probe, O-sulphated-dibenzocyclooctyne (S-DIBO), that was found to selectively label extracellular sialo-glycoconjugates in living cells, bringing imaging of glyco-biomarkers one step closer to novel exciting cancer diagnostics.

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3D/3

Nanoparticles for cancer theranostic: targeting, imaging, and photodynamic therapy

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Cancers are usually treated by surgery, radiotherapy, and chemotherapy. Some of them with weak aggressive potential in the short term do not justify these heavy treatments, and prompt the consideration of minimally invasive treatments. Photodynamic therapy (PDT) is considered as an alternative treatment due to its noninvasive nature and minimal cumulative side effects even after repetitive treatments. Recently, there is considerable research effort in developing nanoscale systems in the fight against cancer, particularly for use in cancer imaging and therapy. In this context, the development of biodegradable and biocompatible drug delivery system based on nanoparticle technology could be of particular interest to achieve the combination of targeting, imaging, drug delivery and photodynamic therapy of cancers. In our laboratory, we have already identified the membrane receptors overexpressed by cancer cells and we have used mesoporous silica nanoparticles carrying 2-photon photosentisizers (2 PS) grafted with ligands specific of these receptors for imaging and therapy. In this study, we used the zebrafish (*Danio rerio*) to develop an integrated model for *in vivo* investigations on new nanotools. The two-photon PDT was applied to the 48 hours post-fecondation (hpf) zebrafish embryos injected with cancer cells previously loaded with Periodic Mesoporous Organosilica (PMO) nanoparticles functionalized with 2 PS (PMO-2PS). The confocal fluorescence microscopy showed the reduction of the xenograft mass after two-photon irradiation. The xenograft reduction was confirmed by cell viability measurement with acridine orange and activated caspase-3 assays.
This work at the interface between fundamental and applied research could lead to the design of effective and biocompatible prototypes for personalized medicine.

3D/4

177Lu-lilotomab versus 177Lu-rituximab in antibody radionuclide conjugate therapy of Non-Hodgkin lymphoma: a radiobiological approach

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We have developed a preclinical radiobiological approach to compare the new antibody radionuclide conjugate (ARC)^{177}lu-labelled lilotomab directed against CD37 receptor*versus* ^{177}Lu-labelled rituximab directed against CD20 receptor in the therapy of non-Hodgkin lymphoma.
DOHH2 and Ramos lymphoma cells were exposed *in vitro* to unlabelled or ^{177}Lu-radiolabelled lilotomab, rituximab, or non-specific cetuximab. A Bliss mathematical model was used to discriminate between immunological (mAb) and radiological (^{177}Lu) cytotoxic effects contributing to final ARC therapeutic efficacy. We investigated the biological (cell death, apoptosis, non-targeted effects, cell cycle arrest, protein expression) and physical (dosimetry) parameters that could affect these two components. *In vivo*, in mice bearing subcutaneous Ramos or DOHH2 tumour xenografts, survival and tumour growth were determined and dosimetry was performed according to MIRD formalism.
We showed in both cell lines that unlabeled rituximab was more cytotoxic than unlabeled lilotomab. However, per Gy, we showed that in the most radiosensitive cell line, the two ARC showed the same cytotoxic efficacy while ^{177}Lu-rituximab was still more efficient than ^{177}Lu-lilotomab in the most radioresistant cell line. These observations were supported by *in vivo* therapeutic efficacy of ^{177}Lu-lilotomab and ^{177}Lu-rituximab. In DOHH2 tumour xenograft model, although rituximab was shown to be more efficient than lilotomab, tumour uptake of the two antibodies was similar and led to the same final tumour growth delay. We hypothesized that in this radiosensitive model, irradiation could counterbalance for the lower efficacy of the lilotomab against rituximab. In the Ramos tumour xenograft model similar therapeutic efficacy could be obtained only if the tumour absorbed dose of^{177}Lu-lilotomab was increased.
We have developed a radiobiological model to compare and predict the therapeutic efficacy of ^{177}Lu-lilotomab versus^{177}Lu-rituximab

Session 4A - Transcription-translation crosstalk in cancer

4A/1

mRNA capping in transcription and translation

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The mRNA cap is a structure added co-transcriptionally to mRNA which selects transcripts for the specific processing and ribosome recruitment required for translation. Formation of the mRNA cap is catalyzed by enzymes, some of which have roles in promoting transcription. Our interest in the mRNA cap initiated with the observation that c-Myc upregulates formation of this structure, which contributes to c-Myc-dependent protein synthesis and cell proliferation. c-Myc increases recruitment of several mRNA capping enzymes and upregulates methioinine metabolising enzymes to promote mRNA cap methylation. Inhibition of the capping enzymes selectively targets cells with deregulated c-Myc, suggesting these enzymes as therapeutic targets. I will discuss our research into regulation of mRNA cap formation, including the signaling pathways that regulate the mRNA capping enzymes, the function of theses enzymes in transcription and translation, and the cellular response to regulated mRNA capping.

4A/2

Epitranscriptome dynamic in colon tumorigenesis

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Recent studies have shown that gene expression can be regulated post-transcriptionally through dynamic and reversible mRNA modifications. The most abundant internal mRNA modification is made of N^6-methyladenosine (m^6A), presents on average in more than 3 sites per mRNA molecule. In mammalian mRNAs, m^6A residues are enriched in 5' untranslated regions (UTRs), in the coding region around stop codons and in 3' UTRs adjacent to stop codons. Suggested functions for m^6A modifications include effects on mRNA splicing, transport, stability and engagement by the translation machinery.**M^6A has been recently identified as a dynamic, reversible chemical modification of mRNA, which regulates crucial cellular pathways and processes such as obesity, immune tolerance and stem cell differentiation.** Another mRNA modification, N^1-methyladenosine (m^1A), that occurs on thousands of different gene transcripts have also been described in eukaryotic cells, from yeast to mammals. Unlike m^6A, m^1A decorates structured regions around canonical and alternative translation initiation sites. **This unique feature is dynamic and positively correlates with protein synthesis, suggesting a functional role for m^1A in promoting translation of methylated mRNA.** Despite significant advances in diagnosis and therapeutic treatment, colorectal cancer (CRC) remains a major cause of mortality and morbidity worldwide. Like any cancer, CRC is the result of complex interactions between genetic and epigenetic alterations. **Our group would like to address the contribution of mRNA methylation to CRC carcinogenesis and maintenance.** First, by means of a bottom-up approach, we are studying m^6A dynamic throughout cancer evolution and correlating its pattern with gene expression. Second, we are manipulating methylation enzymes to assess the effect of both m^1A and m^6A modifications on cancer cell fate.

4A/3

The role of non-coding transcription in regulation of rDNA chromatin state

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In Eukaryotes, ribosomal RNA (rRNA) is produced from ribosomal DNA (rDNA) by RNA polymerase I (RNAPI) in nuclear subdomains, the nucleoli. A growing number of studies showed that rDNA acts as a hub of cellular signals and sensor of genomic instability. The human rDNA clusters, comprising about 300 rRNA genes are located on five chromosomes in head-to-tail tandemly repeated arrays forming Nucleolar Organizer Regions. Yeast's genome contains a single rDNA cluster organized as a linear array of 150-200 repeats. Despite rRNA synthesis being limiting for cell growth, at any given time only a fraction of rDNA copies is transcribed by RNAPI (open), the rest is transcriptionally silent (closed). Even though numerous factors implicated in the regulation of rDNA silencing are known, the epigenetic mechanisms controlling the activity status of individual ribosomal genes, *i.e.* the dynamics of closing and the reasons of keeping them silenced, remain unknown.
We are studying the UPS - long non-coding RNAs, transcribed from rDNA promoter in yeast *S. cerevisiae*. These transcripts accumulate in stress conditions, after rapamycin treatment and in conditions when all rDNA copies are closed. These correlates with chromatin state changes. rDNA has recently become a direct target for anticancer therapy with discovery of several compounds *i.e.* CX-5461 or ellipticine, found to act specifically on rDNA, its transcription and as a trigger for nucleolar stress. These drugs selectively kill tumor cells *in vivo*. The mechanisms underlying this specificity are not understood. It has been shown that progression from pre-malignancy to malignancy in mouse lymphoma associates with activation of silenced rDNA copies through epigenetic modifications and in ovarian cancer cells, increase of active copy number underlies tumor cell sensitivity to CX-5461. We suggest that closed/open copies ratio, and epigenetic state of rDNA chromatin, is a key of anticancer drug action and involves lncRNA.

4A/4

HBZ-mediated shift of JunD from growth suppressor to tumor promoter by inhibition of ribosomal protein S25 expression

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Adult T-cell leukemia (ATL) is an aggressive and fatal malignancy of mature activated $CD4^+$ T lymphocytes associated with human T-cell leukemia virus type 1 (HTLV-1). About 4% of HTLV-1-infected individuals develop ATL, with disease onset occurring after a prolonged latency period of up to 30-50 years' post-infection. T-cell survival and proliferation in carriers are promoted by viral infection, which explains how HTLV-1-infected T cells are able to persist in the T-cell population for such a long period of time.

Viral protein HTLV-1 bZIP factor (HBZ) is a key player in proliferation and transformation of HTLV-1-infected cells, thus contributing to ATL development. HBZ deregulates gene expression within the host cell by interacting with several cellular partners. Through its C-terminal ZIP domain, HBZ is able to contact and activate JunD, a transcription factor of the AP-1 family. JunD is an intriguing member of the AP-1 transcription factor complex behaving differently from c-Jun and JunB. Interestingly, AP-1 complexes characterized in ATL cells contain JunD but not c-Jun and JunB, suggesting that JunD could be involved in the development of ATL, although mechanism mediating this effect remains unclear. Here, we confirm that there is a correlation between *hbz* expression and the increase of *junD* in ATL cells. We also demonstrate that during metabolic stress induced by serum depletion, HBZ maintains cell survival and proliferation by promoting the production of a 34kDa isoform of JunD called DeltaJunD. Furthermore, we showed that at the opposite of JunD, DeltajunD is inducing cell proliferation and cellular transformation. We demonstrated that HBZ induces the expression of DeltaJunD by retaining the mRNA of RPS25, a component of the 40s ribosome subunit into the nucleus. Collectively, these new findings indicate that HBZ acts as a molecular switch to regulate JunD growth properties through protein translation changes.

Session 4B - Translational Research in Colorectal Cancer Treatment

4B/1

The immune system, a double edge sword during colon cancer oncogenesis

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4B/2

BIOCOLON: Translational research assay in metastatic colon cancer: from clinic to basic research

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Heterogeneity and genetic complexity in colon rectal cancers create a considerable challenge for the development of therapy.
An integration of multidimensional analysis of various molecular components, that is, RNA, DNA, methylome, microRNAome and post-translational modifications of the proteome, is necessary for a comprehensive view of the tumor's biology and to drive markers predictive of response and eventual toxicity. The individual response to drugs depends not only on the mechanisms of the disease (pharmacodynamics) but in addition on the handling of the drug by the patient (pharmacokinetics).
In this aim Biocolon essay created a network infrastructure developed on existing relationships among the different institutions of Cancéropôle GSO. The Cancéropôle GSO represents large and diverse structures including patient's treatment, translational, and fundamental biological laboratories.
Patients with metastatic colon rectal disease were included in this assay to focus on pharmacogenetics, pharmacogenetics and genetic analyses in relation to clinical parameters. Patients received a first line chemotherapy by the protocol FOLFIRI, FOLFOX , XELIRI or XELOX , with or without Bevacizumab. Patients were treated in one of the five clinical centers. A written informed consent was signed for the procedures.
Before chemotherapy, tumour specimen were obtained from biopsy or surgical resection. These specimens were formalin fixed paraffin embedded and or frozen. Blood samples were taken for lymphocytes and serum studies. All samples were send to the different laboratories.
Oncology centers and networks ensured that they have standard procedures in place for bio specimen collection and use. Pathologists evaluated all biopsies for tumor content and macro dissection can be performed if necessary to meet criteria of> 50% neoplastic cells and 20% necrosis for genomic isolation. Clinical data with chemotherapy toxicities and tumor response using RECIST criteria every 4 courses, and follow up were registered prospectively.
From 2005 to 2010 ,200 patients were included, 193 analyzed (114 males and 79 females) median age was 69 years (34-90), 139 colon and 54 rectal cancers, all presented metastatic disease (150 primary and 43 secondary).Sixty percent of the patients presented at least 2 metastatic sites and 30% liver metastatic localizations. Primary tumor specimen was obtained in 47% of patients, metastatic specimen in only 0.02% and metastatic and primary specimens in 42%. A chemotherapy doublet combination of 5FU, IRINOTECAN was used in 69% of cases, doublet of 5FU OXALIPLATINE in 21% of cases and a triple combination of 5FU-OXALIPLATINE and IRINOTECAN in 10% of cases. Grade 3 and 4 chemotherapy toxicities were registered for each course.
Globally complete remission, partial remission, and stable disease were obtained in 3%, 45% and 38% respectively. Disease free survival and overall survival were 7 months and 22 months respectively without differences between protocol administrations.

4B/3

Effect of single nucleotide polymorphisms in the xenobiotic-sensing receptors NR1I2 and NR1I3 on the pharmacokinetics and toxicity of irinotecan in colorectal cancer patients.

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Background and Objectives: Nuclear receptors PXR (Pregnane X Receptor, NR1I2) and CAR (Constitutive Androstane Receptor, NR1I3) are key regulators of irinotecan metabolism and ligand-dependent modulation of their activity leads to significant drug-drug interactions. Since genetic polymorphisms can also affect the activity of these xenobiotic-sensing receptors, we hypothesized that they could contribute to the interpatient variability of irinotecan pharmacokinetics (PK) and to the toxicity of irinotecan based regimens. Patients and methods: In a cohort of 109 metastatic colorectal cancer patients treated by irinotecan (180mg/m²) in combination with other drugs, associations were assessed between 21 selected single nucleotide polymorphisms (SNPs) of NR1I2 or NR1I3 and PK parameters or toxicity of irinotecan and metabolites. Results: After adjustment of the tests by UGT1A1*28 genotype and correction for multiple testing, the A allele of NR1I2-rs10934498 was associated with a decreased exposition and an increased degradation of SN-38, the active metabolite (p=0.009 and p=0.017 respectively). The risk of hematological toxicity was associated with NR1I2-rs10934498 and NR1I2-rs2472677 (p=0.009 and p=0.003 respectively). Conclusion: Our results reveal for the first time the involvement of NR1I2 in the pharmacogenetics of irinotecan and suggest that it may help to predict the toxicity of irinotecan low dosing.

4B/4

Molecular subtypes of metastatic colorectal cancer are predictive of patient response to chemo and targeted therapies

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Classification of colorectal cancer (CRC) have been done for years using genetic instability (CIN, MSI) and DNA methylation (CIMP). Recently, through global gene expression profiles of primary tumors, independent groups have proposed new molecular classifications in CRC. The samples analyzed were mostly Stage II-III CRC and mainly prognostic correlations were assessed. However, implication for therapy of these new classifications is not yet really determined.
Our study aimed to assess, in stage IV patients, if these subtypes are differentially responsive to metastatic CRC (mCRC) therapies and are correlated with overall survival (OS) and Progression Free Survival (PFS). To this end, we collected and analyzed tumor samples from three cohorts representing 143 patients (REGP, a prospective monocenter study, COSIVAL a retrospective multicenter study and BIOCOLON a prospective multicenter study). Patients were treated with different regimens as first-line treatment: 79 patients received FOLFIRI regimen, 22 patients received FOLFIRI plus Bevacizumab, 32 patients received FOLFOX regimen. All the samples were analyzed using the gene expression platform previously used to identify CRC molecular subtypes. We demonstrated that: (1) the new molecular subtypes described in less advanced stages can be used to stratify mCRC patients, (2) Marisa's classification is correlated with response to FOLFIRI based-treatment, (3) a particular molecular subtype is associated with a longer OS and PFS when patients were treated with FOLFIRI and (4) a population of KRAS-WT do not respond to Cetuximab.
These results show that patients' treatment could be improved by analyzing the molecular profile of their tumors, and open the way to individualized therapies with better efficacy in mCRC.

4B/5

Immune microenvironment drives colorectal cancer fate

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A tumor mass is a multifaceted tissue comprising transformed cells surrounded by many cell types from the microenvironment. Although cells from the microenvironment are well-known to determine the tumor fate, we previously demonstrated that they may also contribute to a cross-talk existing between two distant tumors, such as the primary and the metastatic tumors. The immune cells, in particular, can have a dual role by participating either in tumor elimination or in tumor progression as well as by participating to the tumors cross-talk. In colorectal cancer (CRC), most studies have highlighted the crucial role of the anti-tumoral immune response in patient's outcome and described the key effector components from primary colon tumors. However, the immunosuppressive mechanisms in CRC primary tumors and metastases have been less studied. Our purpose is to characterize the immunosuppressive components involved in CRC. To that aim, we have developed a mouse model representative of human CRC, by implanting luciferase-expressing-tumor cells orthotopically in the mouse colon. We followed the CRC development by *in vivo* imaging and analyzed the immune infiltrate using flow cytometry. Remarkably, in the same group, mice exhibited different CRC progression profiles and potential dormant tumors derived at primary sites. Furthermore, we observed a massive infiltration of T regulatory cells, macrophages and myeloid suppressive cells in the mice that developed aggressive CRC. We are currently deciphering the immune cross-talk between a primary colon tumor and its liver metastases, using two-tumor orthotopic mouse models. Our work on immunosuppressive components involved in CRC and on cross-talk between tumors could have implications on the ability of therapies to target tumor.

4B/6

Virtual ligand screening identifies the proprotein convertase small molecule inhibitors as new potential colorectal liver metastases therapy

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Proprotein convertases (PCs) located along the constitutive secretory pathway namely Furin, PACE4, PC5 and PC7 are involved in the proteolytic cleavage and/or expression of various cancer-related mediators, making them promising targets in cancer therapy. Their substrates include adhesion receptors, extra cellular matrix-degrading proteinases, and growth-promoting factors and their receptors. Altered levels of PCs were reported to be associated with enhanced invasion and proliferation in various tumor cells and tissues. In a phase I trial (FANG vaccine trial), an autologous tumor-based product incorporating a plasmid encoding GM-CSF and a bifunctional short hairpin RNAi (bi-shRNAi) targeting Furin was found to be beneficial with 90% success rate in patients with advanced cancer. To date and among the PCs, only the X-ray structure of Furin has been reported. We therefore used Virtual ligand screening (VLS) and the ChemBridge database that contain over 600 000 unique molecules to search for compounds able to inhibit this convertase, we selected 1000 molecules that we assessed for their inhibitory effect on Furin using various cellular assays. Of these, 5 molecules were found to inhibit significantly the catalytic activity of Furin, and the malignant phenotype of various tumor cells. Our findings identify new anti-cancer strategy and suggest the potential use of the identified small molecule inhibitors and/or their derivatives as a new class of potent anti-cancer therapeutics.

Session 4C - Les réseaux de cancérologie

4C/1

Le fonctionnement d'un réseau dans son contexte. L'exemple d'Oncolor

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Réseau Oncolor

Les réseaux régionaux de cancérologie sont des organisations relativement récentes dans le paysage sanitaire nés, pour les plus anciens, à l'initiative de professionnels de santé et, pour les plus récents, à la suite des plans cancer. Leurs missions ont été définies en 2007 les situant comme une interface de coordination entre établissements et professionnels. Ces réseaux visent à améliorer l'égalité et la qualité des soins, à mettre en place des outils de partage et de communication et des méthodes d'évaluation. Ils contribuent à l'information des usagers et à la formation des professionnels. Les 3 plans cancer successifs ont permis de conforter leur rôle en insistant aujourd'hui sur leur mission d'appui et d'expertise auprès des Agences régionales de santé. Toutefois, leur évaluation a montré une grande hétérogénéité entre eux. Pour expliquer ces différences, certains éléments managériaux propres au réseau sont déterminants de leur efficacité : adhésion des acteurs, gouvernance, soutien des Tutelles, dimensionnement et professionnalisation des équipes réseau, services rendus effectifs, appropriation des outils et des méthodes du réseau par les professionnels… L'expérience du réseau de cancérologie de Lorraine Oncolor sera présentée à travers 3 projets : référentiels de pratique clinique, formation des professionnels de santé et interface ville-hôpital. Nous préciserons l'organisation d'Oncolor ainsi que les leviers et les difficultés rencontrées depuis sa création en 1998. Nous discuterons des valeurs qui sont en œuvre dans le fonctionnement de ces réseaux : coopération, leadership, émulation, enjeux de pouvoirs, innovations, expression des besoins… Aujourd'hui, la réforme territoriale des régions va nécessiter une réorganisation en profondeur de certains réseaux dans un environnement complexe. Ces réseaux pourront-ils rester ou devenir un lieu d'intelligence collective au service des malades, des professionnels de santé et des Tutelles ?

Session 4D - Magnetic Resonance Imaging for diagnosis and therapy of cancer

4D/1

MRI and Nanoparticles : A Tandem Business

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Iron oxide nanoparticles (IONP) were proposed more 20 years ago as an MRI contrast agent based on their superparamagnetism combined with their cell internalization properties, in vivo by macrophages after parenteral injection, or in vitro by many types of cells. The detection with MRI of small tumour sites are based on the focal decreasing of normal dark signal due to the replacing of normal macrophages within the liver by tumour cells. The clinical using of IONP to detect tumour lymph nodes was finally dropped. Despite many favorable pre-clinical studies and some clinical trials performed specially to evaluate dendritic cell vaccination, the using MRI after ex vivo labelling of therapeutic cells with IONP does not clinical practice. This approach proved, however, unsatisfactory, due to its lack of sensitivity, specificity and the absence of proportionality between the signal detected and the number of cells. The fact that pre-clinical studies are performed obtained at 7T or over magnetic fields, which magnify the local magnetic inhomogeneity and consequently the T2* effect, and the signing of the labelled cells with IONP. Effectively, pre-clinical MRI assays are performed on in vitro samples and in vivo in small animal, essentially in murine using dedicated small animal MR systems. In order to enhance the signal despite the low proton content in examined samples, these systems are equipped with high magnetic field (4 to 11 T), with a resulting T1 effect decreasing and in contrast, a magnitude of T2* effect related to a local enhancing of the magnetic field due to the presence of superparamagnetic nanoparticles. The experts' efforts led to the development of other agents for cellular labelling, namely fluorine agents, which required specific sequences and tools for MRI detection or Gd nanoparticles. The using of IONP as therapeutic probe via magnetic hyperthermia, still clinical combined with external radiotherapy to treat glioma after stereotaxic injection of IONP, becoming a THERANOSTIC probe, the MRI allowing to follow the infusion of IONP. Some other clinical trials were starting applying in other type of tumours. Many physico-chemistry teams work to develop IONP with high magnetic properties, which could be introduced by parenteral way and specifically targeted to tumour site. In order to improve the design of the NP especially their coating, the grafting of one IR-fluorophore allows to assess kinetic and pharmaceutic properties of these THERANOSTIC targeting IONP, and it will be possible to assess the possibility to assess the homing with MRI, without forgetting the overestimation of the provided signal at high magnetic field of small animal dedicated MRI system.

Many teams and works are developed with the aiming to enhance the efficacy in terms of MR contrast, safety effect, and/or blood permanence in comparison to the commercial MRI contrast agents. At contrary, the pre-clinical studies under estimate the effect of magnetic nanoparticles especially based on gadolinium in comparison to clinical studies (performed generally at 1.5 to 4T for not brain studies), allowing to really predict the clinical contrast effect, which could be equivalent or more advantageously results in human. In order to specify the biokinetic and pharmacokinetic parameters, MRI imaging studies should be combined with quantitative studies by quantification of Gd content in each main organ, blood samples and excretion products, allowing to deduce stability of the complexes, the biokinetic and pharmacokinetic properties, and verify the compatibility with contrast agent regulatory requiring and safety. In vitro and in vivo MRI allows to screen the best design of new contrast MRI probes, which could have therapeutic properties as radiosensitization, or hybrid imaging contrast agent as MRI-PET probes, allowing to enhance accuracy of tumour diagnosis and staging.

4D/2

Coordination polymers nanoparticles as contrast agents for MRI and SPECT

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Cyano-bridged coordination polymers at the nanoscale combine the advantages of molecular-based materials and nano-chemistry. We present the synthesis of very small sized (<3 nm) coordination polymers nanoparticles of water-soluble of two types: $Fe_4[Fe(CN)_6]_3$ known as Prussian blue and $Gd[Fe(CN)_6]$, their stabilization with water soluble and biocompatible molecules, study of their toxicity and their use in SPECT and MRI.[1]

First, nanoparticles $Na_{0.41}Fe[Fe(CN)_6]_{0.85}$@(β-GluTEG-$NH_2$)$_{0.60}$with β-GluTEG-$NH_2$ = 1-*O*-{2-[2-((2-Amino)ethoxy)ethoxy]ethyl}-β-D-glucopyranose and $Na_{0.45}Fe[Fe(CN)_6]_{0.86}$@(PEG-$NH_2$)$_{0.22}$and PEG-$NH_2$ = Poly(ethylene glycol) bis(3-aminopropyl) incorporating $^{201}Tl^+$ within the tetrahedral sites of the structure used as nanoprobes in SPECT-CT have a transitional passage through the lung compartments and in the liver and are also eliminated by glomerular filtration.[2]

Furthermore, the nanoparticles of $Gd[Fe(CN)_6]$@D-mannitol have a high relaxivity of 11.4 $mM^{-1}s^{-1}$ and low r_2/r_1ratio and can be considered as positive contrast agents.[3] The performed MRI studies show that these nanoparticles significantly increase the MRI signal with an extended period of intravascular circulation and are eliminated as in the previous case by natural means.[4]

These two studies demonstrate the potential of coordination polymer nanoparticles as nanoprobe in particular for imaging because of the versatility of the chemical compositions, their accessible porosity as well as their ease of synthesis and surface functionalization.

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4D/3

Design of a nanostructured MRI contrast agent

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Magnetic nanoparticles (NPs) offer contrast enhancement for magnetic resonance imaging (MRI), which depends on their composition, size, surface properties, magnetization and aggregation state in the biological environment. These key parameters influence the longitudinal and transverse relaxivities, Ri (relaxation rate per unit concentration in mM) according to the Koening-Keller model.[1] A way to improve relaxometric efficiency is to increase the magnetization per volume unit of the nanomaterial. Here we report our investigation of non-oxidized iron NPs as MRI contrast agents. The synthesis and surface coating of iron NPs is described as well as the stability of the colloidal aqueous solutions obtained, which is supported by Dynamic Light Scatterring studies. The measurement of their relaxivities clearly evidences their increased efficiency for MRI in comparison to iron oxide ones.[2] Preliminary evaluation of their cytotoxicity will also be reported.

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4D/4

Entropic Boltzmann Closure for Radiotherapy

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The majority of patients affected by cancer are nowadays treated by radiotherapy. The main goal of this technique is to target and destroy tumoral cells without damaging the surrounding tissue. On the last decades, a major effort was made to improve technologies involved in the development of this treatment.
Our work consists on the development and validation of a new model designed to simulate the energy deposition of the particles used in radiotherapy, within human tissues. This model is based on a kinetic entropic closure of the linearized Boltzmann equation [1]. This equation takes a lot of computation time to be resolved. To simplify this, we replace fluencies by angular moments, which allows us to get rid of the angular variables and improve the calculation time. We obtain a set of angular moments equations, and we close this set using the Boltzmann's principle of entropy maximization.
We show that this model has an accuracy comparable to references Monte-Carlo codes, and is less time-consuming than these ones. Moreover, we show that this method is applicable to MRI-guided radiotherapy which consists in irradiating a patient under the influence of a magnetic field. Thereby, we are able to highlight some effects that occur on the propagation of particles in the matter, which modify the dose distribution on the interface between materials of different densities. This has to be taken into account in order to prevent creation of hot spots or spread of energy distribution in a human body. Therefore, our model could be applied to future clinical cases and would allow a faster and more efficient way to plan a viable treatment for a patient.

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Session 5A - Translational control in cancer

5A/1

Translational control of coloretal cancer

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5A/2

Mechanisms of translational control by RNA structures and RNA binding proteins in cancer

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Genomic stability is ensured by a network of pathways that constitute the DNA damage response (DDR) and is mainly impaired in cancer to induce tumour development, progression and resistance to treatment. Recently, accumulated evidences have shown that DDR is very tightly related to post-transcriptional events and that these mechanisms act in alliance to maintain cellular genomic integrity. Among the post-transcriptional processes, mRNA translation emerges as a key actor of this interplay. Indeed, RNA binding proteins (RBPs) that regulate mRNA translation impacts genomic instability by ensuring the control of the expression of proteins involved in the DDR. At the same time, DNA repair proteins (DRPs) have been shown to act as translational regulators to sustain the DDR. Our data provide insight into the molecular actors involved in this link and highlight RNA structures, including hairpin or G-quadruplexes, as mediators of translational control induced by RBPs or DRPs that impact tumour development, progression and resistance to treatment in cancer.

5A/3

Active mRNA translation into invadosomes revealed by combination of laser capture and proteomic analysis.

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Invadosomes include podosomes and invadopodia, which are, respectively, present in normal and cancer cells. Invadosomes are dynamic and plastic F-actin-based structures involved in cell adhesion and, in the same time, in the proteolytic degradation of the extracellular matrix. Up today, several studies attempt to identify the molecular composition of invadosomes by using classical protocols combining, for example, differential cell lysis or subcellular fractionation and mass spectrometry analysis. Here, to identify specifically the proteins associated with invadosomes, design a new purification procedure to minimize contamination of other actin structures, while maintaining the invadosome integrity. In this objective, we decided to use laser microdissection to purify invadosome. We used NIH3T3-src cells, which form invadosome rosettes. Using computer-based automation designed to recognize F-actin structures on fixed cells, invadosome rosettes were collected by laser microdissection. After crosslinking reversion, the collected sample was analyzed by mass spectrometry. Interestingly, our results show that this new approach is sensitive and reproducible (e.g. 80% of overlap between experiments) despite the low amount of material. We identified more than 500 proteins identifying new markers involved in various cellular functions including cytoskeleton organization, calcium regulation and mRNA translation. Moreover, functional validation reveals that invadosomes correspond to active sites for protein translation.

5A/4

Loss of 4E-BP1-mediated translational control favors aberrant replication in pancreatic cancer.

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We recently showed that human PDAC (pancreatic ductal adenocarcinoma) and Kras-driven PDAC mouse models harbor a progressive loss of expression of the translational repressor 4E-BP1 from low grade to advanced lesions, suggesting a dysregulation of mRNA translation during PDAC development.
To identify the subset of mRNAs whose translation is sensitive to 4E-BP1 loss, we defined the 4E-BP1-dependent translatome (genome-wide pools of translated mRNA) of pancreatic cancer cells. The most regulated genes were involved in DNA replication, including *RRM2* and *CDC7*. Consistently, mTOR inhibition specifically decreased S-phase entry of pancreatic cancer cells *in vitro* while ablation of 4E-BP1 rendered these cells insensitive to treatment and allowed efficient replication.
The sensitivity of 4E-BP1 KO animals to pancreatic cancer initiation was analyzed using cerulein stimulation, which causes pancreatitis and metaplasia onset. Upon injury, 4E-BP1 deleted mice exhibited more pre-cancerous lesions than their WT counterpart. However, pancreatic tissue regeneration was much faster in 4E-BP1 KO mice, attested by an increased proliferation rate (Ki67), but also a higher replicative stress (γH2AX), corroborating our*in vitro* analysis.
Other studies suggest that sustained replication is a mechanism of chemoresistance in PDAC. Our data provide evidence that 4E-BP1 loss leads to this phenotype, suggesting a link between translation dysregulation and resistance to gemcitabine in PDAC. They also highlight the therapeutic potential of combining actual treatment with eIF4F inhibitors.

5A/5

Primary transcripts of microRNAs encode regulatory peptides

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MicroRNAs (miRNAs) are small regulatory RNA molecules that inhibit expression of specific target genes by binding to and cleaving their messenger RNAs or otherwise inhibiting their translation into proteins. miRNAs are transcribed as much larger primary transcripts (pri-miRNAs), the function of which is not fully understood. We have shown that plant pri-miRNAs contain short ORFs that encode miPEPs, which are regulatory peptides. These peptides enhance the accumulation of their corresponding mature miRNAs, resulting in downregulation of their target genes. The mechanism of miPEP action involves increasing transcription of the pri-miRNA. Synthetic peptides applied to plants specifically trigger the accumulation of their corresponding miRNA, leading to developmental phenotypes, suggesting these peptides might find agronomical applications. Moreover, preliminary results revealed that miPEPs might be active in animals, opening a new field of investigation in medicine.

Session 5B - Molecular oncology and personalized medecine

5B/1

Molecular oncology and personalized medicine : the exemple of colorectal cancer

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5B/2

The RAS-related GTPase RHOB confers resistance to EGFR-tyrosine kinase inhibitors in NSCLC via an AKT-dependent mechanism

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Although lung cancer patients harboring EGFR mutations benefit from treatment with EGFR-tyrosine kinase inhibitors (EGFR-TKI), most of them rapidly relapse. The RHOB GTPase is a critical player in both lung carcinogenesis and the EGFR signaling pathway, therefore we hypothesized that it could play a role in the response to EGFR-TKI. In a series of samples from EGFR-mutated patients, we found that low RHOB expression correlated with a good response to EGFR-TKI treatment while a bad response correlated with high RHOB expression (15.5 vs 5.6 months of progression-free survival). Moreover, a better response to EGFR-TKI was associated with low RHOB levels in a panel of lung tumor cell lines and in a lung-specific tetracycline-inducible EGFRL858R transgenic mouse model. High RHOB expression was also found to prevent erlotinib-induced AKT inhibition in vitro and in vivo. Furthermore, a combination of a new generation AKT-inhibitor with erlotinib induced tumor cell death in vitro and tumor regression in vivo in RHOB-positive cells. Our results support a role for RHOB/AKT signaling in the resistance to EGFR-TKI and propose RHOB as a potential predictor of patient response to EGFR-TKI treatment.

5B/3

Clinical utility of longitudinal plasma analysis in examining clonal evolution and tracking secondary acquired resistance in mCRC patients refractory to targeted therapy

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RAS testing is required by health authorities before initiation of anti-EGFR targeted therapies in mCRC patients. However, even in the selected RAS wt population, responses to EGFR agents are limited in duration. Emergence of RAS/BRAF point mutations during anti-EGFR regimen leads to acquired therapeutic resistance. Characterization of molecular changes in the course of treatment could enable the early adoption of alternate therapies before RECIST progression. Nevertheless, tumor biopsy does not allow serial therapeutic and exhibit limitations especially in regards intra and inter-tumoral heterogeneity of the tumor, patient compliance and potential toxicity. We performed a blinded retrospective exploratory study to evaluate performance of circulating DNA analysis for tracking specific oncogene mutations over time during anti-EGFR therapies. KRAS, NRAS and BRAF mutations we tested in 81 serial plasma samples from 46 mCRC patients refractory to chemotherapy combined with Dasatinib regimen with or without Cetuximab. Data show that 98% of the plasma were found mutant before or during treatment. Also, 50% of KRAS mutant samples were missed by tumor tissue analysis before treatment of the patients scored wt by tumor tissue analysis. Longitudinal plasma analysis showed that 80% of initially wt patients acquired at least one RAS/BRAF mutation during treatment and that 27% of initially mutant patients and 38% of all studied patients acquired at least one newly KRAS, NRAS or BRAF point mutation during treatment. Patients may harbor mutations at very low frequency down to 0.01% before initiation or during treatment revealing the need of a high sensitive technique to detect mutant subclones. Qualitative and quantitative circulating DNA analysis empowers tracking of acquired resistance by examining the real-time clonal evolution of the tumor and might help physicians to adjust patient treatment before RECIST progression.

5B/4

Patient Stratification and Precision Medicine in Pancreatic cancer: a gene blood-signature for gemcitabine treatment

David PIQUEMAL, Fabien PIERRAT, Laurent MANCHON, Roman BRUNO, Marine MORENT, Florian NOGUIER, Bernadette TRENTIN

ACOBIOM

Incidence of metastatic pancreatic cancer (MPC) has markedly increased over the past several decades. Patients diagnosed with pancreatic cancer typically have a poor prognosis partly because the cancer usually causes no symptoms early on, leading to metastatic disease at the time of diagnosis. Median survival from diagnosis is around 3 to 6 months; 5-year survival is much less than 6% and complete remission is still extremely rare.
MPC has been treated for over a decade using a single-agent gemcitabine which has been the standard first-line treatment. Other treatments, like erlotinib and nab-paclitaxel, received approvals based on very modest survival benefits and more recently, Folfirinox treatment shown a median OS of 11.1 months. MPC continues to be a disease with high unmet medical need, requiring either new active agents or a stratification of patients associated with specific companion diagnostics.
From clinical trials and based on a high throughput analysis of NGS data using the proprietary Acobiom genomics platform, Acobiom identified a 11 gene blood-signatures to develop the GemciTest™, a new In Vitro Diagnostic Multivariate Index Assay (IVDMIA) associated with gemcitabine in pancreatic cancer treatment. GemciTest is a quantitative real-time PCR assay and is intended to quantitatively aid in the determination of high probability Progression-Free Survival and Over Survival rates of patients diagnosed with pancreatic cancer and treated with gemcitabine as first-line therapy. As a result, GemciTest™ in combination with gemcitabine treatment targets the good responder patient and improves the overall survival rate by twice for pancreatic cancer patients with a positive testing score (~30% of this population). The establishment of new partnerships will validate the blood-signature in second-line gemcitabine treatment in MPC, but also in other solid tumor such as ovarian or bladder tumors.

5B/5

The mammary ducts create a favourable microenvironment for xenografting of luminal and molecular apocrine breast tumours

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There is a paucity of models for hormone receptor positive (HR+) breast cancer because of the difficulty of establishing xenografts from these tumours. We show that this barrier can be overcome by injecting human tumour cells directly into the mammary ducts of immunodeficient mice. Tumours from 31 patients were infected overnight with a lentiviral vector expressing tdTomato and injected through the nipple into the mammary ducts of NOD-SCID-IL2RG-/- mice. Tumours formed in the mice in 77% of cases after the first injection (6/8 luminal A; 15/20 luminal B and 3/3 molecular apocrine). Four luminal A and one molecular apocrine graft were tested in secondary and tertiary grafts: all were successfully passaged in secondary and 4/5 in tertiary grafts. None of the samples engrafted when injected subcutaneously. The morphology, oestrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR) and Ki-67 profiles of the clinical samples were maintained in the tertiary grafts. We also show that the intraductal approach can be used to test the response to targeted therapy with fulvestrant and palbociclib, using a genetically defined ER+ model. We conclude that the mammary ducts create a microenvironment that is uniquely favourable to the survival and growth of tumours derived from mammary hormone-sensing cells. This approach opens the door to testing genomically-targeted treatment of HR+ tumours in precision medicine programs.

Session 5C - Sciences Humaines et Sociales, épidémiologie et santé publique

5C/1

Plateforme de recherche en prévention primaire des cancers : Mutualiser les compétences pour optimiser la recherche en prévention

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Selon Hawe et Potvin (2009), « la recherche interventionnelle implique l'utilisation de méthodes scientifiques afin de produire des connaissances sur les interventions, sous forme de politiques et de programmes, existant dans le secteur de la santé ou à l'extérieur de celui-ci et qui pourraient avoir une incidence sur la santé des populations ». Elle se base sur le principe qu'un comportement est la conséquence de variables sur lesquelles il est potentiellement possible d'agir. Il peut s'agir de facteurs sociaux, émotionnels ou de croyances en matière de santé. Ainsi, plus d'un quart des décès par cancer pourraient être évités grâce à des changements de comportements individuels ou sociétaux.
Un grand nombre d'actions préventives sont mises en œuvre chaque année par des acteurs différents. Si les interventions sont nombreuses quoique souvent parcellaires, la recherche en prévention est encore peu développée en France. Partant de ce constat, trois centres de ressources en prévention des cancers (Epidaure, le pôle prévention de l'Institut régional du Cancer de Montpellier (ICM) ; le Centre Hygée, plateforme de prévention du Cancéropôle Lyon Auvergne Rhône-Alpes ; et le centre Antéia de la Fondation JDB-Prévention Cancer dans l'Essonne), ont décidé de créer une plateforme de recherche en prévention primaire des cancers.
L'objectif principal de cette plateforme est de mutualiser les compétences des 3 centres Epidaure, Hygée et Antéïa pour développer des interventions de recherche en prévention primaire des cancers avec des acteurs de terrain en apportant expertise et aide logistique pour développer des actions de recherche et entrainer ainsi une vraie synergie des ressources.

Contact : Plateforme.RecherchePrevention@icm.unicancer.fr

5C/2

La Plateforme AAPRISS - Apprendre et Agir Pour Réduire les Inégalités Sociales de Santé - Méthodes et objectifs

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Les mécanismes de construction des Inégalités Sociales de Santé (ISS) mobilisent les Déterminants Sociaux de la Santé (DSS) qui s'accumulent tout au long de la vie. Pour les praticiens, les décideurs et les chercheurs, réduire les ISS nécessite d'apprendre et de travailler ensemble.
Faisant suite au programme de recherche AAPRISS, la Plateforme expérimente un modèle pour favoriser les partenariats avec les collectivités territoriales et des institutions de santé qui a pour but d'apporter les connaissances de la recherche aux programmes de santé ou impactant la santé.
La Plateforme met à disposition des acteurs en charge des politiques publiques et des équipes de recherche l'expertise nécessaire à la prise en compte de la santé et à l'étude des ISS dans les interventions.
La Plateforme travaille soit en partenariat (recherche commune de financements avec les partenaires), soit en mettant à disposition ses compétences et par une offre des formations. Son socle scientifique repose sur l'IFERISS (18 équipes de 12 laboratoires de disciplines diverses).
La démarche de la Plateforme s'appuie sur des méthodes de travail interdisciplinaires expérimentées au sein de l'IFERISS et intersectorielles expérimentées dans le programme AAPRISS.
La Plateforme a co-construit par exemple avec l'agence d'urbanisme et d'aménagement Toulouse aire métropolitaine et Toulouse Métropole une grille d'évaluation introduisant une préoccupation pour la santé dans les choix d'urbanisme.
Différents partenariats, avec la CPAM 31, l'ARS LRMP, le Ministère de la Justice, ou encore le Pôle régional de compétences, la Plateforme EPIDAURE sont en cours.
La Plateforme bénéficie du soutien de la LNCC et du Cancéropôle Grand Sud-ouest
Les connaissances issues de la recherche deviennent des outils d'aide à la décision pour tous les acteurs en charge des politiques publiques. La plateforme contribue ainsi au rapprochement de la recherche et de la décision.

5C/3

E-santé Tabac

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Problématique :
La communication sur le changement social est un élément essentiel des efforts de prévention portés historiquement sur le contenu des messages transmis, sur la façon de se comporter, ou sur le mode de transmission (Courbet, 2014). Ainsi en tenant compte du contexte communicationnel actuel et de la «génération digital native », comment un serious game qui est un jeu combinant une intention sérieuse (pédagogique, communicationnelle…) avec des ressorts ludiques sur le tabac, pourrait-il représenter une stratégie de communication utile à la prévention des cancers ?

Méthodologie :
A partir de l'analyse du discours lors de focus groupe réalisés auprès de 57 jeunes, un prototype de « serious game » a été développé en collaboration avec une société spécialiste en e-santé, le groupe Genious.
Des jeunes scolarisés de la 6ème à la terminale en Languedoc-Roussillon l'ont testé durant l'année scolaire 2015-2016. 6 focus groupes ont été réalisés auprès de 55 élèves (30 filles, 25 garçons), afin d'évaluer la pertinence du jeu et la compréhension du message préventif.
Un questionnaire a été proposé auprès de 183 élèves (93 filles et 90 garçons, moy = 14,12 ans ; écart-type de 2,19) et a permis de recueillir leurs avis sur les dimensions ludique, pédagogique et ergonomique du jeu.

Résultats :
Le test du chi2 croisant le statut tabagique et l'apport de connaissances sur le tabac grâce au jeu, montre que l'apport de connaissances sur le tabac est moins affirmé pour les fumeurs quotidiens ($p=0.039$). En effet, 24 % des fumeurs quotidiens ont acquis des connaissances, versus 59 % pour les fumeurs occasionnel, 40% pour ceux qui ont essayé mais ne sont jamais devenus fumeurs, et enfin 61% pour ceux qui n'ont jamais fumé.

Conclusion :
Il apparaît ainsi que ce prototype de serious game pourrait être développé vers un outil de communication destiné à une population de jeunes non initiée au tabac comme outil de prévention précoce du tabagisme.

5C/4

Evolution des prescriptions de médicaments orphelins en cancérologie: en France et à l'échelle d'un établissement hospitalier

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Les « médicaments orphelins» (OD, Orphan Drug) est le terme consacré aux médicaments destinés aux maladies rares. Ce statut apporte pour les firmes, des incitations financières : exclusivité de marché, remboursement des essais cliniques. Avec l'attribution par la FDA et l'EMA, du statut OD à plus de 500 molécules en développement, cette législation a contribué à l'élaboration de nombreux produits innovants. Du fait de leur prévalence, les cancers rares bénéficient de la législation OD. Aujourd'hui, 50% des anticancéreux mis sur le marché sont des OD, et 7 des 10 médicaments les plus vendus aux USA en 2011 étaient des OD, véritables blockbusters, rapportant pour certains plus de 1Md$ de chiffre d'affaires annuel. La disponibilité de ces médicaments avec leur coût très élevé soulève un débat autour de la soutenabilité de nos systèmes sociaux dans un contexte macroéconomique défavorable.
Dans le cadre d'un projet en émergence du Cancéropôle GSO, nous avons documenté cette situation à plusieurs niveaux :
- nous avons fait un état des lieux des OD anticancéreux mis sur le marché ou en développement.
- nous avons mesuré l'évolution des dépenses des OD prescrits en France,
- enfin, nous avons évalué sur 2 sites hospitaliers pilotes la prescription de ces OD.
Nous avons pu montrer une explosion des demandes de statuts OD avec un 1/4 des demandes en oncologie, concentrées sur un faible nombre de cancers rares, demandes faites par les start-up, mais exploitées par les big pharma, avec une régulation peu sélective par les agences (FDA, EMA), pour des coût de traitement beaucoup plus élevé, avec une forte croissance annuelle, responsable de 2/3 des remboursement d'anticancéreux, pour des molécules au SMR très moyen, impactant le budget des établissements hospitaliers.
Nous proposons de réfléchir, en nous appuyant sur une modélisation microéconomique, à l'impact de la législation des OD, à la stratégie des firmes, et au mode de fixation des prix des médicaments.

5C/5

Tell me how you eat, I will tell you how you are! Assessing the dietary intake in 1762 cancer patients with an ingesta-Verbal/Visual Analogue Scale

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***Purpose*:** Assessing the nutritional intake of cancer patients is a major challenge for the clinicians because weight loss contributes to cachexia, which is very common and leads to poor prognosis. The aim of this novel study was to validate a Visual/Verbal Analogue Scale of food *ingesta* (*ingesta*-VVAS) as a relevant and quick measure of clinical food intake in cancer patients.

***Methods*:** Between January 2009 and December 2011, five experimented dieticians gathered the data, performed the clinical exam and the *ingesta*-VVAS in 1762 oncology patients in the Cancer Institute of Montpellier (ICM) in France. The external validity of the *ingesta*-VVAS was mainly determinate using daily energy intake, based on a 1-day recall. Patients had to answer to "How much do you currently eat on a scale from 0 "*nothing at all*" to 10 "*as usual*". We focused on patients ingested less than 28 Kcal/Kg/day to determine the *ingesta*-VVAS accuracy for assessing the energy intake as a function of the median.

Results: The feasibility of the *ingesta*-VVAS was 97.7%. The scores were significantly correlated ($p<.05$) with energy intake, both in Kcal/day ($\rho = .72$) and in Kcal/Kg/day ($\rho = .67$), especially in undernourished patients ($\rho = .74$). Psychometric proprieties for ingesting less than 28 Kcal/Kg/day with a *ingesta*-VVAS score ≤ 6 were: specificity of 81.7%, positive predictive value of 92.2%, sensitivity of 62.9%, and negative predictive value 46%. The calculated Youden's index was J = 0.45 and the Yule's coefficient Q = 0.77.

Conclusions: A valid *ingesta*-VVAS may generate great interests in clinical practice both for professional - who could adjust their nutrition intervention and reduce cachexia - and cancer patients - who would be more involved in their own dietary management.

5C/6

Posttraumatic stress disorder after lymphoma diagnosis: a prospective study

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Background:
For a number of years investigators have reported trauma-related symptoms such as intrusive memories, avoidant behaviors, and heightened arousal in survivors of cancer. More than one-third of long-term non-Hodgkin's lymphoma (NHL) survivors experienced posttraumatic stress disorder (PTSD) symptoms. Nevertheless, only a few prospective researches showed the development context of PTSD symptoms. The aim of our study was to assess the relation between emotional and cognitive impact of the news of a lymphoma diagnosis and the development of subsequent PTSD symptoms.

Methods:
About 15 days after receiving the lymphoma diagnosis subjects were asked to complete the emotional distress (fear, helplessness, etc) and cognitive dissociation (stunning, disorientation, etc.) peritraumatic questionnaires (at the time of the news or immediately after); 5 weeks after receiving the diagnosis participants completed measures of PTSD (PTSD CheckList-Specific), depression (BDI) and anxiety (HAD) symptoms, and the quality of life questionnaire (SF-36) and coping strategy (WCC).

Results:
Of the 92 participants (55% men, mean aged 46 years), 68.6% had a NHL and 31.4% had a HL. Among them 49% reported a significant emotional distress and 16% a significant cognitive dissociation during or immediately after receiving the lymphoma diagnosis. Five weeks after 43% reported a partial PTSD diagnosis. In a logistic regression model to predict partial PTSD, significant peritraumatic emotional distress and a low level of "mental health" for the quality of life felt were the best predictors.

Conclusion:
This study objectively demonstrates the importance of the emotional impact of the news of a lymphoma diagnosis for the development of cancer-related PTSD symptoms.

5C/7

Quels sont les freins et les facilitateurs à la participation au dépistage organisé du cancer colorectal ? Une étude qualitative par focus groups.

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Détecté à temps, le cancer colorectal se guérit dans 9 cas sur 10. Pourtant, il reste la 2ème cause de mortalité par cancer en France (HAS, 2013). Dans ce contexte, la participation au dépistage organisé doit être améliorée. Suite au récent changement de test de dépistage (passage du test Hémoccult II au nouveau test immunologique) il semble important de s'intéresser au changement de pratiques des usagers. Ainsi, cette étude vise à identifier les représentations sociales (Jodelet, 1984) de la population cible envers le dépistage du cancer colorectal et envers le nouveau test immunologique.

Six focus groups ont été menés avec des personnes issues de la population générale, dans la tranche d'âge concernée par le dépistage organisé (29 participants, 13 hommes et 16 femmes). Les supports utilisés portaient sur les connaissances sur ce cancer, le risque perçu, la participation au dépistage et l'arrivée du nouveau test, le rapport au médecin généraliste et les messages de sensibilisation.

Une analyse de contenu thématique a ensuite été réalisée (Bardin, 1993). Les principaux freins à la participation au dépistage sont : l'absence de symptômes, la procrastination et le manque de temps (nécessité de prendre rendez-vous chez le médecin généraliste), mais également le fait que ce cancer concerne une partie du corps considérée comme sale, liée à un sujet tabou. A l'inverse, les principaux facilitateurs sont : la simplicité pratique du nouveau test, les encouragements de l'entourage (médecin et proches), ainsi que le fait de recevoir un coup de pouce (« nudge »), comme l'invitation à se faire dépister envoyée tous les deux ans. Durant les focus groups, les échanges ont été enrichis par les expériences de cancer relatées, vécues par les participants eux-mêmes ou par leurs proches, et participant au processus de formation des représentations sociales.

Cette étude a permis d'avoir une meilleure compréhension de l'adhérence au dépistage.

5C/8

Présentation du protocole de l'essai randomisé contrôlé international évaluant l'impact sur la survie d'un programme d'activités physiques adaptées chez des patients atteints d'un cancer du côlon de stade II ou III : Etude CHALLENGE.

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Introduction : L'étude interventionnelle internationale CHALLENGE dirigée par Kerry Courneya (Canada) évalue l'efficacité d'un programme supervisé d'activités physiques adaptées sur la survie sans maladie chez des patients atteints d'un cancer du côlon de stade II ou III.

Objectif : L'objectif de ce poster est de présenter le protocole de l'étude internationale CHALLENGE conçu par Kerry Courneya (Edmonton, Canada).

Méthodes : Les patients sont répartis aléatoirement, soit dans le groupe expérimental qui bénéficie d'un programme combinant activité physique et soutien comportemental pendant 3 ans, soit dans le groupe contrôle qui ne bénéficie pas de ce programme. Le critère de jugement principal est la survie sans maladie

Résultats attendus : Le taux de survie sans maladie devrait être plus élevé dans le groupe expérimental que dans le groupe contrôle sur les 10 années de suivi.

Discussion : 962 patients seront inclus dans l'étude afin d'obtenir une grande précision sur l'estimation de l'effet de l'activité physique sur la survie. Au 31 décembre 2013, 250 patients ont été randomisés dans 20 centres canadiens et dans 26 centres australiens. Le Comité de Protection des Personnes (CPP) de l'ICM de Montpellier a validé la pertinence du projet au niveau scientifique et médical et la valeur éthique vis-à-vis des personnes qui vont participer à cet essai. L'objectif pour l'ICM de Montpellier est d'inclure 30 patients.

Conclusion : Il s'agit de la première étude clinique désignée pour véritablement répondre à l'effet de l'activité physique sur la survie. Cela pourrait signifier que l'activité physique n'a pas qu'un effet strictement adjuvant (qualité de vie), d'atténuation des effets secondaires des traitements, mais sur l'évolution tumorale.

5C/9

Time perspective: a main predictor of quality of life in patients with brain metastasis

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BACKGROUND

Brain metastases (BM) are known to impact health related quality of life (QOL). Time perspective (how an individual partitions his/her past, present and future timeframes) has historically been a critical component of psychological adjustment in several disease contexts. No study has examined the role of time perspective on the QOL in patients with BM. We suppose that depressive symptoms mediate the relationship between past-negative time perspective and QOL in BM patients.

METHOD

48 participants were recruited (56% females; 56.7 years ± 12.4) in a consecutive inclusion cohort study called CEREMET-LR and supported by the SIRIC Montpellier Cancer. Participants completed 3 questionnaires, EORTC QLQ-C30 3.0, Zimbardo Time Perspective Inventory (ZTPI), and the Beck Depression Inventory-II (BDI-II). Analyses explored the mediation effects of their depressive symptomology on QOL. Independent variable included past-negative time perspective. Bootstrapping approach and path analysis was used to test the mediation model.

RESULTS

Preliminary analyses: The independent-*t* and Mann-Whitney tests showed that age, genre, marital status and level of study, had no significant statistically difference on QOL and depressive symptomology, and past-negative time perspective ($p > .05$). Path analysis: Depressive symptomology significantly mediated the relationship between past-negative time perspective ($\beta = 5.08$, $p < .01$, CI = 2.39, 7.77) and QOL ($\beta = -2.16$, $p < .01$, CI = -2.96, -1.36). There was a negative indirect association of past negative time perspective on QOL through the depressive symptomatology (-10.98, IC = -17.37, -5.79).

DISCUSSION

The results suggest the past-negative time perspective as a predictor of QOL. Thus, psychological interventions that reframe time perspective could be an effective solution to decrease depressive symptoms and improve QOL in BM patients.

5C/10

Identification des principaux déterminants psychosociaux du maintien en emploi des femmes ayant un cancer du sein : une revue de la littérature

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Introduction : Le maintien en emploi suite au diagnostic de cancer du sein englobe à la fois : le retour au travail et ses délais, et, le quota horaire hebdomadaire. Si les facteurs sociodémographiques, médicaux et professionnels du maintien en emploi ont fait l'objet de nombreuses investigations, les principaux déterminants psychosociaux, sont à notre connaissance peu abordés.

Méthode : Une revue de la littérature (RDL) publiée jusqu'à Juin 2016 a été réalisée sur : Medline, Psycinfo, Psycho & Behavioral Sciences, et SocIndex. Les termes utilisés ont été définis en Mesh et Thesaurus. Une formule booléenne a été constituée. La littérature grise et les bibliographies des articles identifiés ont fait l'objet d'un complément de recherche.
Les études sélectionnées devaient être publiées en langue française ou anglaise et évaluer quantitativement un ou plusieurs déterminants psychosociaux du maintien en emploi des femmes ayant un cancer du sein.
Les niveaux d'évidence ont été évalués à l'aveugle par trois auteurs avant d'établir un niveau final par consensus.

Résultats : Au total, 8132 articles ont été identifiés, dont 17 ont répondu aux critères d'inclusion. Deux articles ont complété notre recherche après vérification des bibliographies de Vidor et al. (2014), et Van Muijen et al. (2013). L'échantillon total est composé de 19 articles.
Les principaux déterminants du maintien en emploi sont : une bonne qualité de vie mentale et physique, une bonne satisfaction de vie et une forte perception de soutien professionnel à toutes les étapes de la maladie. La fatigue semble ne pas avoir d'impact significatif.

Discussion : Les aspects méthodologiques seront discutés. Nos résultats concordent avec les études qualitatives, ainsi que des RDL menées sur la pathologie cancéreuse en général. L'absence de significativité de la fatigue est notamment dû à sa forte colinéarité avec les traitements qui sont prépondérants dans le maintien en emploi.

Session 5D - Delivery and toxicity of nanodrugs

5D/1

Defining remotely activatable nanovectors and instrumentations for cancer diagnostics and therapy

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Cancer targeted therapy aims at reducing unwelcomed effects on healthy tissues and at enhancing drug accumulation at the lesion site. The nature of delivery system (targeting strategy) and use of adapted drug combinations (therapeutic strategy) are of the outmost importance and it is tempting to develop multifunctional targeted and therapeutic particles that targets tumor cells for diagnosis but also induce curing effects.
In parallel, during the last years, Optical Imaging (OI) methods were translated from cell biology in microscopy to intravital microscopy in mice, then to whole small animal imaging and finally OI is entering in the clinic now. Indeed, OI presents great interest in particular for functional medical imaging, pre- or per- or post-operative assistance to surgeons in oncology, surgical reconstruction, micro-vascular surgery, hypoxia follow-up and other applications.
We developed several nanovectors and optical instrumentation that could improve cancer diagnosis and targeted therapy of cancer. The nano-cargos that we study differ by 1) their molecular organization, 2) size (diameter of 2.5 to 250 nm), 3) surface coating, 4) the presence of specific ligands, 5) the drug or prodrug they can deliver and 6) the possible remote activation via physical remote excitation (radiotherapy or phototherapy). A summary of the success and limits of our nanovectors will be presented, with a special emphasis of their interest in surgical applications in oncology as well as for radiotherapy.

5D/2

Multimodal nanoparticles for tumor detection and tracking during radiotherapy

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Cancer treatment includes surgery often combined with chemo- and/or radiotherapy. However, chemotherapy efficacy is limited by drug resistance, poor drug penetration into tumor tissue, and side effects. Radiotherapy efficacy is limited by the tumor cell radioresistance and results may be altered by potential morbidity on normal surrounding tissues. This is critical when the tumor moves with the patient breathing.
A main challenge is to develop highly precise image-guided treatment to deliver high radiation doses to a defined volume without damaging the surrounding normal tissues.
Stereotactic radiotherapy, corresponding to a high precision targeting of the tumor by the beams of ionizing radiations, needs a good image guidance. To date, finding a simple, safe and of course, efficient tumor tracking system remains a challenge to improve actual stereotactic radiotherapy treatment. Our idea is that multimodal nanoparticles could represent good candidates for such tracking system.
Here we made the proof of concept, *in vitro* and *in vivo*, that epithelial tumor cells can incorporate those nanoparticles without any consequent cytotoxicity and that nanoparticle-labelled tumors can be detected in mice, which health status is not altered by the nanoparticles, over at least a 21-day period. Moreover, using phantom mimicking a human thorax, we show that radiotherapy apparatus can actually detect implanted multimodal nanoparticles in 'lung' even through tissue displaying the density of spine.

5D/3

Involvement of targeted and non-targeted effects during alpha or Auger RIT of small volume peritoneal carcinomatosis

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We investigated *in vitro* and *in vivo* the relative contribution of targeted and non-targeted effects in the therapeutic efficacy against tumours of antibodies radiolabeled with alpha particle (^{212}Pb, ^{213}Bi) or Auger electron (^{125}I) emitters. Targeted effects occur in cells directly crossed by ionising particles while non-targeted effects are measured in cells neighboring irradiated cells.
Targeted effects were measured *in vitro* in cells exposed to antibodies radiolabeled with alpha or Auger emitters (donor cells) while non-targeted effects were investigated in recipient cells. Recipient cells consisted of cells not exposed to radiolabeled-mAbs, but grown in medium previously incubated for 2h with donor cells. We showed that the relative contribution of targeted effects *versus* non-targeted effects was higher during alpha RIT than Auger RIT. Alpha particles produced 53BP1 and gamma-H2AX foci in donor cells that could be differentiated in large, medium and small foci, while only small foci were observed in recipient cells. We assumed that large foci would correspond to locally multiply damage sites in DNA. Conversely, Auger RIT led predominantly to non-targeted effects compared with targeted effects. Use of radical scavengers showed that oxidative stress was involved in non-targeted effects. *In vivo*, we showed in athymic nude mice bearing tumor xenograft that non-targeted effects were also involved and participated to therapeutic efficacy of radiolabeled antibodies.
These results indicate that although producing single DNA lesion, non-targeted effects can contribute to the therapeutic efficacy of mAbs radiolabeled with alpha particle or Auger electron emitters. These findings are particularly relevant for targeted therapy in which vectors cannot gain access to every tumor cell. One of the issues raised by these results is also related to radiation protection since non-irradiated tissues can show DNA damage and subsequent possible cell death or cell transformation.

5D/4

Confocal Raman Microscopy for Tracing Oxaphosphinanes (Phostines) in Glioblastom, non epithelial (SNB75)

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Glioblastoma are the most frequently observed cerebral tumors with a poor quality of life, a bad prognosis and an overall survival between 14 and 20 months with no acceptable curative treatment. The pathology management consists in tumor resection, associated with radio- and chemotherapy. Clinicians expect new solutions to control the tumor progression, making surgery easier and enhancing treatment benefits. Oxaphosphinanes (Phostines) a new synthesized drug by Phost'in SAS in Montpellier shows a huge decrease in tumor mass. To understand the drug mechanism of action, Confocal Raman Microscopy is used to trace Phostines intracellular which is not possible by any other similar method on the living cells with no need to any markers. First step of the research is detecting drug intracellular.
Data analysis as K mean cluster Analysis -KMCA- help to distinguish the different cell organelles, using their chemical fingerprints as well as detect the drug. As will be presented the drug position inside and outside the cell is detected. Confocal Raman microscopy with no need to any marker or cell fixation could give us precious information to understand the mechanism of action of the drug by its chemical finger prints.

Session 6 - Scientific Editor Conference

6

Transparent Publishing, Preprints & Open Science: how to share reproducible data

Bernd PULVERER

Chief Editor | The EMBO Journal
Head | Scientific Publications

The biosciences are witnessing a rapid growth and diversification of research. Scientific progress depends on efficient mechanisms to select, quality control, archive, share and find reliable and reproducible research. The research paper remains the predominant mode of sharing peer-reviewed research findings, and a subset of scientific journals play important roles also as a proxy for quality and impact in research assessment. I will discuss how the editorial and peer review process at highly selective journals can be reformed to assess both the interest and quality of the claims made by a researcher, and also the reliability, reproducibility and integrity of the experimental data.
I will discuss forward looking policies and publishing modalities that facilitate sharing and discoverability of research data with minimal delay, focusing on EMBO Source Data policies and technology and Preprint servers. I will discuss the promises and challenges of the nascent preprint movement in the biosciences and highlight how preprints and papers can form a continuum for fast and reliable research communication.
In times of limited funding, the pressures to publish in a subset of journals can increase dramatically. I will discuss the challenges this poses to the publication process in the context of reproducibility and scientific integrity. I will discuss how a metrics centric research assessment process can undermine the quality of the research process, highlighting the San Francisco Declaration for Research Assessment (DORA) and other initiatives.

Session 7 - Making sense of (big) data

7/1

Humanizing the mouse immune repertoire for therapeutic antibody discovery

Allan BRADLEY

Wellome Trust Sanger Institute (Hinxton)

7/2

Large, complex, and rich data sets : the need for "coordinate systems" and imagination

Jacques COLINGE

Institut de Recherche en Cancérologie de Montpellier

Thanks to the evolution of technology, e.g. DNA sequencing and mass spectrometry, it is possible to produce enormous and diverse data sets. The size issue is challenging but informatics and computer hardware offer technical solutions to deal with this aspect of the problem. Complexity is much more challenging and although certain projects directly benefit from the additional statistical power brought by larger numbers of samples, our ability to understand genomes, transcriptomes, and proteomes remains limited. Integrative concepts such as interaction networks are potential coordinate systems to look at complex, multi-level data sets and to extract information. Other options exist obviously. Finally, it should not be underestimated how rich the data generated worldwide are and how many unexpected opportunities they offer to make new discoveries *a posteriori*. Again, there are technical challenges in accessing all these data but solutions exist even if they are incomplete or imperfect. To be creative in extracting new knowledge from existing data is a much more difficult - and exciting! - task. In this presentation, we will evoke these facets of (big) data science in biology and cancer research through illustrations from our and others work.

7/3

The MARS (Matrix of RNA-Seq) viewer project

David PIQUEMAL[1], **Fabien PIERRAT[1]**, Laurent MANCHON[1], Roman BRUNO[1], Bertrand CIROU[2], Victor CAMEO PONZ[2]

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Since the early days of the Human Genome Project, data management has been recognized as a key challenge for modern molecular biology research. Recent years have seen a dramatic increase in the amount of genomic and transcriptomic data produced by typical projects in this domain. Our research program, in association with CINES (Montpellier), focused on transcriptomic data and the RNAseq approach (study of RNA molecules). RNAseq approach is used in a wide variety of applications. These include identifying disease-related genes, analyzing the effects of drugs on tissues, and providing insight into disease pathways. The RNAseq is widely used to characterize gene expression patterns associated with tumor formation. Since RNAseq provides absolute values and does not require any calibration with arbitrary standards, results can be compared at any time with other data, even raised by independent laboratories. Once collected, these data can be digitalized and then easily and reliably compared *in silico* with the growing library of RNAseq databases generated for normal and pathological situations in other laboratories around the world (Human: ~27000 libraries and Mouse: ~42000 libraries. Average size of a library: 1.7GB. Total size: 120TB).
We will highlight challenges that emerge from this flood of data, such as parallelization of algorithms, compression of genomic sequences, and cloud-based execution of complex scientific workflows. This project will aim at the development of the Generic platform called MARS (Matrix of RNA-Seq) with an innovative method and software to analyze, integrate and contextualize large-scale biological data in the fields of Human Health. MARS is made timely by the exponential increase in the throughput of molecular (Omics) approaches to cover the unmet needs in the specific fields of Health.

7/4

Stratifying Patients for Immune Checkpoint Blockade Cancer Therapies

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Non-Hodgkin's B-cell lymphomas (B-NHL) are aggressive lymphoid malignancies which develop in patients due to oncogenic activation, chemo-resistance and immune evasion. Despite the recent emergence of antibodies targeting immune checkpoint blockade, B-NHL frequently deploy several immune escape pathways at a time and patients respond variably to these new drugs. Most problematic there are currently no means to identify a priori which of those B-NHL patients will most benefit of such promising but risky therapeutic strategies.
Meta-analysis of large series of transcriptome microarrays from B-NHL biopsies is necessary to assess their immuno-edition status, but material (datasets) and methods to do this are currently lacking. We now present a new datamining strategy to perform this, and results in large cohorts of ~1500 patients with B-NHL. This approach was validated by matching its results (scores) to phenotypic and clinical hallmarks of B-NHL. Then, immune escape in patients was investigated by this method, and revealed a significant immune escape in most samples of DLBCL and FL, but fewer in MCL and MZL. Both gene expression patterns and overall survival data evidence four stages of cancer immuno-editing in B-NHL:

-non-immunogenic tumors (stage 1),
-immunogenic tumors without immune escape (stage 2),
-immunogenic tumors with immunoescape (stage 3)
-fully immunoedited tumors (stage 4).

So, immune checkpoint blockade therapeutics are only relevant for patients with tumors at immunoescape stages 3 and 4 (~75 % of FL and DLBCL).
These findings will be discussed in the more general context of molecular profilings for cancer treatment.

7/5

Personal medical data linking: Development and validation of a reliable and easy-to-use software tool.

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Objectives

To propose a reliable and easy-to-use tool to link medical databases based on the latest scientific advances in bioinformatics and biostatistics. A semi-automatic linking tool has to provide a list of possible pairs, while optimising the cost (in terms of amount of manual verifications) / effectiveness (in terms of recall and precision of the system) ratio depending on user priorities.

Methods

We developed a package with the R software including the main steps to link two databases: 1- cleaning and data standardizations, 2- management of multiple names and surname or patronymic name, 3- a mixed of deterministic and probabilistic record linkage, 4- output files return a list of linkage. We used the *P. Contiero* probabilistic approach to product global weights in order to distinguish matches from non-matches. For more flexibility, we computed acceptability threshold by unsupervised procedure based on extreme value statistics (EVT) concepts.

Efficiency of our algorithm is evaluated on real data by the cost/efficacy ratio, with the cost defined by the number of manual verifications and efficacy measured with the F-measure indicator.

Results

The F-measure result of our algorithm was 0.99 for a mean computation time of 58s on the evaluation dataset (3,535 x 39,660 identities). The number of manual validations was 188 pairs (5.3% of the source file).

Conclusion

The algorithm is portable, flexible and efficiency. Calibrated with a dataset of a medium size from the French cancer registries, our algorithm can be adapted (by new R-language program lines) to bigger databases or other structured data in order to yield powerful results. However, further evaluations are needed to take into account other kinds of empirical or artificial data.

Session 8 - Pre-clinical models / Le Grand Défi Vivez Bougez

8/1

Tumor cell proliferation and organization dynamics in 3D

Aurélie GOMES, Odile MONDESERT, Jennifer LAURENT, Céline FRONGIA, Olivia CLAYTON, Bernard DUCOMMUN, **Valérie LOBJOIS**

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A tumour is constituted of heterogeneous cell populations that interact with each other in a 3D organized architecture. Models that closely mimic this complex organization are essential for the understanding of the intimate growth mechanisms and for the development of new treatments. MultiCellular Tumor Spheroid (MCTS) is a 3D model that accurately reproduces the organization of a microtumor, recapitulating cell-cell, cell-microenvironment and cell heterogeneity similar to what is found in microregions of a tumor. MCTS is therefore considered as an attractive model to evaluate the activity of new antiproliferative drugs. Using these models, we are interested in understanding the mechanisms controlling the dynamics of proliferation and organization of tumour cell populations. Our studies focus on the cell cycle control and checkpoints dynamics within spheroids. Our work is based on the development of original MCTS expressing fluorescent reporters and markers that are also used to explore the regionalization and the dynamics of the effects of anticancer drugs in 3D by using original HCS and 3D imaging strategies.

8/2

PDX models, why, how and for what aim?

Charles THEILLET

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Patient Derived Xenograft or PDX models derived from patient samples grafted and serially passaged upon immunosuppressed mice are recognized as accurate representations of the disease in the patient and, thus, increasingly appreciated in preclinical testing. We have established close to 100 PDX models from various tumor locations (breast, ovarian, colorectal, pancreas, liposarcoma). Efforts are still ongoing, mainly in chemoresistant triple negative breast, high grade ovarian cancer and liposarcoma. We have shown that these models maintained histological and genetic characteristics of the tumor of origin. We also have determined that they constituted excellent models to monitor genetic fluctuation under treatment. Furthermore, we show that PDX reproduce faithfully the patterns of response to therapy observed in patients.
As such we believe that these models are extremely valuable tools for preclinical studies (we have ongoing examples), but also bring interesting insights in the relation between tumor cells and the stroma. Finally, short term PDX could constitute excellent tools to predict or orient therapy in aggressive disease such as pancreatic or metastatic CRC.

8/3

MPCC Platform: Preclinical models of Digestive Cancers

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The Montpellier scientific community felt the need to set up a platform dedicated to *in vivo* studies in oncology, more precisely for digestive cancers. In this context, the SIRIC Montpellier Cancer helped created, two years ago, the MPCC platform « Modèles Précliniques de Cancers Colorectaux ». Lucile Canterel-Thouennon has been recruited to develop and perform the preclinical experiments. MPCC's aim is to help researchers to better understand the processes behind tumor growth and metastases dissemination, as well as to test new molecules or drug combination to better predict human's response. MPCC's services may include in vivo study design, surgery, treatment, blood collection, tumor growth follow up by imaging, tissues sampling and data analyses.
As of today, we offer three types of surgery: intrasplenic, intracaecal and intrapancreatic grafts. In order to be as close as possible to the human pathology, the intrasplenic graft which gives hepatic metastases has been developed. This model mimics the hepatic metastases observed in colorectal cancers patients.
Intracaecal and Intrapancreatic grafts are two orthotopic models also available. All these surgeries can be performed on immunocompetent mice or on various immunodeficient mice. Working with luciferase transfected cells help to follow tumor localization, tumoral growth through time as well as the tumoral dissemination cell tracking. A panel of colorectal cancer cell lines has already been tested: SW620-luc, HCT116-luc, HT29-luc, CT26-luc… For pancreatic cancer grafts, cell lines already tested include BxPC3.
MPCC closely interacts with various platforms in Montpellier, *i.e.* the Animal, Living animal imaging and Histology facilities, respectively RAM, IPAM & RHEM.

8/4

The Great Live and Move Challenge: Impact and mediating mechanisms of a physical activity intervention implemented among children

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The great live and move challenge (GLMC) is a physical activity (PA) promotion intervention based on the theory of planned behavior (TPB, Ajzen, 1991) and implemented among 6-11 years old French school-aged children since 2013. This study aimed (1) to test the impact of the GLMC on TPB constructs (i.e., attitudes, subjective norms, perceived control, intentions) and PA practice of children, and (2) to identify to what extent the impact of the GLMC on the PA practice of children was mediated by the TPB model. A controlled design was used with 10 schools in the intervention group and 8 schools in the control group. A total of 977 children (Mean age = 8.57) took part in this study. Intervention was one month and a half long and included components targeting both TPB constructs (e.g., presentation of the benefits of PA practice to impact attitudes) and actual PA practice (e.g., playful PA games). Intervention was implemented by both in-the-field education (e.g., school teachers) and public politics stakeholders (e.g., community of communes). Children answered a questionnaire measuring TPB constructs toward PA and weekly PA practice. Of note, a randomized subsample of 148 children (i.e., 69 in the intervention group, 79 in the control group) also wore an accelerometer (Actigraph GT3X+) to evaluate the impact of the GLMC on an "objective" method of PA measurement.

Mixed models analyses revealed that as compared to those in the control group, children in the intervention group reported a significant increase in their level of PA practice (questionnaires and accelerometers), attitudes, subjective norms and intentions (ps<.01). In addition, path and mediation analyses also revealed that the impact of the GLMC on PA practice was partially mediated by changes in attitudes subjective norms and intentions (ps<.05).

The present study thus highlights the relevance and feasibility of the GLMC to impact the PA level of children through the evolution of some psychosocial mechanisms.

Session 9 - New concepts in Oncogenesis

9/1

Cancer cell of origin and tumor heterogeneity

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Different theories have been proposed to explain tumour heterogeneity including the cancer cell of origin. Here, we developed genetically engineered mouse models allowing lineage tracing together with oncogenic activation in different cell lineages of the skin epidermis and the mammary gland and assessed whether the cancer cell of origin controls tumour heterogeneity. I will discuss evidence that the cancer cell of origin controls tumour heterogeneity and the underlying molecular mechanisms that promote differentiation, tumour propagation, EMT and metastasis in primary tumors. These results have important implications for our understanding of the mechanisms controlling tumor heterogeneity and the development of new strategies to block tumor initiation.

This work is supported by the ERC, WELBIO, the FNRS, the Fondation Bettencourt-Schuler and the Fondation Baillet-Latour.

9/2

How does apoptosis influence tissue tension ?

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It is now well established that apoptosis is induced in response to mechanical strain. Indeed, increasing compressive forces induces apoptosis in confined spheroids of tumor cells, whereas releasing stress reduces apoptosis in spheroids cultivated in free suspension 1. Apoptosis can also be induced by applying pressure, as shown in different cultured cells (for review, see 2). During epithelium development, the pressure caused by a fast-growing clone can trigger apoptosis at the vicinity of the clone, mediating mechanical cell competition 3. While the effect of strain has long been known for its role in apoptosis induction, the reciprocal mechanism has only recently been highlighted. First demonstrated at the cellular level, the effect of an apoptotic cell on its direct neighbors has been analyzed in different kinds of monolayer epithelium 4-7. The concept of a broader impact of apoptotic cells behaviors on tissue mechanical strain has only emerged very recently from the characterization of tissue remodeling during Drosophila development. Indeed, we have shown recently that apoptotic cells generate an apico-basal force at the onset of apoptosis, force transmitted to the surrounding tissue and leading to a modification of tissue tension and tissue shape. I will present our recent data revealing that apoptotic cells need to keep strong adhesion to its neighbors in order to be correctly eliminated.

9/3

The evolutionary theory of cancer resistance and how anthropogenic impacts contribute to cancers across animal species and in humans

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Cancer is a pervasive threat to multicellular species and given the potential lethality of many cancers, under-protected populations are expected to be under strong selection to evolve resistance. Despite the likely deep evolutionary history of the establishment and maintenance of these and other resistance mechanisms, cancers are observed across the tree of life and sometimes at high incidence. We argue that many, possibly most, cancers currently observed in animals and in humans are indicators of changed or disrupted ecologies with respect to those in which species evolved for millions of years. We present assessments of human cancers to support our claim.

9/4

Characterization of long-term protective immunity after antitumor-based monoclonal antibody immunotherapy in melanoma

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Tumor antigen (TA)-targeted monoclonal antibody (mAb)-based treatments are considered to be one of the most successful strategies in cancer therapy and mAbs have been the biggest class of new drugs approved for the treatment of cancer during the last decade. For malignant melanoma metastatic stages, treatments were limited but immune checkpoint inhibitors demonstrated a spectacular increase of overall survival, reminding us the remarkable ability of the immune system to detect, eliminate and also "remember" cancer cells. We then focused on the ability of TA-targeted mAbs to exert their antitumoral functions through a direct effect on tumor cells as well as their capacity to activate immune effector cells, through Fc-dependent-mechanisms, to achieve sustained protective antitumoral immunity.
Using the B16F10 melanoma preclinical model, we showed that an immunotherapy based on the use of TA99, a mAb directed against the TYRP1 antigen overexpressed on tumor melanocytes, significantly increases mice survival. Tumor-free mice that received a second graft with B16F10 cells did not developed any tumor after the challenge suggesting the presence of a specific anti-tumor immunity. Supporting this hypothesis, we demonstrated the presence of a melanoma-specific cytolytic endogenous immune response after challenge in TA99-treated mice, a cytolytic response that is further enhanced in mice treated with TA99 and the anti-PD-1 immune checkpoint inhibitor, while anti-PD1 treatment alone has no effect in this model. We also demonstrated the presence of a specific humoral response with an increase of anti-B16F10 immunoglobulins within the sera of protected mice after challenge and showed that when transferred into naïve B16F10-grafted mice those sera delay tumor growth and increase mice survival.
Altogether, these results clearly demonstrated the immunomodulatory effect of an antitumor-based immunotherapy, an effect that can be further potentiate by anti-PD-1 treatment.

9/5

SAMHD1 acts at stalled replication forks to prevent ssDNA-mediated induction of type I interferons

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SAMHD1 protects quiescent cells from HIV-1 by depleting dNTP pools. Mutations in SAMHD1 are implicated in a severe inflammatory disease called Aicardi-Goutières syndrome (AGS) and in chronic lymphocytic leukemia (CLL). However, the mechanism by which SAMHD1 protects cells from chronic inflammation and cancer is currently unclear. Here, we show that SAMHD1 prevents the accumulation of DNA fragments in the cytosol and thus prevents induction of type I interferons (IFNs), especially when cells are exposed to DNA replication stress. SAMHD1 executes this function by degrading nascent DNA at stalled forks and so preventing the release of ssDNA fragments. This resection activity of SAMHD1 is distinct from its dNTP hydrolase activity, and is it important for checkpoint activation and fork restart. Together, these data indicate that SAMHD1 is an important player in the replication stress response and that it prevents inflammation by preventing the release of nascent ssDNA fragments into the cytosol.

Posters - Axis 1
« Cell Signaling and Therapeutic Targets »

P101

The medullary adipocytes contribute to the bone metastasis of prostate cancer and this effect is regulated by obesity

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Background: We have recently demonstrated that mature adipocytes of the periprostatic adipose tissue act as a driving force for the local dissemination of prostate cancer (PCa) through the secretion of the CCL7 chemokine, and that this effect was amplified by obesity. Then, PCa cells metastasize to distant site such as bone. During this dissemination, PCa cells interact with bone marrow where the main components are medullary adipocytes (MedAd)

Objective: We investigated the role of the MedAd secretions in the bone metastasis process of PCa. We also explored the amplification of this effect in obesity and aging, two known risk factor for bone metastasis in PCa.

Methods and results: Using a series of 35 samples from patients, we first showed *in vitro* (Boyden chamber assay) that conditioned mediums from human MedAd (MedAd-CM) were able to chemoattract PCa cells (by contrast to paired conditioned medium obtained from subcutaneaous adipocytes) with a strong amplification by obesity or aging. The chemoattractive potential of medAd-CM was mediated by the chemokine CCL7 which interact with one of its receptor CCR3 on tumor cells, as shown using pharmacological inhibitors, blocking antibodies and gene repression strategies. To validate this effect *in vivo*, we used the murine cell line RM1-BM able to localize to the bone after intra-cardiac injection. We observed that the loss of CCR3 in tumor cells abrogates their bone metastatic homing.

Conclusions: This study show for the first time a mechanism that could explain the increased bone metastatic dissemination of prostate cancer linked to obesity and aging. These data highlight the fact that medullary adipocytes, using the CCR3/CCL7 axis, are able to control the distant dissemination of PCa cells to the bone. In a context of obesity or aging, medullary adipocytes show a different phenotype leading to an increased secretion of CCL7 and enhanced dissemination.

P102

Structural studies of peptidomimetic ligands of TRAIL complexed to proapoptotic Death Receptor 5

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Apoptosis, the programmed cell death, plays a protective role against tumour formation and can be regulated by either the intrinsic or the extrinsic pathway. The latter is stimulated through the activation of cell-surface death receptors (DR) by Tumor necrosis factor-Related Apoptosis Inducing Ligand, or TRAIL. The ligand binding leads to the trimerization of the receptors, which is a necessary step for the apoptosis answer. This TRAIL ligand has the interesting particularity to bind DR5 receptor and to trigger tumor cell apoptosis specifically. This unique property is at the center of several therapeutic assays for cancer cell targeting.
The aim of this study is to use a structural approach in order to study the interaction between DR5 and new peptidomimetic ligands of TRAIL, or $TRAIL^{mim/DR5}$, that can enhance activation of the extrinsic pathway of apoptosis. Several of these different peptides have been produced through solid-phase synthetic chemistry in monomeric, dimeric or trimeric states, and have been shown to selectively bind to DR5 [**1**]. We plan to use NMR spectroscopy to study the molecular details of the interaction between these new ligands and DR5. We have produced a double labelled $^{13}C^{15}N$ protein, and we have begun the assignment of the backbone and interaction studies to map the molecular details of the ligand binding. The other part of this project is to use crystal X-ray diffraction in order to get atomic scale information of the hexameric complex. These data should help us to have a better understanding of the mechanisms by which those new ligands work.

[1] Pavet V, *et al.* Multivalent DR5 Peptides Activate the TRAIL Death Pathway and Exert Tumoricidal Activity. Cancer Res, 2010, 70, 3, 1101-10.

P103

E4F1 is a major regulator of pyruvate metabolism in normal skin homeostasis and skin carcinogenesis

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The multifunctional protein E4F1 is an essential regulator of epidermal stem cell (ESC) maintenance. Here, we found that E4F1 transcriptionally regulates a metabolic program involved in pyruvate metabolism that is required to maintain skin homeostasis. E4F1 deficiency in basal keratinocytes resulted in deregulated expression of *Dlat*, a gene encoding the E2 subunit of the mitochondrial pyruvate dehydrogenase (PDH) complex. Accordingly, E4f1 knock-out (KO) keratinocytes exhibited impaired PDH activity and a redirection of the glycolytic flux toward lactate production. The metabolic reprogramming of E4f1 KO keratinocytes associated with remodeling of their microenvironment and alterations of the basement membrane, led to ESC mislocalization and exhaustion of the ESC pool. Altogether, our data reveal a central role for Dlat in the metabolic program regulated by E4F1 in basal keratinocytes and illustrate the importance of PDH activity in skin homeostasis.
Based on these results and on growing evidences linking pyruvate metabolism to cancer development, we now wish to investigate the functions of E4F1 during skin carcinogenesis, more specifically in melanoma, which is the most aggressive type of skin cancer. Melanoma, through a multistep process, arises from melanocytes and is driven by mutations in the Ras/ Raf signaling pathway. In the early steps of melanomagenesis, nevi which are benign tumors also harboring Ras/Raf genetic alterations, melanocytes display senescent features, which have been described as a barrier against malignancy. Interestingly, it has been shown that PDH is a crucial mediator of this Braf-induced senescence. Moreover, recent results from the lab point out the importance of E4F1 in regulating senescence also through PDH modulation. Taken altogether, these data led us to characterize a potential E4F1 and Ras/Raf cascade interplay, its influence on PDH regulation and how it impacts melanomagenesis.

P104

Role of HSP90/R2TP system in colorectal cancer in mouse

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The Heat Shock Protein 90 folds neo-synthesized proteins into an active state. Many substrates of HSP90 are involved in signaling pathways and related to tumour progression. Inhibition of HSP90 has anti-tumoral effects. Until now, this effect was attributed to the inhibition of receptors and kinases. Identification of the R2TP, a new HSP90 co-chaperon, allowed the identification of a new set of HSP90 substrates. HSP90/R2TP is involved in the assembly of snoRNPs, telomerase RNP, the nuclear RNA polymerases and PIKKs, which play key functions in cellular proliferation and tumorigenesis. R2TP is formed of four proteins: RUVBL1, RUVBL2, PIH1D1 and RPAP3, some of which (RUVBL1, RUVBL2 and RPAP3) are overexpressed in hepatocellular or colorectal cancer. We thus hypothesize that the co-chaperone R2TP could be involved in colorectal carcinogenesis. To study the role of R2TP in intestinal homeostasis and carcinogenesis, we generated a conditional knock-out murine model for *RPAP3*. We showed that *RPAP3* invalidation in whole organism or only in in colon/intestine is lethal at embryonic stage. The invalidation of *RPAP3* in adult intestine using an inducible recombinase (*RPAP3*^{fl}; Villin>Cre-ERT2) leads to a drastic phenotype as soon as 8 days post-induction: erasure of villosity-crypt axis, loss of epithelial layer, distension of small intestine by accumulation of liquid, resulting in death after 10 days. This phenotype is reminiscent of proliferative defects and / or stem cell renewal. so we are investigating this pathway.
In parallel, we address the possibility of a therapeutic window to target *RPAP3* during intestinal tumorigenesis by using heterozygous animals (*RPAP3*$^{fl/+}$*;* Villin>Cre-ERT2) in which tumorignesis is induced either by a chemical treatment (AOM /DSS protocol) or, by a genetic one (Apc$^{LoxP/+}$).
These ongoing experiments will address the role of R2TP in a tissue with a constant turnover and the relevance of R2TP in tumorigenesis.

P105

Deciphering and targeting YAP/TAZ activity in human gastric adenocarcinomas

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Gastric cancer (GC) is the fourth most common type of cancer worldwide, with 738000 deaths annually. Surgical removal of early stage GC tumors is critical to effective treatment, but because of few symptoms accompanying early GC, most GCs are found at an advanced stage.
YAP and TAZ are the key components of the Hippo pathway, a highly conserved pathway which controls organ size and tumorigenesis. YAP and TAZ are co-transcriptional factors that bind to TEAD family proteins and activate oncogenic pathways. Given the association of elevated expression and hyperactivity of YAP/TAZ in many cancers, inhibitory strategies of their nuclear activity represent rational and novel targeted approaches for the treatment of gastric cancer. Recently, a pilot screen identified Verteporfin (Vp) as a small inhibitor of TEAD-YAP interactions which prevented YAP-induced oncogenic growth.
The aim of this project was 1/ to analyse YAP/TAZ activity in gastric cancer cell lines and in Patient Derived primary tumor Xenografts (PDXs) and 2/ to target YAP/TAZ activity in those models by treating the cells with Vp to prevent tumor growth.
Preliminary results showed a nuclear expression of YAP and/or TAZ in 10-30% of GC cells in primary tumors. YAP and/or TAZ nuclear expression appears in front of migration, were the invasive cancer stem cells (CSC) have been described to reside. *In vitro,* Vp treatment decreased YAP/TEAD target genes expression in a dose-dependent manner in GC cell lines and in PDXs and led to a diminution of cellular proliferation. Vp treatment decreased the CSC pool assessed by the inhibition of tumorsphere formation and the decreased expression of the CSC marker CD44. Finally, Vp treatment decreased tumor growth *in vivo* and inhibited the ability of residual cell to initiate tumorspheres along several passages. In conclusion, targeting YAP/TAZ/TEAD could be a promising strategy in the treatment of GC.

P106

FAK (Focal Adhesion Kinase) mRNA variants in colorectal cancer

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Focal adhesion kinase (FAK) is a ubiquitous protein involved in crucial cell signaling pathways. It is currently known that the dysregulation of key cellular process, involving FAK could lead to cancer, including colorectal cancer (CRC). Indeed, FAK is overexpressed in primary colon tumors, liver metastasis and is associated with poor CRC patient's outcome. FAK expression and activity rely on complex levels of regulation such as alternative splicing. There are at least eight FAK mRNA splice variants and we previously demonstrated that some variants were associated with poor patient prognosis in acute myeloid leukemia. This highlights the concept that FAK mRNA variants might influence cancer progression. Here, our work focuses on the identification of FAK mRNA variants involved in CRC. We have previously developed a representative mouse model that mimics well the CRC progression in patients. Indeed, we implant orthotopically, into the caecum of immunodeficient mice, four different human colorectal cell lines that express both luciferase and tdTomato reporter genes. This approach allows us to monitor CRC development *in vivo*, using bioluminescence and fluorescence imaging, and to analyze, using capillary electrophoresis and real-time PCR, the expression of FAK mRNA variants. Depending on the cell line, various CRC progression profiles, tumor growth rate and ability to produce metastases, were observed. Remarkably, we detected three mRNA variants (FAK^0, FAK^6 and FAK^{28}) that were differentially expressed over time and at the different tumor sites. We currently investigate the roles of these three FAK mRNA variants in various steps of CRC progression. Those variants of FAK or their corresponding protein isoforms may pave the way for new targets in anti-CRC therapy.

P107

A phosphoproteomic screen reveals how to exploit adaptative response to targeted therapies towards cell signalling for a better response of PI3K-hitting drugs in the clinic.

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PI3K signaling is increased in more than 50% of all cancers. However, clinical results using PI3K-hitting drugs are less clear than anticipated. The shutdown of such a critical signal forces the cancer cell to change its signaling network, reducing the efficiency of their targeted drugs.
We analyzed the importance of PI3K signal node in pancreatic cancer, where its increased activity is associated with a poor prognosis. We have identified one isoform of PI3K, p110α, involved in the control of pancreatic tumorigenesis. While p110α is expressed physiologically in the pancreatic cells, inflammation and oncogenic Kras are responsible for the overexpression of another isoform of PI3K, p110γ, in in situ genetic model of PDAC. Indeed, we observe that 10% of pancreatic cancer patients presents p110γ mRNA overexpression, event which is not associated with a changed prognosis, while alterations of p110α mRNA expression or mutations of its encoding gene is associated with a worse prognostic.
Interestingly, in all pancreatic cell lines tested, addition of serum changes the sensitivity from a mostly p110γ-sensitive to mixed p110α/γ-sensitive profile independently of the level of mRNA expression of each isoform. To demonstrate for the first time that there is a differential adaptive response to the constant inhibition of each PI3K isoforms, we performed a time course large scale phosphoproteomic analysis and mapped PI3K isoform-specific signaling that were triggered by serum activation. The pharmacological long-term inhibition of these enzymes allowed the identification of phosphopeptides which were induced by p110γ inactivation only or p110α-only or induced by the inhibition of all the isoforms of PI3Ks.
We now aim to validate these early modifications of signaling networks upon PI3K inhibition. These data make the rational for the combinative use of PI3K isoform-specific drugs in subset of pancreatic cancer patients for a better response in the clinic.

P108

A central role for synthenin on the SRC metastatic function in colorectal cancer

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The oncogene and non-receptor tyrosine kinase SRC is a master regulator of cell growth and adhesion and hyperactive SRC is a potent driver of human colorectal metastasis. How SRC promotes this malignant process remains unclear. Exosomes are small vesicles secreted by cells, with an important role in intercellular communication and numerous studies indicate that cancer cells exploit the exosomal pathway to promote metastasis. Yet, little is known about the molecular mechanisms that regulate the biogenesis of cancer exosomes. Recently, we have characterized a molecular machine involving heparanase, syndecan heparan sulfate proteoglycans, syntenin-ALIX as important for the biogenesis of a subpopulation of exosomes (Syntenin exosomes) and potentially controlling the *in trans* activity of heparan-sulfate dependent signaling complexes. By phosphoproteomic analyses of SRC-dependent colon carcinogenesis, we also identified Syntenin and ALIX as prominent SRC substrates in this cancer. Here we addressed the role of the Syntenin pathway on SRC oncogenic activity in CRC. We first observed a large increase of Syntenin protein level in metastatic samples of patients with CRC. Second, we found that Syntenin knock-down in CRC cells dramatically affected anchorage-independent cell growth and invasion. The increased transforming properties observed following SRC expression in these tumor cells was also totally dependent upon Syntenin expression. Importantly, the functional defects observed following Syntenin depletion was largely restored when incubating these cells with a conditioned medium (CM) from the corresponding parental CRC cells, suggesting a role for Syntenin exosomes in SRC transforming activity. Finally, we have started addressing the underlying mechanism of these Syntenin pro-tumoral functions and identified important SRC phosphorylation sites in the Syntenin sequence. Overall, our results would support an important role of Syntenin on SRC metastatic function in CRC.

P109

Roles of EMT transcription factors in controlling cell clonal dynamics and invasiveness during emergence of tumor resistance in breast cancer subtypes.

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This project explores the mechanisms of mammary gland morphogenesis, as a model for breast carcinoma progression. Mammary gland morphogenesis results from the coordination of distinct cell responses (proliferation, differentiation, motility, invasiveness, apoptosis) integrated by numerous pathways, including Wnt, EGF, FGF, Notch, SHH, Myc and hormonal activation. For the purpose of this study, we feel it is critical to analyze individually the impact of these pathways in modulating proliferation, differentiation, motility, invasiveness, apoptosis, intercellular cohesion, and polarity in cells involved in a coherent morphogenetic migration. Our first model describes the primary emergence of invading breast carcinoma cells from mammary epithelium. Cells are treated with defined drugs or will be transfected with various constructs (under validation) enhancing or repressing specific pathways such as Slug, in addition to constructs allowing the monitoring of cell structures by GFP labeling for video microscopy.
We have designed improved 3D models to analyze the impact of EMT-TF in a 3D environment. Our system allows monitoring simultaneously the mentioned pathways at a cellular level for three weeks, a period adjusted to test chemotherapy drugs.

P110

Impact of systemic inflammation in pancreatic cancer cachexia

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One of the hallmark of pancreatic ductal adenocarcinoma (PDAC) is cancer-associated cachexia (CAC). Cachexia is a systemic wasting syndrome characterized by a progressive loss of skeletal muscle and fat mass, observed in patients with chronic diseases. The prevalence of CAC is often correlated with systemic inflammation, modifications that may favor muscle protein breakdown and white adipose tissue (WAT) lipolysis.
Pancreatic carcinogenesis is initiated in mice owing to the pancreatic expression of the oncoprotein $Kras^{G12D}$ which is mutated in 90% of PDAC (KC mice, Pdx-1-Cre; $Kras^{G12D/+}$). We previously demonstrated that pancreatic Kras pathway activation facilitates expression loss of the G protein coupled somatostatin receptor sst2, an anti-inflammatory receptor. Consistently, sst2 global heterozygoty in a pancreatic $Kras^{G12D}$ background (KCS mice, Pdx-1-Cre; $Kras^{G12D/+}$;$sst2^{+/-}$) accelerated the progression of Kras-initiated neoplastic lesions by promoting a pro-tumoral inflammatory reaction.
Intriguingly, we now show that KCS mice also developed a lethal systemic inflammatory reaction within 16-weeks of age, as revealed by an increase of blood Neutrophil/Lymphocyte Ratio (NLR). KCS mice progressively presented weight loss associated with UCP-1 positive staining in WAT (a marker of lipolysis found in cachexia syndrome). This systemic pro-cachectic inflammation resulted from sst2 heterozygoty in the bone marrow, as it was abrogated in KCS mice transplanted with wild type bone marrow, or provoked in KC mice transplanted with $sst2^{+/-}$ bone marrow.
Altogether, we show that sst2 expression in hematopoietic lineage cells regulates CAC. Underlying mechanisms are currently under investigation. These preliminary results place sst2 as an endogenous anti-inflammatory brake that decreases oncogenic signals involved in cancer development and cachexia.

P111

Integrating omics approaches for the elucidation of metastatic melanoma resistance mechanisms to targeted therapies

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Being one of the most intrinsically resistant cancers to chemotherapeutic agents, in addition to its strong ability to develop acquired resistance, malignant melanoma (MM) remains a therapeutic challenge. Understanding the mechanisms governing MM chemoresistance is essential to guide therapeutic choice for improving treatment efficiency and to propose new therapeutic targets.

To investigate the development of MM chemoresistance, we focus on the identification of molecular determinants that could drive this capacity. We established *in vitro* CAL1 cell lines resistant to classical chemotherapeutic agents as vinca alkaloids (CAL1R-VAs) and A375 cell lines resistant to targeted therapy as MAPK inhibitors (A375R-iMAPKs), by submitting parental cell lines to continuous exposing of these drugs during several months.

Micro-array data analysis followed by functional assays revealed for the first time that resistance in CAL1R-VAs was associated to an altered lysosomal function and to an upregulation of the unfolded protein response. To examine the molecular mechanisms which drive the acquisition of MM resistance to VAs and to iMAPKs, getting functional insights is essential. We propose to investigate resistant cell metabolomics by performing magnetic resonance imaging as well as transcriptomics.

Among potentially interesting transcripts, long non-coding RNAs (lncRNAs) are promising candidates. LncRNAs begin to be documented in melanoma, being associated to invasiveness and tumor aggressivity. To highlight the presence of lncRNAs in resistant cell lines, lncRNA-dedicated microarray will be tested on the CAL1R-VAs and A375R-iMAPKs versus parental cell lines. After experimental validation of these lncRNA candidates, functional assays as RNA interference (siRNA) will confirm their functional relevance. Finally, deciphering their action mechanisms will be investigated through RNA pulldown coupled to mass spectrometry, which will identify their cellular interaction partner.

P112

Custom TAG-RNAi for safe therapeutics against Cancer

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Cyclin D1 (CycD1) is a component of the core cell cycle machinery. By interacting with CDK4/6 it drives the G1 phase of the cell cycle. CycD1 is over-expressed in most human cancers and the targeting of CDK4/6 kinases provides a novel therapeutic hope. Encouraging clinical data demonstrate the power of CDK4 inhibition by Palbociclib in breast cancer, but some patients do not respond well to this drug. In addition, the rationale for CDK4 inhibition is proposed for the blockade of cancer cell cycle but not for cancer cell killing. Palbociclib alone is therefore not meant to cure cancer and should be administered in combination with other chemotherapies. Because CycD1 is also known to bare CDK4 kinase-independent functions, we focus on its putative impact on tumor maintenance. By RNA interference (RNAi), we found that CycD1 targeting leads to tumor mass regression associated with increased apoptosis. To elevate RNAi against CycD1 as a therapeutic solution, we developed a new technology, called TAG-RNAi, meant to specifically knock-down CycD1 in vivo and avoid the unwanted off-target effects of small interfering RNAs. Then, we explored CycD1 expression in healthy adult post-mitotic organs to predict potential side-effects of its targeting in cancer patients. Via Tandem-HTRF based on the use of several antibodies raised against different epitopes of the same bait, we revealed CycD1 in adult's tissues which raises questions about the safety of its targeting in clinics. However, by combining these two technologies, we are able to quickly design specific siRNAs against oncogenic mutations that could serve for the body-wide safe silencing of mutated CycD1 only in cancer cells.

P113

Radiosensitization of Glioblastoma Stem Cells by inhibition of STAT3

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Glioblastoma multiforme (GBM) represents the most common and lethal primary brain tumor. The standard treatment for glioblastoma patients involves surgical resection with concomitant radio and chemotherapy. Despite today's clinical protocol, the prognosis for patients remains very poor with a median survival of 15 months according to tumor radio and chemo-resistance. Tumor resistance and GBM treatment failure may be explained by the presence of highly radioresistant Glioblastoma Stem Cells (GSCs). The transcription factor STAT3 was found to be constitutively activated in different tumors and involved in radioresistance. In our previous work, we showed that STAT3 was constitutively activated by phosphorylation on Tyr705 and Ser727 residues and played a critical role in self-renewal of GSCs.

In this present work, we studied radiosensitization of two GSC lines isolated from patients by direct inhibition of STAT3. For this purpose, we used Stattic, a small non-peptidic molecule interacting with the SH2 domain of STAT3. First, we observed that Stattic treatment inhibits both STAT3 phosphorylations in a dose-dependent manner. Then, we found that radiations increased STAT3 phosphorylation preferentially on Ser727. For determination of conjugated effect of STAT3 inhibition with radiations, we used infra-cytotoxic dose (<IC20) of Stattic which doesn't affect cell viability to exclude inhibitory effect alone. We showed that Stattic treatment before cell irradiation induced the decrease of surviving fraction of both GSCs compared to untreated condition. These data suggest that STAT3 inhibition could potentiate radiation effect by increasing GSCs self-renewal inhibition. Finally, we investigated the activation of STAT3 on GBM tissue microarray (79 patients) and confirmed the preferential activation by phosphorylation on Ser727. Taken together, our results suggest pSer727-STAT3 as a potential target for radiosensitization of highly radioresistants GSCs.

P114

Single domain antibodies as novel biosensors of active RHOA protein

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RHOA small GTPase belongs to a subfamily acting as a molecular switch activating major signaling pathways that regulate cytoskeletal dynamics and a variety of cellular responses such as cell cycle progression, cytokinesis, migration and polarity. This protein has been strongly implicated in tumorigenesis by deregulation of its expression and/or activation. However, recent developments in the field underlies the need to reassess RHOA role in cancer. Fully understanding of its spatial and temporal activity may be the key to solve this disputed issue. RHOA activity resides in a few percent of GTP loaded protein, which is finely tuned by a crosstalk between regulators of the GTPase cycle. Manipulating a single RHO at the expression level often induces imbalance in the activity of other RHO GTPases, suggesting that more specific tools targeting these active pools are needed to decipher RHOA functions in time and space.
Our expertise in isolating recombinant antibodies by *phage display* allowed us to isolate one scFv that distinguishes selectively the active form of RhoB *in vitro*[1]. As these scFv failed to work efficiently for intracellular expression, we used single domain antibodies, also known as VHH or nanobodies. We produced a novel fully synthetic *phage display* library of humanized nanobodies (NaLi-H1) and validated it against several target antigens by the selection of high affinity binders and many functional intrabodies[2]. We screened the NaLi-H1 library to develop conformational sensors of the GTP loaded active conformation of RHO subfamily. We obtained several high affinity nanobodies against RHOA's active form which we characterized as RHO signaling blocking intrabodies.

1.Chinestra P et al. Generation of a single chain antibody variable fragment (scFv) to sense selectively RhoB activation. PLoS One 2014.
2.Moutel S et al. NaLi-H1: A universal synthetic library of humanized nanobodies providing highly functional antibodies and intrabodies. Elife 2016.

P115

Transcriptional regulation of RIP140 expression by the Wnt signaling pathway in colorectal and gastric cancer cells

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Gastrointestinal cancers which include colon (CRC) and gastric (GC) cancers are amongst the main causes of death worldwide. They arise through multistep processes in which genetic and epigenetic alterations accumulate in a sequential order. The aberrant activation of the Wnt/β-catenin signaling pathway is involved in the development and progression of these cancers. Recently, it has been shown that the transcriptional coregulator RIP140 is involved in sporadic colorectal carcinogenesis. In the intestinal epithelium, RIP140 regulates cell proliferation by inhibiting the Wnt signaling pathway. It has been also revealed that RIP140 expression decreased during tumorigenesis at both the mRNA and protein levels. Here, we have investigated the regulation of RIP140 gene expression by the Wnt signaling pathway in colorectal and gastric cancer cells.
The effect of Wnt signaling on RIP140 expression in CRC and GC cells was tested by qRT-PCR and reporter assays. Our results showed that Wnt signaling activation by LiCL or SB216763 inhibits RIP140 mRNA accumulation. In transient transfection experiments, activation of the Wnt pathway (by LiCl or through ectopic expression of active β-catenin) inhibits transcription of the human and mouse RIP140 promoters suggesting that this downregulation occurs at the transcriptional level. The use of RIP140 promoter deletion mutants in transient transfection indicates that this regulation implicates the proximal region of RIP140 promoter. The mechanisms of this regulation have been further deciphered through the reanalysis of ChIP-seq data which revealed the recruitment of TCF/β-catenin close to the RIP140 gene. Further experiments are in progress to determine whether cross-talks with other signaling pathways (such as the Notch pathway) could play a role in the regulation of RIP140 gene expression.

P116

MDM2 regulates serine metabolism and redox homeostasis in cancer cells

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The Mouse Double Minute 2 (MDM2) oncoprotein is recognized as a major negative regulator of the p53 tumor suppressor. Here we show that MDM2 is recruited to chromatin independently of p53 to regulate a transcriptional program implicated in amino acid metabolism and ROS homeostasis. Genome-wide studies highlight an important role for members of the ATF family of transcription factors in tethering MDM2 to its target genes. MDM2 recruitment to chromatin is a tightly regulated process that occurs during oxidative stress, serine/glycine deprivation and is modulated by the pyruvate kinase M2 (PKM2) metabolic enzyme. Moreover, interfering with endogenous MDM2 and exogenous serine availability impaired the channeling of glucose-derived carbon sources into glutathione (GSH) metabolism, impacting on the redox state and growth of cancer cells. Collectively, our data illustrate a previously unsuspected function of the MDM2 oncoprotein in the control of the redox state of cancer cells.

P117

The E-cadherin/catenin complex and the intercellular adhesion of breast cancer cells are positively regulated via phosphorylation by the Syk tyrosine kinase in breast cancer cells

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The spleen tyrosine kinase Syk was mainly studied in hematopoietic cells. Our lab first demonstrated that Syk is also present in mammary epithelial cells and that its expression is lost in malignant breast cancer cells. Using mouse xenograft models injected with Syk-transfected cells we and others established that Syk acts as a tumor and metastasis suppressor. Moreover, clinical studies reveal a correlation between reduced Syk expression and a decreased survival and increased metastasis risk in breast cancer. A quantitative phospho-proteomic approach allowed to identify novel potential Syk substrates involved in intercellular adhesion.
Phosphorylation assays with recombinant proteins demonstrated that E-Cadherin (E-Cdh), α, β and p120-catenin (Ctn) are direct Syk substrates. Using mass spectrometry, we identified the tyrosine residues phosphorylated by Syk and generated phospho-Tyr-peptide-specific antibodies. Using immuno-fluorescence Syk was shown to colocalize with E-Cdh at adherents junctions (AJ). Syk transfection increased E-Cdh and Ctns phosphorylation at AJ in a kinase-dependent manner. This was biochemically confirmed by immunoprecipitation and Western blot experiments. Phosphorylated Ctns are still associated with E-Cdh and vice versa.
In 2D culture, Syk transfection stimulated intercellular contact formation. Correspondingly, in Syk-knockdown cells the 2D and 3D cell-cell re-aggregation was decreased. Conversely, cell migration and invasion were inhibited by Syk transfection and stimulated by Syk knockdown. At the molecular level, Syk transfection increases the interaction between the E-Cdh/Ctn complex with zonula occludens proteins and the actin cytoskeleton.
In conclusion, Syk seems to play a positive role in the formation and maintenance of AJ via the phosphorylation of the E-Cdh/Ctn complex. Loss of Syk expression or function might lead to the disruption of these complexes and consequently promote invasion and metastasis.

P118

The role of Cyclin A2 in colon homeostasis and colorectal cancer (CRC)

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Colorectal cancer (CRC) is a disease affecting from the epithelial cells lining the colon or rectum. Treatments used for colorectal cancer may include some combination of surgery, radiation therapy and chemotherapy. Once metastasis has occurred, the patients 5-year survival falls dramatically. Therefore, it is important to define the mechanism leading to development and metastasis spreading of CRC in order to find more efficient therapies. During tumor progression, cancer cells can undergo an Epithelial to Mesenchymal Transition (EMT) associated with the acquisition of invasive and stem cell properties. Cyclin A2 is known as a key regulator in cell proliferation. Interestingly, Jean Marie Blanchard's lab found a novel function of CyclinA2 in regulating cell invasion and EMT. They also found that CyclinA2 expression is increased in primary tumor, but decreased in hepatic metastasis in CRC patients. In order to study the *in vivo* relevance of CyclinA2 in EMT and metastasis in colorectal cancer, I will use two mouse models: the experimental metastasis mouse model and the Azoxymethane/Dextran Sulphate Sodium (AOM/DSS) model. In the former mouse model, I will check the impact of Cyclin A2 inactivation on metastases spreading by cecal injection of CRC cell lines bearing an inducible shCyclinA2. For the second model,mice will be exposed to an AOM/DSS treatment that results in the development of colitis associated carcinogenesis in 60 days. In this model, I will study *cyclin A2 fl/fl ERT2 Villin-Cre* mice*,* where the expression of Cre under the Villin promoter can be induced by tamoxifen treatment, and induce cyclin A2 inactivation at different stages of carcinogenesis.

P119

Crosstalk of the transcription factor RIP140 with the Notch signaling pathway in colon cancer

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The RIP140 protein is a transcriptional co-regulator which represses the activity of many transcription factors and is involved in various physiological processes. By combining in vitro and in vivo experiments, we recently demonstrated that RIP140 controls intestinal homeostasis and could play a tumor suppressor role in colorectal cancer. Indeed, RIP140 regulates intestinal cell proliferation and differentiation by inhibiting the Wnt/β-catenin signaling pathway. Interestingly, both in intestinal homeostasis and tumorigenesis, a strong crosstalk exists between Wnt and Notch signaling pathways. For instance, in colon cancer cells, Notch signaling is a downstream target of β-catenin hyperactivation and the HES1 gene (the major effector of the Notch pathway in the intestine) is regulated by the Wnt pathway.
In order to define if and how RIP140 controls the Notch pathway in human colon cancer cells, we set up various experiments using the HES1 gene as the main output of the Notch signaling. In reporter assays, a positive NICD-dependent effect of RIP140 on RBPJ dependent transcription was observed in various colorectal cell lines. This effect of RIP140 is not only observed on HES1 but also on HES5 gene transcription. By contrast, in RT-qPCR and Western blot experiments, the modulation of HES1 expression by NICD ectopic expression revealed that RIP140 exerts a negative NICD-dependent effect on HES1 expression. This effect has been also tested on other Notch direct or indirect target genes. These data suggest that the effects of RIP140 on the Notch signaling are very complex. In addition, the effect of RIP140 on Wnt and Notch crosstalk has been tested using modulators of both pathways. Finally, our data demonstrated that the Notch pathway has a positive effect on RIP140 expression. Further experiments such as ChIP assays are in progress to clarify the molecular mechanisms of the interplay between RIP140 and the Notch pathway.

P120

Uncovering the Syk signaling network in breast cancer cells from phospho-proteomics data

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The Syk tyrosine kinase is a well-characterized actor of immune cell signaling with an onco-suppressive function in mammary epithelial cells, but the molecular mechanisms underlying its role in breast cancer remain unsolved. The identification of realistic cell signaling networks from experimental data is a key objective of computational biology research when mechanistic information is lacking. Here, we report the generation of an interaction-based network of signaling pathways controlled by Syk in breast cancer cells. Pathway enrichment of the Syk targets, previously identified by quantitative phospho-proteomics, confirmed that Syk is engaged in cell adhesion, motility, growth and death. Using the components and interactions of these pathways, we assembled a comprehensive network covering Syk signaling in breast cancer cells. To generate in silico hypotheses on Syk signal propagation, we developed a method to rank paths between Syk and its targets. To improve the selection of biologically relevant paths, we annotated the network according to the experimental datasets and applied a random walk process to better estimate the importance of individual interactions. Searching for near-shortest paths toward selected Syk targets in this weighted network leads to the identification of specialized subnetworks of Syk signaling. Molecular and cellular biology experiments allowed to discriminate between candidate mechanisms that underlie the impact of Syk on the regulation of cortactin and ezrin, two proteins involved in cell adhesion and motility. The Syk network was further extended with the results of our biological validation. (supported by Plan Cancer ASC14021FSA).

P121

Notch pathway in EGFR-driven lung tumorigenesis and resistance

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Lung cancer is the leading cause of cancer-related death worldwide. The major problem to fight against cancer is the resistance of cancerous cells to therapies. So, identifying new pathways involved in the biological processes necessary for the survival of lung tumoral cells is therefore paramount for developing new clinical approaches to prevent disease recurrence. The development of targeted therapies for patients with altered activity of EGFR has improved substantially life expectancy for these subtypes of patients, although therapy resistance appears in 30 to 50% of cases.

We have recently demonstrated, that K-Ras^{G12V}-driven NSCLCs are addicted to the Notch pathway in transgenic mice model. Then inhibition of the Notch pathway seems to be promising in KRas tumors but could it also be the case in other type of lung cancer as in EGFR mutated tumors? In this project, we are studying the involvement of the Notch pathway in tumorigenesis induced by the EGFR mutant L858R. We have shown, *in vitro*, that expression of the EGFR oncogene induced an activation of the Notch pathway and that the inhibition of this pathway blocked the proliferation induced by the oncogene. We also performed *in vivo* studies and observed an activation of the Notch pathway in the murine EGFR $^{T790M/L858R}$ bronchial tumors. Moreover, the inhibition of the Notch pathway blocked the lung tumorigenesis suggesting that the Notch pathway is also involved in tumorigenesis induced by mutated EGFR. Notch having been shown to be involved in drug resistance in several cancers, we are now studying the effect of combination of Notch and EGFR inhibition sensitive and resistant cell lines and we have shown that the combination was more efficient than each inhibition alone in both sensitive but more interestingly also in resistant cells. These results suggest that Notch inhibition could have a potential interest to treat EGFR mutated lung tumors.

P122

Translational control in cancer stem cells

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Translation of mRNA into protein is the final step in the gene-expression pathway, which mediates the formation of the translatome from genomic information. Several mechanisms, such assignaling pathways, translation factors availability, alternative open reading frame and alternative initiation pathways account for real time translatome remodeling. Moreover, an emerging concept suggests that ribosome is heterogeneous and can be "reprogrammed". These "specialized ribosomes" would preferentially engage certain mRNA at the expense of others and therefore drive cell phenotype and favor cell adaptation. From a more pathological standpoint, many studies have correlated deregulation of both translation machinery composition and activity with cancer initiation and evolution.

Despite significant advances in diagnostics and therapeutic treatment, colorectal cancer (CRC) remains a major cause of mortality throughout the world and occurrence of metastasis represents the primary cause of death. Metastasis process, chemoresistance and tumor recurrence is powered by a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity: the cancer stem cells (CSC). CSC might well represent a perfect model to test whether the translation apparatus takes an active part in tumor initiation, progression, and metastasis.

Our goal is to demonstrate that protein synthesis is differentially regulated depending on cancer cell subpopulation and determine whether ribosomal heterogeneity could impact tumoral evolution and plasticity.

Studying the translational control in CSCs will have great benefits for our understanding of both cellular biology and clinical medicine and eventually lead to the development of new therapies able to target CSCs preventing recurrence and metastasis.

P123

Overexpression of flotillins, new marker of metastatic development, disrupts Cadherin-mediated intercellular adhesion

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Adherens junctions (AJs) are one of the four major types of intercellular adhesion structures, playing a critical role in tissue homeostasis. AJs formation is mediated by adhesive transmembrane glycoproteins called cadherins. Perturbation of cadherins-complexes is associated with cancer cell invasion leading to metastatic development.

We identified flotillins 1 and 2 as new regulatory partners of cadherins, essential for the formation of AJs in epithelial cells (Guillaume et al, J Cell Science 2013). These ubiquitous and highly conserved proteins oligomerize to form molecular scaffolds in cholesterol-rich membrane microdomains. Recently, the overexpression of flotillins has been observed in many invasive carcinomas and is associated with a poor prognosis. How overexpressed flotillins participate in the acquisition of invasive properties by tumor cells remains unknown.

To answer this question, we stably overexpressed both flotillins in non-tumoral cells from mammary epithelial origin (MCF10A and NMuMG) and examined the consequences on cadherin-related processes. Using a cellular aggregation *in vitro* assay, we show that the cadherin-mediated intercellular adhesion was strongly impaired in our cellular models overexpressing flotillins (MCF10A-F1F2 and NMuMG-F1F2) compared to parental cells. We detected a switch from E- to N-cadherin expression (at the mRNA and protein levels) associated with deep changes in the morphology of cadherin-mediated cell-cell contacts. MCF10A-F1F2 and NMuMG-F1F2 cells clearly lost their epithelial morphology and exhibit an increase in their invasive properties in 3D matrix *in vitro*, suggesting they undergo an epithelial to mesenchymal transition (EMT).

To conclude, our study demonstrates that flotillin-overexpression is sufficient to induce invasive properties, notably by altering cadherin-mediated intercellular adhesion, and brings out flotillins as new potential cancer therapeutic-targets.

P124

Human endogenous retrovirus: a new 'multi-face' target for immunotherapy

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Human endogenous retroviruses represent about 8% of the human genome and are subdivided in different subfamilies. The most recent family, HERV-K is described as the most active in many pathologic contexts especially in cancers such as colorectal cancer or breast cancer.
Indeed, HERV-K protein expression is observed in many cancer cell lines and biopsies but its exact role is not well known. However, recent works showed that it was involved in the tumorigenesis, cell transformation and metastasis of many cancers.
Melanoma is the most dangerous type of skin cancer associated with a poor prognosis and low survival. HERV-K (HML-2) mRNA expression had been observed in a high percentage of melanoma cancer cell lines and human biopsies.
We have developed a fully human antibody (IgG1) HA-137 able to specifically bind the HERV-K transmembrane envelope protein (TM). Since HERV-K envelope proteins reach the cell membrane, we speculate that it could be considered as cancer-associated neo antigens targeted by HA137.
Using HA137, our preliminary data showed that HERV-K TM expression is heterogeneous among melanoma cancer cell lines.
However, HA137 displayed promising anti-tumor abilities. It inhibited cell proliferation suggesting that HERV-K is also involved in the survival and proliferation of cancer cells. In addition, we demonstrated that HA137 is also able to eliminate cancer cells through ADCC mechanisms *in vitro*.
Our results strongly suggest that HERV-K TM represent a very promising and innovative target for direct immunotherapy. Furthermore, since it had been suggesting that HERV-K TM might play a role in the anti-tumoral immune response impairment because of its immunosuppressive abilities, we also speculate that HA137 may counteract this immune break and modulate the tumoral microenvironment to enhance antitumor response.
This project is supported by GSO (Emerging Project Program)

P125

Sortilin controls the EGFR internalization and limits the tumor growth

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In normal cells, tyrosine kinase receptors such as the Epidermal Growth Factor Receptor (EGFR) drive the microenvironment messages into the cells and induces homeostatic signals including cell proliferation, migration and survival. Hence, the rapid internalization and degradation of the EGFR are under a tight spatial and temporal control to limit the proliferative signaling and maintain the cell integrity. In cancer cell, EGFR trafficking aberrations can lead to cancer progression and widely affect the therapeutic response. Because multi facets of EGFR trafficking remain unresolved and that EGFR internalization represents a crucial step for signal termination, we tested the role of Sortilin, a member of the Vps10 proteins in the EGFR regulation after ligand induced EGFR internalization. Here, we show that the loss of Sortilin in tumor cells enhances the cell proliferation by sustaining the EGFR signaling notably at the cell surface and promotes consequently the tumor growth. In lung cancer patients, high expression of Sortilin is correlated with a better survival. The present study reveals for the first time, that the Sortilin is a new regulator of EGFR intracellular trafficking by controlling its internalization to limit the tumor growth. Taken together, our results heighten the attention on protein trafficking in cancer, and shed the light on the Sortilin that might serve as novel prognostic biomarker in cancer.

P126

Rôle of tuft cells during intestinal tumorigenesis

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Sixty years ago, ultrastructural observations of the gastro-intestinal tract allowed the morphological identification of tuft cells. Until their recent characterization by our group, tuft cells have been shown to express cellular markers such as DoubleCortin-Like Kinase 1 (Dclk1), which was initially described as putative quiescent stem cells. Interestingly, several reports also identified Dclk1^{+ve} cells in early adenomatous intestinal lesions, sharing with tuft cells from the healthy tissue, all the known tuft cells markers. Importantly these tumoral « tuft-like cells » have been described in mouse and human lesions.

This project will focus on the intestinal tuft cells capacities to promoting initiation and progression of tumorigenesis. We will investigate:

1 - Dclk1^{+ve} cells status: Tumor Initiating Cells vs Tumor Propagating Cells. To determine if Dclk1^{+ve} cells are TIC, we used a mouse model related with intestinal tumorigenesis devoid of tuft cells [Apc$^{\Delta 14/WT}$; Pou2f3$^{KO/KO}$]. We have showed that if tumorigenesis occurs without tuft cells, the number of intestinal lesions is significantly decreased. As complementary experiment, Pou2f3 deficient mice will be challenged with the well-established AOM-DSS treatment, which induce carcinogenesis within the large intestine, thus being more relevant for CRC.

2 - How tuf cells could promote tumorigenesis. We are performing a transcriptomic analysis and an immunophenotyping on tumors Apc$^{\Delta 14/WT}$and Apc$^{\Delta 14/WT}$; Pou2f3KO/KO.

Recently, we have highlighted that tuft cells are able to secrete alarmins (IL25) during Th2 immune response. So, we suggest that microenvironment could induce cytokines-secreting tuft cells and so, promote tumor development.

P127

The role of primary cilia in colon homeostasis and tumor development

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Glycylation, a posttranslational modification of microtubules, is crucial in the maintenance of primary cilia. We previously identified an unexpected role of the tubulin glycylase TTLL3 in the regulation of colon homeostasis and tumorigenesis. Specifically, we observed a decreased number of primary cilia in mice deficient for the glycylase TTLL3, which is the only glycyclase expressed in the colon. TTLL3-/- mice display no obvious abnormalities in the steady state. However, when exposed to chemically induced colon carcinogenesis, TTLL3-/- mice are more susceptible to tumor formation. Importantly, TTLL3 expression levels were significantly downregulated in human primary colorectal carcinomas and metastases as compared to healthy colon tissue, suggesting a link between TTLL3 regulation of primary cilia and colorectal cancer development. This is supported by our recent observation that the number of primary cilia decreases during chemically induced colon carcinogenesis in mice. Notably, we discovered that primary cilia in the colon are mostly expressed by fibroblasts. To better characterize the role of primary cilia in murine colon, we now study the consequences of a complete loss of primary cilia in intestinal fibroblasts. For this, we study two independent ciliary conditional knockout mice, kinesin-3A (Kif3A) and intraflagellar transport 88 (Ift88), both essential for cilia formation. Specific deletion in intestinal fibroblasts is obtained by crossing with colVI-cre-transgenic mice. We are presently analyzing those mice for altered colon homeostasis and altered susceptibility for induced colon carcinogenesis. In addition, we aim to understand the underlying mechanisms.

P128

Factors produced by aggressive breast cancer cells dictate their interactions with mesenchymal stem cells through chemokine production

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Recent studies have highlighted the potential role of mesenchymal stem cells (MSC) in cancer growth and metastasis. The aim of this work was to understand whether the aggressiveness of breast cancer cells could affect the type of interactions of MSC with cancer cells, in particular through the release of chemokines by MSC. By treating MSC with the conditioned medium of metastatic MDA-MB-231, or non-metastatic MCF-7 breast cancer cells, we observed that a number of chemokines were differentially produced by MSC. We have analyzed the mechanisms underlying the regulation of chemokines in MSC. We have shown that stimulation of NF-kB pathway played a central role in this phenomenon and identified the factors released by metastatic cancer cells underlying this phenomenon. We propose a model in which MSC cooperate with metastatic breast cancer cells to promote their aggressiveness.

P129

Role of Dock5 in the microtubules-dependent stabilization of the sealing zone in osteoclasts

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Centre de Recherche en Biologie cellulaire de Montpellier

Bone metastases are a frequent complication of cancers that result in pain and pathological fractures. To overcome the unfriendly nature of bone, tumor cells recruit resident cells to enlarge the bone cavity and create a more suitable space for growth. In osteolytic metastases, tumor cells secrete growth factors that enhance osteoclast-mediated bone resorption. It results in the release of bone-trapped growth factors which in turn stimulate tumor growth in a "vicious circle". Inhibiting osteoclast resorption could interrupt this circle and be an alternative to current treatments that induce clinical side effects by reducing the osteoclast number and therefore affecting their interaction with osteoblasts and bone formation. Osteoclast function is dependent on a podosome-rich structure stabilized by acetylated microtubules, the sealing zone, which attaches tightly the osteoclast to the matrix creating a favorable acidic microenvironment for bone degradation. We showed that the guanine exchange factor, Dock5, is necessary for osteoclast function. Indeed, *Dock5* genetically deleted osteoclasts are not able to assemble podosomes into the sealing zone and have a dramatically impaired resorbing activity leading to a higher bone density in mice. Interestingly, these osteoclasts show a lower (1) level of acetylated tubulin and (2) number of osteoclasts with long acetylated microtubules. More, *Dock5* knock out reduces the length and duration of microtubule growth phases whereas their growth speed remains unaffected, as measured by tracking the microtubule plus end-binding protein EB3-GFP we expressed in osteoclasts. To understand the molecular mechanisms driving the microtubule-dependent podosome organization into the sealing zone, we performed proteomic analyses with Dock5 as bait in osteoclasts. We found Memo1, which is involved in microtubules regulation, as a partner for Dock5 and characterized its role in sealing zone formation using siRNA and surexpression tools.

P130

La tension membranaire comme rapporteur de l'activité du suppresseur de métastase CD82/KAI1 dans le cancer du sein

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Centre de Biochimie Structurale

La tétraspanine CD82/KAi1 est un des rares produits de gènes suppresseurs de métastases. Elle agit en bloquant la dissémination métastatique grâce à sa liaison au récepteur Darc exprimé sur les cellules vasculaires, en rendant le microenvironnement incompatible à la survie des métastases et en régulant de nombreuses fonctions cellulaires telles que l'adhésion, la migration, l'endocytose ou la transition épithélio-mésenchymateuse. De façon intéressante la plupart de ces fonctions sont aussi connues pour être régulées par la tension membranaire. Celle-ci résulte des forces de liaison des lipides entre eux et des forces qui connectent la membrane au cytosquelette sous-jacent, notamment via des protéines d'ancrage telles que l'ezrine. Par ailleurs, CD82/Kai1 pourrait être liée à l'actine via la tétraspanine CD81 ou les protéines partenaires de la famille EWI, qui lient l'ezrine. Notre hypothèse est donc que CD82/Kai1 pourrait agir comme suppresseur de métastases par un effet sur la tension membranaire. Nous présenterons dans ce poster les premières mesures de la tension membranaire en étirant des tubes membranaires par spectrométrie de force à l'aide d'un microscope à force atomique.

P131

SOX9, a tumor suppressor that controls the oncogenic Wnt/ß-catenin signaling in the colon.

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The activity of the SOX9 transcription factor is frequently decreased in colorectal cancer due to inactivating mutations and/or ectopic expression of the MiniSOX9 variant, a dominant negative inhibitor of SOX9. We identified a heterozygous inactivating mutation of SOX9 (L142P) in the DLD-1 colon cancer cell line and we show that a doxycycline inducible expression of the wild SOX9 in these cells significantly reduces the cell growth, the colonospheres development, the activity of the oncogenic signaling pathway Wnt/beta-catenin and the expression of c-myc oncogene. Furthermore, we show that SOX9 inhibits the development of tumors and metastasis in mice grafted with colon cancer cells expressing a doxycyclin induced SOX9. These observations indicate a tumor suppressor activity for SOX9 in intestinal epithelial cells. Nevertheless, we show that this tumor suppressor activity does not require SOX9 transcription factor function but is rather due to an interaction of SOX9 with nuclear ß-catenin resulting in an inhibition of the activity of the Wnt/beta-catenin signaling pathway. Conversely, we show that siRNAs targeting SOX9 also inhibit the growth of both DLD-1 and HCT116 cells, thus suggesting that a critical level of active endogenous SOX9 is needed to maintain the growth of colorectal cancer cells.

P132

Discoidin Domain Receptors (DDRs) are involved in Renal Cell Carcinoma EMT

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Renal Cell Carcinoma are highly metastatic tumors with 10% survival rate at 5 years. Extracellular matrix components such as fibronectin or collagen are implicated in cancer metastasis. In carcinoma collagens bind two families of receptors, integrins and Discoidin Domain Receptors (DDRs). There are two DDRs, DDR1 and DDR2. DDR1 is expressed mainly in epithelial cells and DDR2 in mesenchymal cells. Both are expressed in Renal Cell Carcinoma.

In order to study the role of these receptors in Renal Cell Carcinoma development we treated the mouse Renal Cell Carcinoma cell line Renca with collagen and found a profound phenotypic change from epithelial to elongated cells. In vitro assays showed an increase in cell migration in presence of collagen without affecting cell proliferation and adhesion. All these data suggest that collagen induces Renca cell epithelial to mesenchymal transition (EMT).

Signaling pathway studies showed activation of long lasting Src and Erk activation, without affecting FAK phosphorylation suggesting a major implication of DDRs in collagen inducing Renca cell activation.

DDR1 and DDR2 are expressed in Renca cells and are found associated at cell-cell junctions. siRNA inhibition of these receptors emphasized a specific role of DDR in maintenance of cell-cell contacts and activation of these receptors inhibited these contacts and induced the elongated cell phenotype. Consequently, DDR1 and DDR2 silencing and collagen activation of Renca cells decreased E-cadherin and beta-catenin expression, 2 hallmarks of EMT. Moreover, transcription factors implicated in EMT, such as Zeb2 and Twist1, were upregulated when Renca cells were stimulated with collagen.

In conclusion, in absence of collagen activation, DDR1 and DDR2 have a role in maintenance of Renca cell-cell junctions. When these receptors are activated by collagen Renca cells undergo EMT, lose their junctions and migrate more actively.

P133

Role of store-operated calcium channels in glioma

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Gliomas are primary brain tumors whose most aggressive and most lethal form is glioblastoma multiforme. The current standard therapy of glioblastoma is safe maximal resection followed by concurrent radiotherapy and chemotherapy with temozolomide (TMZ) and subsequent TMZ treatment. Despite multimodal treatment, more than 90% of patients have recurrence of the tumor and the average life expectancy does not exceed 15 months. Within the tumour, a cell subpopulation called glioblastoma stem cells, that shares some intrinsic properties with normal stem cells, are more resistant to radiation and chemotherapy and therefore may be responsible for the tumor relapse.

The Store Operated Calcium Channels (SOCs) are ion channels that transduce signals from the microenvironment by supporting a sustained calcium entry. Previous studies highlighted a critical role for these channels in several types of cancers. In glioblastoma, transcriptomic analysis unveiled a major role of calcium signaling pathways and demonstrated an overexpression of STIM1 protein, the calcium level sensor of the endoplasmic reticulum and activator of SOCs.

In our ongoing studies, we found that C6, U87, GL261 glioma cell lines as well as stem cells derived from human glioma express the proteins that build-up SOC-type channels and have calcium entries. Pharmacological inhibition of SOCs using YM-58483 and SKF-96365, dose-dependently reduces proliferation and stemness (assessed by the ability to form spheres) of GL261, C6 and U87 cells. Studies are underway for the cells derived from patients.

Our results identify SOCs as major actors for growth and stemness maintenance in glioblastoma.

P134

The anti-leukemic drug nilotinib inhibits metastatic properties of colorectal cancer cells by targeting the receptor tyrosine kinase DDR1

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Clinical-approved drugs designed to target well-defined oncogenes may be of broader clinical interest through off-target-dependent mechanisms. Accordingly, we observed that the tyrosine kinase (TK) inhibitor nilotinib, developed to target imatinib-resistant BCR-ABL oncoprotein in chronic myeloid leukemia, also inhibits invasive properties of colorectal cancer (CRC) cells. Remarkably, nilotinib strongly reduces liver metastasis formation following injection of CRC cells in the spleen of nude mice. As ABL is not deregulated in CRC, we speculated the involvement of an alternative target. A recent chemical-proteomic analysis identified DDR1 as the highest affinity target of nilotinib (Rix *et al.*, Blood, 2007) suggesting that this protein could mediate nilotinib activity in CRC cells. Consistent with this hypothesis, our data demonstrate that DDR1 is abundantly expressed in CRC and promotes invasive and metastatic properties of CRC cells. Importantly, this pro-invasive function of DDR1 requires its TK activity. We next demonstrated that the nilotinib responses observed in CRC are largely mediated through inhibition of DDR1 as the expression of a nilotinib-resistant DDR1/T807I receptor counteracts all the inhibitory effects of this drug in CRC cells. The clinical relevance of these observations was supported by transcriptomic data demonstrating that the level of DDR1 expression is associated with a shorter relapse free survival and by biochemical analyses showing that DDR1 catalytic activity is highly increased in metastatic nodules compared to the primary tumor of the same patient. Additionally, phosphoproteomic analyses revealed the RAS independent nature of DDR1 signaling and pointed BCR as an essential DDR1 substrate for its pro-invasive activity. Altogether, these data suggest that the targeting of DDR1 by nilotinib may be of therapeutic value in metastatic CRC.

P135

High-throughput detection of clinically targetable alterations using next-generation sequencing

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Next-generation sequencing (NGS) has revolutionized the therapeutic care of patients by allowing high-throughput and parallel sequencing of large numbers of genes in a single run. However, most of available commercialized cancer panels target a large number of mutations that do not have direct therapeutic implications and that are not fully adapted to low quality formalin-fixed, paraffin-embedded (FFPE) samples.
Here, we designed an amplicon-based NGS panel assay of 16 currently actionable genes according to the most recent recommendations of the French National Cancer Institute (NCI). We developed a panel of short amplicons (<150 bp) using dual-strand library preparation. The clinical validation of this panel was performed on well-characterized controls and 140 routine diagnostic samples, including highly degraded and cross-linked genomic DNA extracted from FFPE tumor samples. All mutations were detected with elevated inter-laboratory and inter-run reproducibility. Importantly, we could detect clinically actionable alterations in FFPE samples with variant allele frequencies as low as 1%. In addition, the overall molecular diagnosis rate was increased from 40.7% with conventional techniques to 59.2% with our NGS panel, including 41 novel actionable alterations normally not explored by conventional techniques.
Taken together, we believe that this new actionable target panel represents a relevant, highly scalable and robust tool that is easy to implement and is fully adapted to daily clinical practice in hospital and academic laboratories.

P136

Identification of non-competitive inhibitors of cytosolic 5'-nucleotidase II: implication in cancer treatments resistance.

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The cytosolic 5'-nucleotidase II (cN-II) catalyzes the hydrolysis of purine nucleoside 5'-monophosphates (NMP) into nucleosides and inorganic phosphate in order to regulate the intracellular nucleotide pools. In addition, this enzyme has been identified as an important therapeutic target in hematological cancers. Indeed, the enzyme activity has been recently correlated with resistance to several chemotherapies in relapsed patients. In this respect, we applied an innovative approach using *in silico* methods in order to design new and potent inhibitors against this enzyme. First, a chemical library of 300 fragments was screened by NMR using the recombinant enzyme and led to the identification of two sub-groups of fragment binders. These cN-II ligands were further selected according to their capability to inhibit the main enzyme activity. A fragment growing strategy guided by molecular docking was considered starting from adenine and bi-aryl moieties. This allowed the building of new compounds based on their structure-activity relationships. Chemical synthesis of about 20 compounds was achieved by including a structural diversity to better meet the conformational degrees of freedom of the final compounds. Among them, five compounds issued from assembled fragments were able to induce a strong inhibition of the 5'-nucleotidase activity *in vitro*, and the most potent ones were identified as non-competitive inhibitors. Biological evaluation in cancer cell lines showed synergic effect with existing anticancer drugs. Structural studies using X-ray crystallography could bring new insights in the inhibition mechanism by which these compounds are perturbing the quaternary structure organization of the enzyme. Altogether, the strategy developed herein allowed a follow-up, step by step, of the drug discovery process leading to new original non-competitive inhibitors against cN-II.

P137

Treating cancer as an infectious disease with antibiotics

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Cancer stem cells (CSC) are defined as the driving force of tumorigenesis and the seeds of chemoresistance and metastasis. As such, selective targeting of CSC could be the "Achille's heel" of chemo-resistant tumors since it may prevent both tumoral relapse and secondary tumor formation. CSCs are often cultured in non-adherent conditions in order to form microtumor-like spheroids. This cell culture model is often used as a surrogate to evaluate tumorigenic potential. In a recent publication, we have shown that Penicillin-streptomycin cocktail, routinely used in monolayer cell culture to prevent bacterial contamination, suppresses sphere forming ability in suspension culture. We identified streptomycin (SM) as the source of this inhibition and recapitulated its effect in various colorectal cancer cell lines. SM treatment decreases CSC pool, triggers massive apoptosis, and "surviving cells" become incapable to self-renew when passaged in SM-free medium. Consistently, our last results show that SM impacts "sphere nucleation" -which relies on CSC phenotype- rather than "sphere growth", fueled by highly proliferative progenitor pool. SM belongs to the aminoglycoside (AG) family, which interferes with prokaryotic protein synthesis by binding to bacterial ribosomal RNA. Remarkably, sphere forming inhibition was not observed with other AG. This suggests some sort of specificity that would directly relate to SM structure. Our latest results with SM derivatives suggest that the underlying mechanism involves SM binding with "specific off target" eukaryotic RNA(s) and subsequent alteration of RNA(s) processing or function. Consequently, SM can be modified to improve this interaction and modulate its selectivity. The use of antibiotic as RNA ligand capable of impairing cancer stem cells abilities regardless of genetic status is a novel concept that has not yet been tackled in cancer biology. If confirmed, this could lead to the development of innovative therapeutic approaches.

P138

Focal Adhesion Kinase (FAK) : key protein in Pancreatic ductal adenocarcinoma progression

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Pancreatic ductal adenocarcinoma (PDAC) remains a deadly cancer. One of the PDAC hallmarks is to be composed for 80% of a fibrotic stroma. Cancer-Associated Fibroblasts (CAFs) are the most abundant stromal cells, and promote tumorigenesis and metastasis. Notably, by producing large amounts of extracellular matrix (ECM) proteins and ECM remodeling enzymes, CAFs generate ECM tracks used by tumor cells to invade. On another hand, activation of the Focal Adhesion Kinase (FAK), a protein tyrosine kinase, is involved in connective tissue remodeling by normal fibroblasts.

In human pancreatic tissue, we identified that FAK activity expressed by fibroblastic cells is very low in normal tissues and highly increased in CAFs. FAK increased activation in CAFs correlates with TNM stage T3 (tumor staging in which cancer has grown outside the pancreas into nearby surrounding tissues). Pharmacological and genetic FAK inhibition within activated fibroblasts results in a significant decrease of tumor cell invasion both *in vitro* and *in vivo*. Indeed, spheroid invasion assay composed of pancreatic tumor cells and fibroblasts expressing either FAK-Wild-Type (FAK-WT) or FAK-Kinase-Dead (FAK-KD) shows that FAK inhibition specifically within fibroblasts reduces fibroblast and tumor cell invasion into matrix. Moreover, orthotopic syngenic co-grafting of pancreatic tumor cells with either FAK-WT or FAK-KD fibroblasts show that FAK inactivation within fibroblasts dramatically decreases lung metastasis. Finally, pharmacological FAK inhibition in primary cultures of CAFs from PDAC patients diminishes collagen I and LOXL2 (Lysyl oxidase like 2, enzyme implicated in collagen fiber maturation) expression and deposition.

In conclusion, FAK activity within CAFs is a crucial regulator of CAF-induced tumor metastasis, effect likely due to the formation of collagen tracks used by tumor cells to invade. Thus, targeting FAK activity in PDAC patient appears to be a promising strategy.

P139

p53-independent functions of the MDM2 oncoprotein in metabolism

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The Mouse Double Minute 2 (MDM2) oncoprotein is recognized as a major negative regulator of the p53 tumor suppressor. We recently showed that MDM2 is recruited to chromatin independently of p53 to regulate a transcriptional program implicated in amino acid metabolism and redox homeostasis (Riscal *et al*., Mol Cell 2016). Genome-wide studies highlight an important role for members of the ATF family of transcription factors in tethering MDM2 to its target genes implicated in serine metabolism. MDM2 recruitment to chromatin is a tightly regulated process that occurs during oxidative stress, serine/glycine deprivation and is modulated by the pyruvate kinase M2 (PKM2) metabolic enzyme. Moreover, interfering with endogenous MDM2 and exogenous serine availability impaired the channeling of glucose-derived carbon sources into glutathione (GSH) metabolism, impacting on the redox state and growth of cancer cells. In the meantime, we demonstrated that MDM2 functions in metabolism extend beyond these chromatin-associated activities and that a significant fraction of MDM2 protein also localizes inside mitochondria independently of p53. I will present our latest unpublished data showing how mitochondrial MDM2 controls the activity of the electron transport chain (ETC) and the in vivo relevance of these mitochondrial functions of MDM2 in genetically engineered mouse models. Collectively, our data illustrate a previously unsuspected function of the MDM2 oncoprotein in metabolism of both normal and cancer cells.

Posters - Axis 2
« Genome Dynamics and Cancer »

P201

DNA methylation dynamics and its functional impact during the early stages of intestinal tumorigenesis

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Cancer initiation and progression represent the outcome of the progressive accumulation of genetic and epigenetic alterations. Global changes in the epigenome are now considered as a common hallmark of malignancies. However, most of our present knowledge represents the result of the comparison between fully established malignancies and their surrounding healthy tissue. Such comparison is not informative about the epigenetic contribution to the very early steps of cancer onset. By performing DNA methylation and gene expression profiling of *Lgr5*$^+$ intestinal stem cells we found that part of the phenotype resulting from the constitutive activation of the Wnt pathway upon *Apc* loss is acquired via differential epigenetic regulation of key biological processes controlling the balance between self-renewal and differentiation. In particular, we found that intestinal stem cells become less responsive to the pro-differentiation stimuli exerted by the surrounding microenvironment via the BMP/TGF- signaling. This altered responsiveness reduces the fate determination of intestinal stem cells toward terminal differentiation resulting in the accumulation of those cells. By using conditional genetic *ex vivo* models (intestinal organotypic cultures) we found part of these oncogenic effects to be reversible via the modulation of the machinery responsible for *de novo* methylation of the DNA.
Overall, this work confirms that the epigenetic remodeling is an early event in tumorigenesis that is necessary for cells to acquire their oncogenic potential. The functional impact of our findings on cancer initiation *in vivo* is currently under investigation.

P202

Loss of 4E-BP1-mediated translational control favors aberrant replication in pancreatic cancer.

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We recently showed that human PDAC (pancreatic ductal adenocarcinoma) and Kras-driven PDAC mouse models harbor a progressive loss of expression of the translational repressor 4E-BP1 from low grade to advanced lesions, suggesting a dysregulation of mRNA translation during PDAC development.
To identify the subset of mRNAs whose translation is sensitive to 4E-BP1 loss, we defined the 4E-BP1-dependent translatome (genome-wide pools of translated mRNA) of pancreatic cancer cells. The most regulated genes were involved in DNA replication, including *RRM2* and *CDC7*. Consistently, mTOR inhibition specifically decreased S-phase entry of pancreatic cancer cells *in vitro* while ablation of 4E-BP1 rendered these cells insensitive to treatment and allowed efficient replication.
The sensitivity of 4E-BP1 KO animals to pancreatic cancer initiation was analyzed using cerulein stimulation, which causes pancreatitis and metaplasia onset. Upon injury, 4E-BP1 deleted mice exhibited more pre-cancerous lesions than their WT counterpart. However, pancreatic tissue regeneration was much faster in 4E-BP1 KO mice, attested by an increased proliferation rate (Ki67), but also a higher replicative stress (γH2AX), corroborating our *in vitro* analysis.
Other studies suggest that sustained replication is a mechanism of chemoresistance in PDAC. Our data provide evidence that 4E-BP1 loss leads to this phenotype, suggesting a link between translation dysregulation and resistance to gemcitabine in PDAC. They also highlight the therapeutic potential of combining actual treatment with eIF4F inhibitors.

P203

Transcriptional mechanisms mediated by Fra-1 and Fra-2 in Triple Negative Breast Cancer

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Fra-1 and Fra-2 belong to the FOS family of oncoproteins that heterodimerize with other partners, such as the JUN family members, to form the AP-1 transcriptional complex (Activator protein 1). They are often overexpressed in several types of epithelial cancers among which the highly aggressive Triple Negative Breast Cancer (TNBC). Indeed, targeted therapies for TNBCs are still lacking, which justifies the undeniable need to better define the molecular mechanisms driving their aggressiveness.
Despite their well-characterized role in tumorigenesis, very little is known about Fra-1 and Fra-2 transcriptional mechanisms allowing them to differentially control the expression of their target genes.
Using chromatin immunoprecipitation followed by deep-sequencing (ChIP-seq), we were able to (1) identify the complete set of binding sites for Fra-1 and Fra-2 in a TNBC reference cell line, MDA-MB231, (2) characterize their binding sites by analyzing the histone modification status and (3) study their interaction with other AP-1 members such as c-Jun. Analyses of these data revealed a large overlap between Fra-1 and Fra-2 binding sites and highlighted their preferential binding to regions having enhancer characteristics. Using transcriptomic data already available in our laboratory as well as data provided by Fantom5 consortium, we were able to assign enhancers bound by Fra-1 and Fra-2 to their putative target genes (collaboration with C. Lecellier and A.M. Maqbool, IGMM). Among the genes with the highest fold-changes in the transcriptomic study is TGFB2, which is down-regulated by Fra-1. A ChIP-qPCR approach in the presence or in the absence of Fra-1 underlined a role for Fra-1 in the repression of the transcriptional initiation on the TGFB2 gene. Further mechanistic models are currently being explored using chromosome conformation capture approaches.

P204

A novel mechanism involved for a G-quadruplex ligand-mediated growth inhibition of cancer cells

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G-quadruplexes are « non-canonical » DNA structures that can be stabilized by molecules called G-quadruplex ligands (G4L). These G4L were first found to inhibit telomerase activity in cancer cells, limiting, in this way, cell proliferation. However, it has been recently proposed that some G4L can have anti-proliferative effect through telomerase-independent pathways. The mechanisms by which G4L have telomerase independent effects are currently the subject of an extensive investigation in the field. We are working on a triarylpyridine G4 ligand (named 20A) that promotes DNA damage response (DDR), ROS production, autophagy activation and cell proliferation inhibition. Interestingly, depending on the concentration of the ligand used, 20A triggers either a G2/M phase arrest or cell death.
To explore the mechanisms underlying the cytotoxic effect of 20A, we decided to investigate the role of ROS on 20A-induced cellular responses in HeLa cells. Our results revealed that the addition of antioxidants inhibits the activation of autophagy and DDR, and reduces the G2/M phase arrest induced by the ligand, supporting the idea that ROS are required for the occurrence of such responses. Moreover, inhibition of both ATM and autophagy sensitize HeLa cells to cell death induced by the ligand, suggesting the contribution of DDR and autophagy in the regulation of cell death process. Further studies are in progress to elucidate the impact of autophagy and ROS on the regulation of 20A-induced DDR and cell cycle arrest.

P205

The DNA polymerase Kappa regulated by the USP7 de-ubiquitinase maintains the Chk1 protein level

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The progression of the replication forks is constantly challenged during the S-phase of the cell cycle due to endogenous or exogenous fork barriers (1). Fork blockage is signaled through the activation of ATR/Chk1 checkpoint pathway and can be overcome by specialized DNA polymerases (DNA Pol) recruited at the barrier. The most conserved specialized DNA polymerase (2), the DNA Pol Kappa, can also participate in the signaling of the fork blockage since it is required for fork restart and optimal Chk1 phosphorylation in response to replication stress (3). In addition, we have shown that Pol kappa and Chk1 are partners in nucleus and that protein level of Chk1 is affected by the Pol kappa protein level itself in mammalian cells. This observation led us to explore how Pol Kappa is regulated and we recently found that Pol Kappa is ubiquitinated onto the chromatin. We also identified USP7 as a novel regulator of Pol Kappa, also known to regulate Chk1.

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P206

Chemotherapeutic drugs rapidly alter transcriptional programs in Acute Myeloid Leukemia via the ROS/SUMO pathway

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Acute Myeloid Leukemia (AML) is a group of severe hematological malignancies with dismal outcome, as most patients relapse after initial treatment. Their treatment has little improved for the past 4 decades and principally consists of intensive chemotherapy involving one anthracycline, such as daunorubicin (DNR), and cytarabine (Ara-C), a nucleoside analog.
We have previously shown that the ROS/SUMO pathway following which Reactive Oxygen Species generated by DNR and Ara-C inhibit SUMOylation, a post-translational modification of the ubiquitin family, plays a critical role in the AML apoptotic response to these drugs (Bossis et al., Cell Reports, 2014). Combining proteomic, transcriptomic and genomic studies, we now report that one of the earliest effects of DNR in AMLs is a rapid ROS/SUMO pathway-dependent transcriptional reprogramming, which primarily affects the expression of genes involved in cell death control and inflammation.
At the molecular level, we report that: (i) DNR, and to a lesser extent Ara-C, (as assayed in whole transcriptome analyses) upregulates genes involved in cell death control and inflammation within only 2 hours of treatment, i.e. before chemosensitive cells enter into apoptosis, (ii) concomitantly to transcriptome changes, DNR (as assayed by ChIP-seq) induces a massive decrease in the presence of SUMOylated proteins on chromatin, in particular at gene promoters, which participates in transcriptional activation, (iii) DNR-induced *de*SUMOylation and gene regulation involve Reactive Oxygen Species (ROS) produced by NADPH oxidase and (iv) the most rapidly *de*SUMOylated proteins (as assayed by quantitative proteomics) are primarily transcription factors, transcriptional co-regulators and chromatin organizers, which is consistent with fast induction of transcriptional changes.
Our work thus points to the modulation of chromatin SUMOylation as key for the rapid regulation of genes most likely crucial in AML cell response to chemotherapies.

P207

Atypical heterochromatin controls telomere maintenance

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Alternative Lengthening of Telomere, or ALT, involves telomere maintenance by recombination and is prevalent in a subset of human cancers. The ATRX heterochromatin factor is often inactivated in ALT tumors suggesting a link between ALT and defective heterochromatin. Likewise, abrogation of the SUV39H heterochromatin enzyme in mouse embryonic stem cells induces typical ALT features. Here we explore the impact of heterochromatic activities on telomere maintenance by recombination. At odds with the current model implying an inhibitory role for heterochromatin, we demonstrate that aberrant recombination results from excessive heterochromatin formation at telomeres. Telomeric heterochromatin is mostly enforced by the histone H3 methyl-transferase SETDB1 and this stimulates transcriptional elongation at telomeres and the recruitment of several recombination factors, including BRCA1 and the SMC5/6 complex, critical for ALT maintenance. In mouse embryonic stem cells, disrupting SUV39H or ATRX increases SETDB1 recruitment to telomeres, while SETDB1 knock-down disrupts ALT in human cancer cell lines. Based on these findings, we propose a new model for the epigenetic control of telomere maintenance in mammals.

P208

Efficient role of IgH 3′ regulatory region deficient B-cells in the development of oil granulomas

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Contrôle des réponses immunes B et des lymphoprolifération

Functional B-cells are essential for the formation of oil granulomas. B-cells development is a complex process that involves multiple genic rearrangements (V D J recombination, class switch recombination (CSR) and somatic hypermutations (SHM)). During this process, various signals will direct B-cells towards specialization in distinct cellular subsets (mainly B-1, marginal zone B-2 and follicular zone B-2). All of these steps require a strict control of the expression of the immunoglobulin heavy chain locus (IgH). This regulation is provided by various cis-regulatory elements spread along the locus. The 3' regulatory region (3'RR), which extends for 30 kb and contains 4 transcriptional enhancers, is located at the 3' end of the locus, and is the key element for SHM, CSR and for IgH locus transcription during the mature B-cell stage. The 3’RR is also a potent lymphoma oncogene deregulator. Ongoing recombination and mutation all along B-cell development make the IgH chain locus a hotspot for oncogene translocations marking numerous lymphomas. We investigated if 3’RR-deficient B-cells remain efficient to develop oil granulomas in response to pristine. Oil granulomas are considered as tertiary lymphoid tissues constituted of monocytes, granulocytes, T-cells and B-cells. Their formation is regulated by several cytokines. B-cells expressing an IgH 3’RR-deficient allele were similarly recruited to wild type allele expressing B-cells in granulomas. No differences were observed between 3’RR-deficient mice and control mice for granuloma numbers, cellular composition and ability to express mRNA transcripts for several pro- and anti-inflammatory cytokines. Altogether these results suggest a normal role for 3’RR-deficient B-cells in the development of an acute B-cell-mediated inflammatory response. The 3’RR might be considered as a potential target for anti-lymphoma pharmacological therapy without significant impact on the normal immune and inflammatory networks.

P209

Replication stress and checkpoint response in colorectal cancer

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Colorectal cancer (CRC) is the third most frequent malignancy worldwide. Chemotherapy remains one of the cornerstones of CRC treatment, FOLFOX/FOLFIRI protocols being among the most common CRC chemotherapy regimens. These drug combinations target DNA replication, inducing replication stress (RS). At the cellular level, this RS is managed by the ATR/Chk1 pathway, a major arm of the DNA Damage Response (DDR) network. When activated by RS, ATR phosphorylates its downstream effector Chk1, which spreads the checkpoint signaling throughout the nucleus. The highly proliferative behavior of most cancer cells induces high levels of intrinsic replicative stress, making these cells addicted to ATR/Chk1 checkpoint signaling. Targeting this pathway has been an emerging therapeutic rational in recent years. Overloading and/or inhibiting the checkpoint signaling may thus be efficient in selective killing of cancer cells.
Furthermore, ATR heterozygous mutations are found in a CRC subset. We consequently hypothesized that such mutations could impact the way cells respond to RS. To test this hypothesis, we isolated wild type and heterozygous clones from HCT116 cell line harboring the same mutation in ATR that is found in patients. Corresponding revertant ATR wild-type clones were also engineered from mutants using specific ZFNs.
We showed that the heterozygous mutations affecting the ATR pathway sensitize cells to a variety of therapeutic agents. Moreover, we identified synergistic effects of some of these drugs when coupled to an ATR inhibitor both *in vitro* and *in vivo*. Our goal is now to characterize the molecular mechanisms behind these phenotypes (DNA replication kinetics, checkpoint activation, DNA breaks, apoptosis induction…) to determine how mutations affecting the ATR pathway could modulate the treatments outcomes. Thus, our study may improve therapeutic support for CRC.

P210

A Novel DDR-Dependent function of the DDX19 Helicase in coordination of replication and transcription through R-loops resolution

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DNA damage is a challenge to genome integrity that cells deal with by activating elaborate DNA Damage Response (DDR) pathways so to delay cell division and facilitate DNA repair. Coordination between transcription and replication is crucial to avoid formation of aberrant structures byproducts generated by interference between these two essential cellular processes, notably DNA/RNA hybrids or R-loops, which can generate double strand breaks.
By means of an *in vitro* screen aimed at identifying new DDR genes we isolated Ddx19, a DEAD-Box helicase involved in mRNA export at the nucleopore, as a novel DDR gene candidate. We provide evidence *in vivo* and *in vitro* that DDX19 is a novel helicase required for R-loops resolution in mammalian cells independently of its interaction with the nuclear pore. We have also observed by live cell imaging that Ddx19 relocalizes from the cytoplasmic face of the nucleopore to the nucleus upon DNA damage in a DDR-dependent manner. To better characterize DDX19 relocalization upon treatment with DNA damage agents and in cancer cells, we have recently generated stable cells lines expressing GFP-DDX19 and produced new antibodies against Ddx19. The data presented propose a novel, DDR-dependent function of Ddx19 in DNA repair, independent from its role in mRNA export, in the clearance of aberrant R -loops, whose persistence threatens genomic stability.

P211

Rapid DNA Replication Fork Collapse by Artemis and XPF limits genetic instability upon acute replicative stress

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Replicative stress leads to the accumulation of stalled DNA replication forks, which can in turn leave a fraction of genomic loci incompletely replicated, major hotspots for uncontrolled chromosomal breakage and rearrangement. The endonucleolytic activity of Mus81 is known to limit the occurrence of chromosomal instability by controlling the cleavage of these unresolved loci after prolonged exposure to replicative stress. Here, we unveil that the endonucleases Artemis and XPF can also induce stalled DNA replication forks cleavage at a much earlier time point than Mus81 following acute replicative stress. We found that Artemis and XPF function through non-epistatic pathways all along S and G2 phases of the cell cycle in stressed cells. We also showed that both nucleases are required for a proper cell cycle progression in untreated normal diploid cells, suggesting that they catalyze DNA cleavage at endogenous stalled DNA replication forks. Finally, we found that rapid chromosomal breakage controlled by Artemis and XPF upon replicative stress are important to prevent mitotic segregation defects and transmission of chromosome breaks to daughter cells. Collectively, these results reveal that a Rapid Replication Fork Collapse (RRFC) at stalled forks by Artemis and XPF in response to acute replicative stress contributes to limit chromosomal instability.

P212

Transcriptional deregulation in hepatoblastoma patients points to a new oncogenic mechanism and treatment

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Hepatoblastoma (HB) is the most common paediatric liver cancer that develops on a normal liver (NL). HB diagnosis and tumour staging are based on histopathological assessment of biopsies, radio-imaging and serum alpha-fetoprotein (AFP) levels. Treatment of HB associates cisplatin-based chemotherapy with either the surgical resection of the primary tumour, or liver transplantation. This treatment is effective for 70-80% of patients. However, the outcome is less satisfactory for patients with high-risk tumours, poor response to CT and/or lung metastasis. There is an urgent need for new agents to address the issues of the unresponsive tumours and tumour relapse in HB management.

In this study, we completed polyA+ sequencing of HB and matching NL samples from 24 child patients and several tumoral hepatic cell lines. Four-gene signature distinguishing NL and 3 different sub-groups of tumors was further validated by RT-qPCR in a larger collection of HB samples. We then focused on the most proliferative group that is transcriptomically similar to HB-derived Huh-6 and HepG2 cell lines and exhibits an overexpression of the Fanconi Anemia (FA) pathway. The FA pathway has been previously shown to be responsible for replication-dependent removal of interstrand DNA crosslinks and can counteracts the effects of DNA-damaging drugs such as cisplatin.

Our results showed that the treatment of HB cell lines with a combination of cisplatin and inhibitors of FA pathway had an additive effect on cell survival. FA pathway inhibitors totally blocked the activation of key components of the FA pathway FANCD2 and FANCI, and the formation of nuclear foci of repair. Moreover, a persistence of histone H2AX phosphorylation after FA pathway inhibition was observed confirming the inability of cells to repair DNA damages. In conclusion, FA pathway inhibitors sensitize cancer cells to DNA damages and can be used for HB treatment in combination with cisplatin.

P213

Activity-based protein profiling: a chemical biology strategy to identify epigenetic modulators as novel anticancer targets

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DNA methyltransferases (DNMTs) are epigenetic effectors which catalyze DNA methylation, one of the most studied epigenetic marks. In cancers, together with an overall hypomethylation, a specific hypermethylation of the promoters of the tumour suppressor genes (TSGs) is observed, which leads to their silencing. These abnormal DNA methylation patterns participate to the maintenance and the progression of tumour. Today, the mechanisms that direct this specific hypermethylation of TSG promoters and their transcriptional repression in cancers are still unknown. The aim of my project is to identify the DNMT partners that address specifically these enzymes in TSG promoter regions, since they can constitute new anticancer "epitargets".

To identify such partners we adopted a chemical biology approach based on the use of in-house non-nucleoside DNMT inhibitors (flavonoid and bisubstrate analogues) as bait to trap the DNMT partners. We designed and synthesized about twenty chemical probes, which are then used in an adapted Activity-Based Protein Profiling (ABPP) technique to trap DNMT partners. We evaluated these synthesized chemical probes using various assays available in our laboratory: *in vitro* DNMT assays and a cellular assay measuring the reexpression of a hypermethylated reporter gene. All this allowed us to select the relevant probes to carry out ABPP directly in living cells and involving a bioorthogonal chemistry step to functionalize our probes. This functionalization allowing the DNMT partners purification and then their characterization by proteomic and sequencing analysis in collaboration.

Thus, thanks to the powerful ABPP technique, we applied this adapted method in various cell lines to identify cancer-specific DNMT partners. Those could represent new anticancer targets and could help to specifically target DNMT in cancer cells and prevent the shortcomings of clinically-used DNMT inhibitors from the perspective of secondary effects.

P214

Regulation of SAGA by the TTT co-chaperone in colorectal cancer

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Cell fate decisions are regulated by many different mechanisms. Among them, transcription represents a crucial step and involves several macromolecular complexes that activate or repress specific genes in response to external cues. In the lab, we study how one such complex, the SAGA co-activator, is regulated in the context of colorectal cancer.

Colorectal carcinomas show an overexpression of subunits from the triple T complex (TTT), a highly conserved Hsp90 co-chaperone. Indeed, the TTT complex is composed of three components, TTI1, TTI2 and TELO2, that stabilize and assemble phosphoinositide 3 kinase-related kinases (PIKK). To be active, all PIKKs need to be assembled into functional complexes. Remarkably, the largest subunit of the SAGA complex, TRRAP, belongs to the PIKK family but is the only one lacking catalytic activity. TRRAP was first discovered as a co-activator for the MYC and β-catenin oncogenes, which are two key players in colorectal carcinogenesis. TRRAP is known to activate the transcription of proliferation and stress-inducible genes and is also crucial for the function of another co-activator complex, TIP60.

The aim of this project is to decipher the role of TTT in SAGA and TIP60 assembly, recruitment and activity via the regulated incorporation of the TRRAP subunit. By taking advantage of the CRISPR/Cas9 methodology, we have generated cell lines expressing TELO2 fused with an Auxin-Inducible degron (AID). This construction allows quick, reversible and tunable degradation of TELO2 protein upon auxin treatment. After 6 hours, TELO2 is undetectable by Western blot analysis of HCT116 cell extracts, followed by the down-regulation of TRRAP and mTOR steady-state levels 48 hours later. We are now characterizing the phenotypic consequences of TTT and TRRAP down-regulation on HCT116 cells proliferation and gene expression, to identify the exact contribution of TELO2 to SAGA and TIP60 functions.

P215

The histone H4-K20 methyltransferase SETD8 is a potential therapeutic target in Multiple Myeloma

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Multiple Myeloma (MM) is a malignant plasma cell disease that accumulates within the bone marrow. Despite the recent progress in understanding the pathogenesis of MM, this cancer is still incurable and the identification of new therapeutic strategies is therefore essential. In addition to genetic mutations, recent studies have pinpointed that epigenetic alterations, such as histone/DNA methylation and miRNA expression, are also important players in MM. We show here that a high expression level of the lysine methyltransferase SETD8 is an adverse MM prognosis factor that is associated with poor patient survival. SETD8 is the sole enzyme responsible for the monomethylation of histone H4 at lysine 20 (H4K20me1), which has been linked to chromatin compaction, DNA repair and cell-cycle progression. We found that the compound UNC0379 (a derivative of quinazoline) can specifically inhibit SETD8 and leads to a rapid G0/G1 arrest followed by apoptosis in human MM cell lines (HMCLs). Remarkably, SETD8 inhibition is also efficient on primary cancer cells from patients without significant toxicity on the non-myeloma cells, suggesting a specific addiction of cancer cells to SETD8 activity. Melphalan is an alkylating agent commonly used in MM treatment. Since SETD8 is involved in DNA-damage responses, we investigated the effect of combining low dose of UNC0379 with Melphalan on HMCLs. Our results show that this drug combination enhances the appearance of DNA breaks, as observed by the accumulation of 53BP1 foci and gH2AX signal. Furthermore, GSEA analysis of patients with high *SETD8*expression also shows a significant enrichment of genes involved in DNA repair, MYC-MAX targets and MAPK pathway. Altogether, these results demonstrate the SETD8 importance for MM cells survival/proliferation and suggest that SETD8 inhibition may represent a promising strategy to improve conventional treatment of MM.

P216

Rad18, a promising factor of glioblastoma resistance to therapy?

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Cancer stem cells (CSCs) are thought to be responsible for therapeutic resistance of tumors. CSCs have been implicated in progression and recurrence of the most frequent and aggressive brain tumor - glioblastoma. Within the Cancéropôle Grand Sud-Ouest we have analyzed the expression of a candidate protein, Rad18, in glioblastoma CSCs (gliospheres). Interestingly, gliospheres were characterized by high level of Rad18 expression compared to the same differentiated cells or other cancer cell lines. Similarly, we have found high Rad18 expression in surgical samples of patients with glioblastoma primary tumors (Kermi et al., 2015).
Rad18 is an ubiquitin ligase essentially implicated in the translesion DNA synthesis facilitating the cells to continue the DNA replication even in the presence of DNA damage. We have shown that high levels of Rad18 are sufficient to shut down the DNA damage checkpoint and induce resistance to DNA damaging agents in mammalian cells thus mimicking a natural situation in early Xenopus embryos that display high Rad18 expression and an extraordinary resistance to DNA damage. In addition, we have shown that Rad18 down regulation sensitizes glioblastoma cells to cisplatin (Kermi et al., 2015).
In light of these findings, we hypothesize that high levels of Rad18 may be responsible for glioblastoma resistance to therapy. Our work is now oriented towards understanding the exact mechanisms of Rad18-induced resistance as well as therapeutical applications of our findings. For this purpose, we have generated stable glioblastoma cell lines and CSCs with knock-down of Rad18 as well as mouse cell lines with ectopic expression of Rad18 to understand the mechanisms of cancer resistance to therapy related to Rad18 expression levels. Preliminary results show that Rad18 expression is relevant to resistance of glioblastoma to therapeutic treatments.

Reference:
Kermi C, et al. Dev Cell. 2015;34(3):364-72.

P217

Detrimental exon skipping of immunoglobulin transcripts in plasma cells: towards a new splicing therapy in the treatment of plasma cell tumors.

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Aberrantly rearranged immunoglobulin (Ig) genes are frequent and usually considered sterile and innocuous due to nonsense-mediated mRNA decay. Alternative splicing can however yield internally deleted proteins from such nonproductively V(D)J-rearranged loci.
We show that nonsense codons from variable (V) Igk exons promote exon-skipping and synthesis of V domain-less k light chains (DV-kLCs). The expression of such truncated-Ig (DV-kLCs) impaired plasma cell differentiation and antibody responses. DV-kLCs have intrinsic toxic effects and induce ER stress-associated apoptosis in plasma cells (PCs). Altogether, we identify a "truncated-Ig exclusion" (TIE) checkpoint dampening PC differentiation by eliminating cells expressing non-functionally rearranged Igk alleles. The TIE-checkpoint thus mediates selection of long-lived PCs with limited ER stress supporting high Ig secretion (Srour et al, J Exp Med 2016).
Based on these results, a patent was applied to increase the production of truncated-Ig lacking variable domain using antisense oligonucleotides (AON). This exon skipping therapy could open new avenues for plasma cell neoplasms (including multiple myeloma) treatment.

Keywords: Exon skipping, Immunoglobulin, Antisense oligonucleotides, Splicing therapy

Acknowledgments: This work was supported by grants from Fondation ARC (#PGA120150202338 and SFI20121205821), Ligue Contre le Cancer (comité Haute-Vienne), Comité Organisation de la Recherche sur le Cancer du Limousin (CORC) and Fondation pour la Recherche Médicale.

P218

Role of the transcriptional coregulator RIP140 in hereditary colorectal cancer

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Colorectal cancer (CRC) is a common disorder with familial forms such as Lynch syndrome which exhibit microsatellite instability (MSI) due to loss of function of the DNA mismatch repair (MMR) system. However, some clinically diagnosed families do not exhibit MMR gene alterations (Lynch Like Syndrome or LLS), thus implicating new candidate genes. The regulation of MMR gene expression by the transcription factor RIP140 (that we recently shown to be involved in sporadic colorectal carcinogenesis) was investigated by using different human colorectal and murine cell lines displaying a deregulated expression of RIP140. Our data show that RIP140 regulates the expression of *MSH2* and *MSH6* genes, both at the mRNA and protein levels. Luciferase reporter assays demonstrate that these regulations occur at the transcriptional level. In addition, *MSH2* and *MSH6* gene expression was found significantly correlated with that of RIP140 in a cohort of 396 CRC patients ($p<0.001$). To define the functional consequences of these regulations, we first analyzed the effect of RIP140 on cell sensitivity to different cytotoxic drugs. RIP140 expression was associated with an increased resistance to several drugs including oxaliplatin, 5-fluorouracil and SN38. In parallel, the microsatellite and chromosomal stability is currently being analyzed in cells with altered RIP140 expression. Finally, a frame shift mutation in the RIP140 coding sequence (RIPMSI) which generates a truncated protein has been detected in cells from MSI CRC. The sequencing of tumor DNA from 93 MSI CRC patients confirmed the presence of the RIPMSI mutation in about 15% of the cases. In conclusion, by decreasing the expression of genes implicated in maintenance of genome integrity, the mutation in the RIP140 gene might explain microsatellite instability in familial CRC patients where no MMR gene mutation is found.

P219

Recognition of LINE-1 derived DNA by the cGAS-STING pathway leads to inflammation in Fanconi Anemia

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Chronic inflammation favors tumorigenesis, negatively influencing patient prognosis. Yet, the underlying molecular mechanisms are poorly understood. We will present data showing that increased endogenous retroelement-associated reverse transcriptase activity contributes to induce a pro-inflammatory response in the Fanconi Anemia (FA) cancer susceptibility syndrome. Indeed, thereby generated nucleic acids are recognized through the cGAS-STING pathway and sustain the inflammation. Furthermore, reverse transcriptase inhibitor (RTi) treatment decreases pro-inflammatory cytokine production induced by chemotherapy regimen and in FA cells. We will discuss the involvement of endogenous reverse transcriptase activities in sustaining pervasive chronic inflammation, and the potential use RTi in preventing tumor-inducing inflammation.

P220

Modeling the diversity of genetic regulations in cancers

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Gene expression is tightly controlled to ensure a wide variety of cell types and functions. These controls, whose deregulations are often implicated in oncogenesis, take place at the DNA/RNA levels and are associated with different regulatory regions: promoters, enhancers, untranslated regions, etc. While these regions remain the same for the different cells, the diversity of their responses is ensured by the combination of hundreds of features that can come into play: specific nucleotidic composition, presence/absence of binding sites of specific TFs or RBPs, etc. One today challenge is then to decipher the different DNA features that are responsible for a specific gene expression profile in a specific cell type. Our computational approach is based on two steps. First, a linear model with LASSO penalty is trained to build a gene expression predictor on the basis of sequence features. We then evaluated the performances of our model by computing the correlation between the predicted and observed expression. Depending on the data, we show that the inferred model is not equally efficient for all genes but only fits certain classes of genes with specific genomic features. In a second step, we thus run a classification tree on the results of the linear model to identify these genes that are well or badly fitted by the model. This approach was run on numerous gene expression data of the TCGA database and allowed us to highlight several important features of gene expression control. For instance, basic information like dinucleotide frequency of promoter regions have very high predictive power. We also highlighted several regulations (nucleotide composition and/or regions) specifically associated to certain cancers. Our study provides a framework to study gene regulation and the influence of specific DNA features. As our model is built on personalized data, we now aim at testing the effect of individual genomic variations and nucleotide polymorphisms.

P221

Identification of cellular determinants of replication forks stalling

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During the replication of the genome, the replisome encounters many obstacles that induce replication forks stalling. These impediments activate the S phase checkpoint that leads to the activation of a network of proteins in order to restart the replication forks. Nevertheless, in a normal cellular environment the level of stalled forks is low. By contrast, cancer cells replicate DNA under suboptimal conditions that precipitate the collapse of replication forks. Most of the molecules used in chemotherapy preferentially target cancer cells by increasing the amount of stalled forks to a lethal dose. Unfortunately, cancer cells often become resistant to chemotherapeutic treatments. Our main goal is to uncover cellular determinants of stalled forks formation in particular in response to chemotherapeutic treatment.

To this purpose we are using the iPOND method coupled with mass spectrometry (iPOND-MS) to identify systematically proteins recruited to stalled replication forks. This method allowed us to discover that FANCD2 and FANCI are specifically associated with stalled forks. More recently, we found that the effect of camptothecin on replication forks dynamic is dependent on transcription activity and on WSTF/BAZ1B.

We are now focusing on aphidicolin, an inhibitor of DNA polymerases, and on 5-fluorouracile (5-FU), a drug routinely used in chemotherapeutic treatments with a complex mode of action. Using iPOND-MS, we were able to detect key proteins of forks response to replicative stress such as BRCA1, TOPBP1 and BARD1. If this result was expected for aphidicolin, it was more surprising for 5-FU since it is not clear how it interacts with replication forks. We will validate the best hits using a siRNA-based approach in order to uncover new determinants of replicative stress. The identified candidates could be used in the future as biomarkers of response to chemotherapeutic treatments such as 5-FU.

P222

Synthetic lethal pharmacological targeting of dihydroorotate dehydrogenase and checkpoint kinase 1 in transformed cells

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Our recent data showed that upon knockout of E4F1 transcription factor transformed cells elicited major mitochondrial dysfunctions including a drastic reduction in orotic acid levels. Furthermore, E4F1 controls the transcription of Chk1 kinase and transformed cell survival relies on the coordination of these metabolic and checkpoint activities. Dihydroorotate dehydrogenase (DHODH) is the one mitochondrial enzyme that takes part in the fourth and rate-limiting step of de novo pyrimidine biosynthesis by converting dihydroorotic acid to orotic acid. Reduction in nucleotide pools through DHODH inhibition has been demonstrated to effectively reduce cancer cell proliferation and tumour growth. The current study sought to investigate whether this anti‑proliferative effect could be enhanced by combining Chk1 kinase inhibition. The pharmacological activity of DHODH inhibitor teriflunomide was more selective towards transformed mouse embryonic fibroblasts than their primary or immortalized counterparts and this effect was amplified when cells were subsequently exposed to PF477736 Chk1 inhibitor. Flow cytometry analyses revealed significant cell cycle perturbations along with the conversion of two cytostatic effects into cytotoxicity. Associating these inhibitors also sensitized human triple negative breast cancer cell line SUM159 to dihydroorotate dehydrogenase inhibition. The main characteristic of this effect was the sustained accumulation of teriflunomide-induced DNA damage as cells displayed increased gamma-H2AX staining and concentration-dependent phosphorylation of Chk1 on serine 345 upon exposure to the combination. Assessing the efficacy of this combination in a relevant in vivo model is necessary before this strategy can be considered as a suitable alternative to conventional chemotherapies.

P223

Control of alternative end joining by the chromatin remodeler p400 ATPase

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Repair of DNA double-strand breaks occurs in a chromatin context that needs to be modified and remodeled to allow adequate access to the different DNA repair machineries. Of particular importance for the maintenance of genetic stability is the tight control of error-prone pathways, such as the alternative End Joining pathway. In this work, we show that the chromatin remodeler p400 ATPase is a brake to the use of alternative End Joining. Using specific genomic reporter substrates we observe that p400 depletion increases the frequency of alternative End Joining events, and induces the generation of large deletions following repair of double-strand breaks. The increase of alternative End Joining events was in large part under the dependence of DNA resection mediated by CtIP. Moreover, p400 depletion leads to the recruitment of poly(ADP) ribose polymerase (PARP) and DNA ligase 3 at DNA double-strand breaks, driving to increased sensitivity to PARP inhibitors. Together these results show that p400, acts as a brake to prevent alternative End Joining-dependent genetic instability and could be a potential target for therapy in association with PARP inhibitors and/or used to orientate therapy according to p400 status.

P224

HDAC9 and resistance of breast cancer to targeted therapies

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Estrogens play a pivotal role in the etiology of breast cancer (BC) and endocrine therapy remains the main first line treatment. Estrogen receptors (ER) are finely regulated by transcriptional complexes including histone deacetylases (HDACs). HDACs and their inhibitors regulate histone lysine acetylation, an epigenetic mark important in the regulation of gene expression.
A strong overexpression of class IIa HDAC9 was observed in the most aggressive human breast cancer cell lines. Ectopic expression of HDAC9 in MCF7 luminal BC cells led to an increase in cell proliferation and to a decrease in apoptosis. Inversely, knock-down of HDAC9 expression in MDA-MB436 basal BC cells reduced cell proliferation. Interestingly, HDAC9 expression decreased the efficacy of HDAC inhibitors to reduce cell proliferation.
Moreover, in MCF7 cells, HDAC9 decreased the expression of endogenous ERα at the mRNA and protein levels and inhibited its transcriptional activity. HDAC9 led to a decreased sensitivity to the anti-proliferative effects of the partial antiestrogen 4-hydroxy-tamoxifen OHTam and was found to be strongly overexpressed in antiestrogen-resistant MCF7 cells. By global transcriptome analysis, we identified several genes (including MUC1, SMC3 or S100P) regulated in the same way upon HDAC9 overexpression or OHTam resistance. Finally, in a large panel of BC biopsies, *HDAC9* expression was significantly increased in tumors of the basal subtype and associated with poor prognosis. High HDAC9 levels were also associated with worse prognosis in patients treated with OHTam.
Altogether, these results indicate that HDAC9 intricately interacts with ERα signaling in BC cells, impacted mammary carcinogenesis at multiple levels and is a key factor in the response to HDAC inhibitors and to antiestrogens.

Posters - Axis 3
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P301

The mammary ducts create a favourable microenvironment for xenografting of luminal and molecular apocrine breast tumours

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There is a paucity of models for hormone receptor positive (HR+) breast cancer because of the difficulty of establishing xenografts from these tumours. We show that this barrier can be overcome by injecting human tumour cells directly into the mammary ducts of immunodeficient mice. Tumours from 31 patients were infected overnight with a lentiviral vector expressing tdTomato and injected through the nipple into the mammary ducts of NOD-SCID-IL2RG-/- mice. Tumours formed in the mice in 77% of cases after the first injection (6/8 luminal A; 15/20 luminal B and 3/3 molecular apocrine). Four luminal A and one molecular apocrine graft were tested in secondary and tertiary grafts: all were successfully passaged in secondary and 4/5 in tertiary grafts. None of the samples engrafted when injected subcutaneously. The morphology, oestrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR) and Ki-67 profiles of the clinical samples were maintained in the tertiary grafts. We also show that the intraductal approach can be used to test the response to targeted therapy with fulvestrant and palbociclib, using a genetically defined ER+ model. We conclude that the mammary ducts create a microenvironment that is uniquely favourable to the survival and growth of tumours derived from mammary hormone-sensing cells. This approach opens the door to testing genomically-targeted treatment of HR+ tumours in precision medicine programs.

P302

Brief intraperitoneal radioimmunotherapy of ovarian peritoneal carcinomatosis using radiolabeled 16F12 mAb: towards a clinical Phase 0 study

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Ovarian cancer is the first cause of death from gynecologic malignancy. It has a bad prognosis mainly because patients are diagnosed at a stage where tumors have spread through the peritoneal cavity (peritoneal carcinomatosis, PC). Moreover, 70% of women with ovarian cancer will have a recurrence within 3 years.
We have settled a new therapeutic approach, namely brief intraperitoneal radioimmunotherapy (BIP-RIT), aiming at treating ovarian PC with radiolabeled antibodies at the surgery block, immediately after tumor resection. Based on the principle of hyperthermic chemotherapy (CHIP), BIP-RIT consists of incubating peritoneal cavity for 30 min with high activities of radiolabeled mAbs before extensive washing to remove unbound radioactivity. To target specifically ovarian PC, we have developed a murine 16F12 mAb directed against anti-mullerian hormone type II receptor (AMHRII) expressed by a majority of ovarian cancer. Depending on the nature of the radioisotope, the radioactive form of the mAb can be used for tumor imaging (^{89}Zr for PET,^{111}In for SPECT) or for therapy (Auger, beta- or alpha particle emitters). The so-called theranostic radiopharmaceutical allows a personalized approach by diagnosing and selecting patients whose tumors express high levels of AMHRII and by predicting the tumor and healthy tissues absorbed dose (dosimetry).
Our preclinical data using 16F12 mAb labelled with^{213}Bi or ^{177}Lu indicate that BIP-RIT allows to reach a tumor-to-blood uptake ratio 3 times higher than with intraperitoneal RIT. We also showed that detection of tumors was possible using ^{111}In.
We have started a partnership with a company dedicated to development of radiopharmaceuticals, clinicians and ASN (Autorité de Sûreté Nucléaire) in order to settle a clinical phase 0 to start in 2019. This study aims at confirming the beneficial distribution of radiolabeled 16F12 mAb following BIP-RIT vs IV-RIT before planning a clinical phase 1.

P303

Pharmacological targeting of cancer-associated fibroblasts in pancreactic cancer

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Pancreatic ductal adenocarcinoma (PDAC) presents an exuberant stroma. In this stroma, Cancer-Associated Fibroblasts (CAFs) secrete large quantities of extracellular matrix and soluble proteins that promote cancer cell survival and chemoresistance. We discovered a pharmacological approach inhibiting CAF's deleterious effects by targeting protein synthesis through activation of the G protein coupled somatostatin receptor sst1 expressed in CAFs. The association of this molecule (somatostatin analogue SOM230, pasireotide) and chemotherapy (gemcitabine) has shown an anti-tumor effect *in vitro* and in an immunocompromised murine model (Duluc et al. EMBO Mol Med, 2015).

Our project aims now to demonstrate the therapeutic effect of this drug in immunocompetent mouse models of PDAC, and to clarify its mechanisms of action.

We developed a model of orthotopic syngeneic grafting of pancreatic cancer cells in immunocompetent mice, which mimics the human pathology with development of a desmoplastic reaction. We also use the reference immune transgenic KPC mouse model for the study of PDAC (*Pdx-1-Cre ; LSL-Kras*$^{G12D/+}$ *; LSL-Trp53*$^{R172H/+}$). Animals are treated with the combination of SOM230 and gemcitabine. *In vitro*, the isolation of pancreatic stellate cells (PSCs, precursor cells of CAFs) allows to study the mechanisms of their activation into CAFs.

Longitudinal monitoring of tumor volumes by ultrasound has shown a significant reduction in tumor growth, thus demonstrating the effectiveness of the combination therapy GEM-SOM230, which was confirmed by histology. On the other hand, the expression of sst1 receptor by CAFs was confirmed by immunohistochemistry. On isolated PSCs, sst1 is expressed *de novo* during the activation of PSCs into CAFs, simultaneously with the acquisition of excessive protein synthesis properties.

Inhibition of protein synthesis in CAFs represents a promising strategy for the treatment of PDAC, by targeting the microenvironment.

P304

Optimisation et mécanismes d'action d'un anticorps monoclonal dirigé contre la Claudine-1

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Colorectal cancer (CRC) is one of the major causes of cancer-related deaths in the Western world. When localized, CRC is often curable by surgery, but the prognosis of patients with metastatic disease remains very poor. The current treatment of metastatic CRC (mCRC) relies on therapy combining chemotherapy (5-fluorouracil, irinotecan and oxaliplatin in bi- or tri-association) and targeted therapies with antibodies such as Cetuximab, Panitumumab (anti-EGFR) or bevacizumab (anti-VEGF). However, relapses are observed in most cases due to the occurrence of drug resistance. Therefore, more therapeutic options are required particularly by identifying new molecular targets that can be reached by antibodies

We previously showed that Claudin-1 (CLDN1), a major constituent of tight junctions, is overexpressed at the membrane of CRC cells which makes it a good target for antibodies. Besides, CLDN1 is differentially expressed in the new mCRC molecular subtypes. We have then developed a monoclonal antibody (mAb) against CLDN1, called 6F6, and demonstrated that targeting CLDN1 with 6F6 mAb resulted in decreased growth and survival of CRC cells in vitro and in vivo.

Thereby, the aim of my thesis is to increase the efficiency of 6F6 mAb and to understand its mechanism of action. Using DiFi cells (colorectal cancer cell line) we showed, in 3D culture, a strong decrease in spheroids size and cell survival after treatment with 6F6 mAb. In order to investigate signaling pathways affected by the interaction of 6F6 mAb/CLDN1, phosphokinomic profiles of Difi xenografts treated by 6F6 mAb was explored using the Pamgene technology. Results showed a higher phosphorylation level of FGFR2 in 6F6 treated xenografts that was confirmed by Immunoblot. We are now investigating the links between 6F6 mAb/CLDN1 and the FGFR2 pathway.

P306

New formats of human recombinant antibody libraries

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Phage display selection of human antibodies has proven its usefulness to identify antibodies for therapy. This presents several advantages over the hybridoma technology. In particular, the system does not require animal immunization, is fast and cheap, allows the isolation of human-mouse cross-reacting Ab that can be used both for pre-clinical characterization in mouse and in human therapy, and because of their human origin the identified antibodies are less likely to be immunogenic in patients. For therapeutic applications, the most widely used format is the glycosylated IgG produced in mammalian cells. Since phage display is done in *E. coli* (scFv or Fab), several steps are required from the selection to the IgG characterization.
The objective of my PhD thesis is to design a more efficient Ab library by addressing two limitations of currently available synthetic repertoires:
- Optimization of the library size. Our main goal is to identify the critical determinants of Ab repertoire functional diversity to construct a library with the smallest possible size yet diverse enough for the efficient selection of monoclonal Ab. This will be done by crossing NGS data obtained in Human and Zebrafish to identify the critical factors that shape individual repertoires and introduce them in the design of our synthetic library.
- Direct production of functional full IgG. In current Ab libraries, several reformatting steps are necessary before testing Ab in an IgG format. This limits the evaluation of the potency of an Ab in functional systems that rely on Fc activity (ADCC, CDC). Our new display system will allow a direct reformatting from phage to active IgG by using an universal plasmid that expresses antibody molecules both in E. coli and in mammalian cell lines and a site-specific recombination system to directly generate an IgG-producing stable cell line
Altogether, my project will result in a more efficient and easier to use recombinant human antibody library.

P307

Influence of age and gender on the release of circulating cell-free DNA in human

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Circulating cell-free DNA (cirDNA) is constituted of nuclear and mitochondrial DNA fragments released by cells into circulating fluids, such as blood and lymph. Cell-death mechanism (apoptosis or necrosis) or active secretion appears as the main mechanisms of release. Its clinical potential as a biomarker for diagnosis, therapeutic monitoring and prognosis of many chronic diseases, particularly in oncology, is now widely studied. We recently reported the first clinical validation and the first demonstration of clinical utility of the cirDNA analysis in oncology as companion test. High cirDNA concentrations have been widely described in many types of cancer including colorectal cancer. Alternatively, low cirDNA concentrations are found in healthy individuals. It has also been shown that in many pathological cases, the presence of a pro-inflammatory environment (macrophages, lymphocytes, cytokines) as well as significant tissue damages are all factors that increase cirDNA release into the bloodstream. Cellular Aging, a phenomenon compiling senescence and cell death increased with a chronic inflammatory state call "inflam-aging" may suggest that age can impact cirDNA total concentration. In addition, physiological differences between men and women such as hormonals levels in particular, could potentially be the cause of cirDNA concentration differences between both genders. To our knowledge, no other studies reported direct comparison of age and gender in both nuclear and mitochondrial cirDNA in a large cohort. Here we present data collected on 101 healthy individuals and 214 colorectal cancer patients.

P308

Colon cancer resistance to Irinotecan-based therapy: determining MAPK p38 isoforms contribution by the use of intrabodies.

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We recently demonstrated that MAPK p38 pathway is involved in Irinotecan sensitivity in human colorectal adenocarcinoma cell lines, and that MAPK p38 phosphorylation correlates with resistance to Irinotecan-based treatment in clinical samples of metastatic colorectal tumor. More precisely, in resistant cell lines, p38 α and β isoforms show a high phosphorylation level, and sensitivity of the cells can be restored by pharmacological inhibition of the p38 MAPKs. However, current tools used to study the MAPK p38 pathway have several limitations: pharmacological inhibitors are not specific to a single p38 isoform and are hampered by off-target effects; the use of down (RNAi) or up-regulation of wild-type or mutant MAPK gives biased information on the endogenous protein; the measure of the p38 activity by following target activation lacks specificity owing the intermingling of cellular pathways.

The aim of our project is to develop new tools to specifically detect the phosphorylation of each of the MAPK p38α and β isoform in living cells. These tools will be then used to study the dynamics and the localization of p38 activation in human colorectal adenocarcinoma cell lines resistant and sensitive to Irinotecan. The approach will develop and use intrabodies, which are small recombinant antibody fragments (scFv format) expressed in cells, to target MAPK p38α and β and their active forms. As MAPK p38 are soluble and spread evenly in cells we will use a pair of scFv, one recognizing the protein and the other the phosphorylated form of each MAPK p38α and β. Simultaneous expression of both scFv as intrabodies fused with fluorophores in human cell lines will permit to study the activation of each endogenous p38 by FLIM-FRET in a spatial and temporal way. Such antibodies will help to better understand the involvement of each p38 in the drug resistance and how p38 MAPK is activated within the live cell.

P309

Reversible p53 inhibition prevents cisplatin ototoxicity without blocking chemotherapeutic efficacy

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Research background:
Cisplatin (CDDP) is a widely-used chemotherapy drug, but with significant ototoxic side effects. To date, the mechanism of CDDP-induced ototoxicity remains unclear, and hearing preservation strategies without impacting chemotherapeutic efficacy of CDDP in patients is lacking.

Methods:
Here, we examined the molecular pathway of CDDP ototoxicity from the cellular to the whole system. In addition, to identify a protective strategy that would be suitable for clinical use, we evaluated the efficiency of hearing protection with systemic and local administration of a reversible inhibitor of p53 in CDDP intoxicated adult mice. Finally, to check whether the systemic administration of p53 inhibitor would interfere with the anticancer effects of CDDP, we used two xenograft models of triple-negative human breast cancer with either wt or mutant p53 status.

Results:
We found activation of the ATM-Chk2-p53 pathway to be a major determinant of CDDP ototoxicity. However, prevention of CDDP-induced ototoxicity is hampered by opposite effects of ATM activation upon sensory hair cells: promoting both outer hair cell death and inner hair cell survival. Encouragingly, however, genetic or pharmacological ablation of p53 substantially attenuated cochlear cell apoptosis, thus preserving hearing. Importantly, systemic administration of a p53 inhibitor in mice bearing patient-derived triple negative breast cancer protected auditory function, without compromising the anti-tumor efficacy of CDDP, and even sensitizes TP53 mutant tumors to CDDP.

Conclusion:
Altogether, these findings highlight a novel and effective strategy for hearing protection in CDDP-based chemotherapy.

P310

Identification de déterminants du métabolisme et du transport influent sur la sensibilité des cellules de cancers prostatiques aux inhibiteurs de kinase

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De plus en plus d'inhibiteurs de kinase (IKs) sont testés dans le cancer de la prostate avec des succès mitigés, essentiellement par manque de rationnel dans le choix de la molécule et de la dose. Les IKs sont sujets à des biotransformations et un transport transmembranaire intenses *via* des enzymes de phase I et II et des transporteurs contrôlés pour la majorité par le récepteur nucléaire PXR (*Pregnane X Receptor*, gène *NR1I2)*. Certains IKs sont eux-mêmes des ligands de PXR, pouvant induire leur propre métabolisme ou le métabolisme de drogues associées. PXR est surtout exprimé dans le foie et le tractus gastro-intestinal, mais aussi dans des tumeurs épithéliales où il jouerait un rôle dans la chimiorésistance en modulant le catabolisme et l'efflux des drogues. A ce jour une seule étude a révélé l'expression de PXR dans des tumeurs de prostate sans en avoir évalué l'impact sur la réponse aux traitements utilisés dans cette indication.
Nous avons donc testé l'hypothèse que PXR peut influencer la réponse aux IKs dans les lignées de cancer de prostate. Ces lignées androgéno-dépendantes et androgéno-indépendantes expriment PXR et certains de ses gènes cibles à différents niveaux, suggérant une certaine compétence métabolique. Pour évaluer si la modulation de ces gènes modifie la réponse aux IKs, nous avons surexprimé PXR et validé son caractère inductible en présence du ligand agoniste SR12813. Les résultats préliminaires montrent que cette surexpression module la sensibilité à l'erlotinib, au géfitinib et au vémurafénib.
Enfin, nous avons étudié l'effet ligand d'un panel d'IKs sur PXR, certains déjà suggérés dans la littérature mais aussi d'identifier de nouveaux IKs comme ayant un effet agoniste sur PXR, (coll. Patrick Balaguer) pouvant expliquer les réponses cellulaires observées et servir de rationnel pour des combinaisons de drogues ou expliquer des interactions médicamenteuses.

P311

Markers of resistance to chemo and anti-EGFR therapy in colorectal cancer

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The Colorectal cancer is the third most common cancer and represents the second cause of cancer death in France. Today, therapeutic strategies have evolved through the combination of conventional chemotherapy based on 5-FU, oxaliplatin and/or irinotecan and targeted therapies directed against the EGF receptor (Cetuximab and Panitumumab) or against VEGF (bevacizumab). However, half of patients treated with these protocols have an innate resistance to treatment, and the other half will develop a resistance over time. That's why identifying new drug targets to fight against the drug resistance phenomenon could allow rapid and significant therapeutic advances.
In this perspective, the aim of my project is to identify new targets involved in resistance to cetuximab, panitumumab and erlotinib using genetic screens based on RNA interference. Short Hairpin RNA (ShRNA)-based loss-of-function genetic screens will allow us to identify genes that can modulate the cellular response to anti-EGFRs revealing genes whose suppression cause drug sensitivity (synthetic lethal interactions). We will use this powerful technology to identify genes whose inhibition confers sensitivity to cetuximab, panitumumab and erlotinib (Collaboration with NKI, Amsterdam, leader team for this technology). Currently we work to confirm our four potential targets, which are highlight by this screening.
Furthermore, the project has been extended to studying the results of two other screening performed on colorectal cancer lines resistant to chemotherapy (oxaliplatin and irinotecan) that gave us promising results.
The perspectives of this project are to improve cancer therapies already on the market and / or to develop an effective targeted therapy for patients non-responding to EGFR inhibitor and / or chemotherapies.

P312

Evaluation de la sensibilité de lignées de glioblastomes canin caracterisées a la radiothérapie et a l'effet oncolytique d'une souche sauvage attenuée de myxomavirus

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L'association de virothérapie oncolytique à la radiothérapie est une approche thérapeutique prometteuse afin d'améliorer le mauvais pronostic associé aux glioblastomes (GBM) chez des patients humains. Le chien semble être un modèle animal translationnel pertinent pour des essais précliniques de cette stratégie thérapeutique innovante, étant donné que les principales caractéristiques pathologiques des GBM canins spontanés sont identiques à leurs homologues humains (Fernández F. et al., Vet J 2016;209:125-32). La caractérisation in vitro de lignées cellulaires de GBM canins et l'évaluation des modalités de traitement cités ci-dessus (i.e. radiothérapie et virothérapie oncolytique) sont des conditions nécessaires avant tout étude in vivo sur des chiens atteints de GBM.
Les objectifs de ce projet sont (1) de caractériser 5 lignées cellulaires de GBM canin et (2) d'évaluer la sensibilité de ces lignées à la radiothérapie et à une souche sauvage d'un myxomavirus SG33.

P313

PD-1 blockade potentiates immunomodulatory functions of a tumor antigen targeting monoclonal antibody

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Tumor antigen (TA)-targeted monoclonal antibody (mAb)-based treatments are considered to be one of the most successful strategies in cancer therapy and mAbs have been the biggest class of new drugs approved for the treatment of cancer during the last decade. For malignant melanoma metastatic stages, treatments were limited but immune checkpoint inhibitors demonstrated a spectacular increase of overall survival, reminding us the remarkable ability of the immune system to detect, eliminate and also "remember" cancer cells. We then focused on the ability of TA-targeted mAbs to exert their antitumoral functions through a direct effect on tumor cells as well as their capacity to activate immune effector cells, through Fc-dependent-mechanisms, to achieve sustained protective antitumoral immunity.

Using the B16F10 melanoma preclinical model, we showed that an immunotherapy based on the use of TA99, a mAb directed against the TYRP1 antigen overexpressed on tumor melanocytes, significantly increases mice survival. Tumor-free mice that received a second graft with B16F10 cells did not developed any tumor after the challenge suggesting the presence of a specific anti-tumor immunity. Supporting this hypothesis, we demonstrated the presence of a melanoma-specific cytolytic endogenous immune response after challenge in TA99-treated mice, a cytolytic response that is further enhanced in mice treated with TA99 and the anti-PD-1 immune checkpoint inhibitor, while anti-PD1 treatment alone has no effect in this model. We also demonstrated the presence of a specific humoral response with an increase of anti-B16F10 immunoglobulins within the sera of protected mice after challenge and showed that when transferred into naïve B16F10-grafted mice those sera delay tumor growth and increase mice survival.

Altogether, these results clearly demonstrated the immunomodulatory effect of an antitumor-based immunotherapy, an effect that can be further potentiate by anti-PD-1 treatment.

P314

Combinatorial strategy targeting the tumor microenvironment of triple-negative breast cancer with anti-protease antibody

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New treatments are required for triple-negative and hormono-resistant breast cancers. In breast cancer, the aspartic protease cathepsin D (Cath-D) is an independent marker of poor prognosis. Cath-D is overproduced by breast cancer cells and the pro-enzyme is hyper-secreted into the tumor microenvironment. Liaudet-Coopman's team has made major contributions to the understanding of oncogenic roles of cath-D released in excess by cancer cells in the extracellular space of breast cancer.
With the support of the LabEx MabImprove, Liaudet-Coopman's team generated human monoclonal antibodies by phage display to target Cath-D secreted in the breast tumor microenvironment. Two scFv cloned into human IgG1 format (F1 and E2 IgG1) inhibited triple-negative and ER^+ breast cancer cell wound healing, colony formation and three-dimensional outgrowth in Matrigel. Anti-Cath-D IgG1 F1 and E2 significantly reduced tumor growth of triple-negative MDA-MB-231 breast cancer cells in nude mice. These results suggest that antibody-based targeting of Cath-D may have therapeutic efficacy for breast cancer treatment.
The objective of my PhD thesis is to develop a combinatory strategy to target the tumor microenvironment of triple-negative breast cancers with anti-Cath-D antibodies. First, we will evaluate the expression of Cath-D in different subtypes of breast cancer in order to determine which patients could benefit from a treatment with anti-Cath-D antibodies. We will study the therapeutic effect of anti-Cath-D IgG alone or in combination with chemotherapy in several breast cancer models (PDX (patient-derived xenograft), mouse mammary cancer cells in syngenic mouse, transgenic mouse model of breast carcinogenesis). Finally, we will assess the in vivo mechanisms of action of anti-Cath-D antibodies.

P315

Hypoxia effect on circulating DNA release

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Circulating cell free DNA (cirDNA) constitute novel biomarkers with promising clinical applications in management of patients in oncology, such as screening, prognosis survival and monitoring disease progression. In several cancer types, hypoxia appear **as** a key factor in **various** processes of tumor progression such as proliferation, angiogenesis, tumor metastasis and drug resistance.
Recent studies showed a correlation between the deprivation of tumor microenvironment in oxygen and the presence of circulating cell free DNA in the plasma. However, the mechanisms and factors influencing the release are so far poorly none.
Towards this goal we initiated a program aiming at evaluating the variation of extracellular/circulating cell free DNA under hypoxia conditions *in vitro* and *in vivo*, using an ultrasensitive qPCR based assay. The first objective of this study consists in evaluating of extracellular cell free DNA in the culture medium of human cell lines derived from colorectal cancer patients as well as healthy individuals. The second objective consists in determining the amount and origin of circulating cell free DNA in the plasma of mice model exposed to intermittent hypoxia or room air, grafted or not by murine epithelial lung cancer cells (TC1).
Our results confirm the presence of extracellular DNA in normoxia and hypoxia conditions, and the exposure to intermittent hypoxia influence the release of cirDNA in mouse plasma. Further investigations will shed light on mechanistic origins of circulating cell free DNA to improve the applications of cirDNA analysis in cancer patients.

P316

Colon organoids characterization and early mechanisms of carcinogenesis in FAP patients

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Context: Familial Adenomatous Polyposis (FAP) is caused by germline mutations in *Adenomatous polyposis coli* (APC) gene, which down regulates Wnt signaling pathway. FAP is associated with a 100% lifetime risk of developing colorectal cancer. Carcinogenesis in the colonic mucosa is complex and mechanisms of adenoma development and carcinoma transformation in FAP remain unclear.

Aim: As animal models for FAP do not accurately reflect the multistep process occurring in human disease, we developed a 3D culture model, i.e. human colon organoids established from FAP.

Methods: Colon organoids were established from adenomatous and non-adenomatous crypts of FAP patients and from healthy controls (HC). We modulated the culture conditions by selectively depleting Wnt3a, R-spondin and EGF to study human adenoma formation.

Results: FAP organoids (n=8) grew without addition of Wnt3a but HC organoids (n=6) did not. However, FAP organoids remained dependent on both R-spondin and EGF. Compared to HC organoids, they were hyperproliferative and immature, as shown by significant increase in the number of Ki67 and CD24/CD44 positive cells respectively. Adenomatous organoids were larger and displayed more budding than non-adenomatous ones, mimicking aberrant crypts formation in adenomas. They were also more dependent on EGF. Preliminary results of gene expression suggested different stemness phenotypes between adenomatous and non-adenomatous areas.

Conclusion: The organoid model of FAP presents characteristics of the human pathology and thus will allow the investigation of carcinogenesis and the development of new chemopreventive drugs for FAP patients.

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Preclinical studies of new in situ therapeutic agent derived from dendrimer combined with Nitro-Imidazole and rhenium-188 complex

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AFPREMED

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and the third most deadly cancer worldwide, with more than 500,000 new cases emerging annually. In this context we have recently focused our interest on *In-situ* anticancer treatment of hepatic tumors using 5th generation polylysine dendrimer as supravector of emitters for β emitter complexes of Nitro-Imidazole probes with rhenium-188 [1].

The aim of the present non-clinical study was to determine the therapeutic efficacy and safety of this agent in an experimental liver cancer model (human HCC cell line HegG2) in mice.

Methods: Protocol was carried out in accordance with the strict French ethical requirements relating to animal testing. 5.0×10^6 cells were subcutaneously injected into mice (from Harlan Laboratories, France with following characteristics : Athymic nude, male , 4-6 weeks of age). Once tumor established, 4 mice lots were treated with a single dose of the test item (1, 2, 2.5 and 3 mCi repectivly) compared to control lot. By the end of the study (six weeks post-test compound administration), the tumors were collected for histological analysis.

Results: The treatment was well tolerated. In fact, a significant decrease of tumor volume occurred in all treated groups compared to control group. These results were further confirmed by histological analysis. Large tumor mass only observed in tumor sections from mice in the control group, were disappeared in favor of normal tissues in treated groups.

In conclusion, this novel therapeutic strategy has giving promising experimental results by showing an anti-tumor activity in this experimental liver cancer model in mice under the tested conditions.

[1]- Belhadj-Tahar and Coll. WO/2015/104589, 2015

P318

Clinical utility of longitudinal plasma analysis in examining clonal evolution and tracking secondary acquired resistance in mCRC patients refractory to targeted therapy

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RAS testing is required by health authorities before initiation of anti-EGFR targeted therapies in mCRC patients. However, even in the selected RAS wt population, responses to EGFR agents are limited in duration. Emergence of RAS/BRAF point mutations during anti-EGFR regimen leads to acquired therapeutic resistance. Characterization of molecular changes in the course of treatment could enable the early adoption of alternate therapies before RECIST progression. Nevertheless, tumor biopsy does not allow serial therapeutic and exhibit limitations especially in regards intra and inter-tumoral heterogeneity of the tumor, patient compliance and potential toxicity. We performed a blinded retrospective exploratory study to evaluate performance of circulating DNA analysis for tracking specific oncogene mutations over time during anti-EGFR therapies. KRAS, NRAS and BRAF mutations we tested in 81 serial plasma samples from 46 mCRC patients refractory to chemotherapy combined with Dasatinib regimen with or without Cetuximab. Data show that 98% of the plasma were found mutant before or during treatment. Also, 50% of KRAS mutant samples were missed by tumor tissue analysis before treatment of the patients scored wt by tumor tissue analysis. Longitudinal plasma analysis showed that 80% of initially wt patients acquired at least one RAS/BRAF mutation during treatment and that 27% of initially mutant patients and 38% of all studied patients acquired at least one newly KRAS, NRAS or BRAF point mutation during treatment. Patients may harbor mutations at very low frequency down to 0.01% before initiation or during treatment revealing the need of a high sensitive technique to detect mutant subclones. Qualitative and quantitative circulating DNA analysis empowers tracking of acquired resistance by examining the real-time clonal evolution of the tumor and might help physicians to adjust patient treatment before RECIST progression.

P319

Effect of single nucleotide polymorphisms in the xenobiotic-sensing receptors NR1I2 and NR1I3 on the pharmacokinetics and toxicity of irinotecan in colorectal cancer patients.

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Background and Objectives: Nuclear receptors PXR (Pregnane X Receptor, *NR1I2*) and CAR (Constitutive Androstane Receptor, *NR1I3*) are key regulators of irinotecan metabolism and ligand-dependent modulation of their activity leads to significant drug-drug interactions. Since genetic polymorphisms can also affect the activity of these xenobiotic-sensing receptors, we hypothesized that they could contribute to the interpatient variability of irinotecan pharmacokinetics (PK) and to the toxicity of irinotecan based regimens.

Patients and methods: In a cohort of 109 metastatic colorectal cancer patients treated by irinotecan (180mg/m²) in combination with other drugs, associations were assessed between 21 selected single nucleotide polymorphisms (SNPs) of *NR1I2* or *NR1I3* and PK parameters or toxicity of irinotecan and metabolites.

Results: After adjustment of the tests by *UGT1A1*28* genotype and correction for multiple testing, the A allele of *NR1I2*-rs10934498 was associated with a decreased exposition and an increased degradation of SN-38, the active metabolite (p=0.009 and p=0.017 respectively). The risk of hematological toxicity was associated with*NR1I2*-rs10934498 and *NR1I2*-rs2472677 (p=0.009 and p=0.003 respectively).

Conclusion*:* Our results reveal for the first time the involvement of *NR1I2* in the pharmacogenetics of irinotecan and suggest that it may help to predict the toxicity of irinotecan low dosing.

P320

Regional solid tumors database in Limousin

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An oncology clinical database is an evaluable resource to assess patient care and research. The existence of heterogeneous databases and the lack of communication between them result ignorance of target population and also constitutes a barrier to investment in our institutions for national and international cancer clinical trials. The Regional Base of Solid Tumors project (RBST) aims to centralize all information relating to cancer patients care in Limousin. The objective is to analyze patients' management, follow-up and also to facilitate translational research in cancerology. This multicentric retrospective and prospective database centralizes administrative and medical records (medical history, biological check-up, medical imaging, histology …) contained in our different hospital software applications. Several web technologies are used: HTML and CSS to display, PHP to functionality and SQL to the query tool. Javascript and AJAX technologies are also used. Data extraction and data integration in XML format are automated through the implementation of half connector. An identity monitoring and reconciliation protocol are created. The RBST database is composed of 2 modules: RBST-Evaluation that permits to register and evaluate patients care and follow-up; RBST-Research, corresponding to a pseudo-anonymized database to facilitate development of translational research and clinical projects through the implementation of a complex queries tool within the database. The different steps identified in the development of this database, the necessity to standardize input information and their different sources will be described. The RBST database by its capacity to automatically embed standardized data from multiple sources create a critical mass of knowledge and expertise. Thus, clinicians have a global vision of care and follow-up for their patients. RBST contributes to enhance quality of cancer care and facilitates implementation of transversal structuring projects.

P321

Virtual ligand screening identifies the proprotein convertase small molecule inhibitors as new potential colorectal liver metastases therapy

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Proprotein convertases (PCs) located along the constitutive secretory pathway namely Furin, PACE4, PC5 and PC7 are involved in the proteolytic cleavage and/or expression of various cancer-related mediators, making them promising targets in cancer therapy. Their substrates include adhesion receptors, extra cellular matrix-degrading proteinases, and growth-promoting factors and their receptors. Altered levels of PCs were reported to be associated with enhanced invasion and proliferation in various tumor cells and tissues. In a phase I trial (FANG vaccine trial), an autologous tumor-based product incorporating a plasmid encoding GM-CSF and a bifunctional short hairpin RNAi (bi-shRNAi) targeting Furin was found to be beneficial with 90% success rate in patients with advanced cancer. To date and among the PCs, only the X-ray structure of Furin has been reported. We therefore used Virtual ligand screening (VLS) and the ChemBridge database that contain over 600 000 unique molecules to search for compounds able to inhibit this convertase, we selected 1000 molecules that we assessed for their inhibitory effect on Furin using various cellular assays. Of these, 5 molecules were found to inhibit significantly the catalytic activity of Furin, and the malignant phenotype of various tumor cells. Our findings identify new anti-cancer strategy and suggest the potential use of the identified small molecule inhibitors and/or their derivatives as a new class of potent anti-cancer therapeutics.

P322

Cardiac failure adverse drug reaction with protein kinase inhibitors: from pharmacovigilance to basic pharmacology

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Introduction: Protein Kinase Inhibitors (PKI) used in oncology are source of serious Adverse Drug Reactions(ADR) and cardiac failure (CF) is a common ADR for many of them. On-target or Off-target mechanisms could be source of ADRs. To understand the underlying mechanism of the PKI-induced CF is crucial to manage the ADR and to predict ADR of new drugs. We aimed to identify the target(s) involved in PKI-induced CF using the international drug safety database.

Methods: This study was realized with data from the international pharmacovigilance (PV) database managed by the WHO, and with pharmacodynamics (PD) data. A literature review was realized to select molecular targets possibly involved in the CF mechanism. CF cases were identified in VigiBase® from Jan 2001 to Mar 2015. Disproportionality of CF was calculated for the selected PKI with Adjusted Reporting Odds Ratios (aROR). Pearson correlation coefficients were calculated between the affinity (pKd) of the drugs for the selected molecular targets and the aROR to identify the more probable target involved in the CF mechanism.

Results: Fifteen (15) PKI presented available PV and PD information: afatinib, axitinib, bosutinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, ruxolitinib, sorafenib, sunitinib and vandetanib. For these drugs, 141601 cases were extracted from VigiBase® and 2594 cases of heart failure were identified. Disproportionality was calculated with aROR and ranked. According to the literature review, 21 molecular targets were suspected to be involved in the PKI-induced heart failure. For two of them, the affinity was significantly correlated with the aROR: ABl1 and ABl2 tyrosine kinases.

Conclusion: This method was developed to improve pharmacological knowledge about known drugs using PV data. For CF, two possible targets of PKI were identified to possibly lead the ADR mechanism: Abl1 and Abl2 non-receptor tyrosine kinases.

P323

Crizotinib and Vemurafenib targets in glioblastoma stem cells

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor in humans and carries a poor prognosis. Glioblastoma stem cells (GSCs) are believed to be involved in the mechanisms of tumor resistance, therapeutic failures and recurrences after a conventional glioblastoma therapy. Therefore, elimination of GSCs might be a prerequisite for the development of successful therapeutic strategies. *ALK*,*ROS1* and *MET* are targeted by Crizotinib, a tyrosine kinase inhibitor which has been approved for the treatment of *ALK*-rearranged non-small cell lung cancer. BRAF is a major component of the MAPK signaling pathway and mutations are occasionally observed in adult GBMs. Vemurafenib is a RAF inhibitor used in treatment of melanoma with $BRAF^{V600E}$ mutation. In this study we investigated *ALK*,*ROS1, MET* and *BRAF* status in nine glioblastoma stem cell lines and tumors from which they arise.

Nor genomic rearrangements (or amplifications) neither genomic mutations of *ALK, ROS1* and *MET* were found. One glioblastoma stem cell (GSC) line presented $BRAF^{V600E}$ mutation and was tested to evaluate the potential effect of Vemurafenib, compared to GSC $BRAF^{WT}$. Vemurafenib inhibited cellular proliferation with IC_{50} values similar in the two GSC lines, and no significant modification of BRAF protein expression was observed after treatment of both GSC lines with Vemurafenib. While we did not observe a reduction of ERK1/2 phosphorylation in GSC^{V600E}, a paradoxical elevation of phosphorylated ERK1/2 levels was observed upon BRAF inhibition in GSC^{WT}.

In this study, we show that *ALK, ROS1* and *MET* are not impaired in glioblastoma stem cells therefore the use of crizotinib to eradicate the GSC is not a valid strategy.

No individual effect of Vemurafenib was observed in GSC^{V600E}, but further investigation of associations of this drug with other agents to induce a response in GSC^{V600E} is warranted as it has been effective in colorectal and thyroid cancers.

Posters - Axe 4
« Cancers : enjeux individuels et collectifs »

P401

Plateforme de recherche en prévention primaire des cancers : Mutualiser les compétences pour optimiser la recherche en prévention

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Selon Hawe et Potvin (2009), « la recherche interventionnelle implique l'utilisation de méthodes scientifiques afin de produire des connaissances sur les interventions, sous forme de politiques et de programmes, existant dans le secteur de la santé ou à l'extérieur de celui-ci et qui pourraient avoir une incidence sur la santé des populations ». Elle se base sur le principe qu'un comportement est la conséquence de variables sur lesquelles il est potentiellement possible d'agir. Il peut s'agir de facteurs sociaux, émotionnels ou de croyances en matière de santé. Ainsi, plus d'un quart des décès par cancer pourraient être évités grâce à des changements de comportements individuels ou sociétaux.
Un grand nombre d'actions préventives sont mises en œuvre chaque année par des acteurs différents. Si les interventions sont nombreuses quoique souvent parcellaires, la recherche en prévention est encore peu développée en France. Partant de ce constat, trois centres de ressources en prévention des cancers (Epidaure, le pôle prévention de l'Institut régional du Cancer de Montpellier (ICM) ; le Centre Hygée, plateforme de prévention du Cancéropôle Lyon Auvergne Rhône-Alpes ; et le centre Antéia de la Fondation JDB-Prévention Cancer dans l'Essonne), ont décidé de créer une plateforme de recherche en prévention primaire des cancers.
L'objectif principal de cette plateforme est de mutualiser les compétences des 3 centres Epidaure, Hygée et Antéïa pour développer des interventions de recherche en prévention primaire des cancers avec des acteurs de terrain en apportant expertise et aide logistique pour développer des actions de recherche et entrainer ainsi une vraie synergie des ressources.

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P402

Evolution des prescriptions de médicaments orphelins en cancérologie: en France et à l'échelle d'un établissement hospitalier

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Les «médicaments orphelins» (OD, Orphan Drug) est le terme consacré aux médicaments destinés aux maladies rares. Ce statut apporte pour les firmes, des incitations financières : exclusivité de marché, remboursement des essais cliniques. Avec l'attribution par la FDA et l'EMA, du statut OD à plus de 500 molécules en développement, cette législation a contribué à l'élaboration de nombreux produits innovants. Du fait de leur prévalence, les cancers rares bénéficient de la législation OD. Aujourd'hui, 50% des anticancéreux mis sur le marché sont des OD, et 7 des 10 médicaments les plus vendus aux USA en 2011 étaient des OD, véritables blockbusters, rapportant pour certains plus de 1Md$ de chiffre d'affaires annuel. La disponibilité de ces médicaments avec leur coût très élevé soulève un débat autour de la soutenabilité de nos systèmes sociaux dans un contexte macroéconomique défavorable.

Dans le cadre d'un projet en émergence du Cancéropôle GSO, nous avons documenté cette situation à plusieurs niveaux :

- nous avons fait un état des lieux des OD anticancéreux mis sur le marché ou en développement.
- nous avons mesuré l'évolution des dépenses des OD prescrits en France,
- enfin, nous avons évalué sur 2 sites hospitaliers pilotes la prescription de ces OD.

Nous avons pu montrer une explosion des demandes de statuts OD avec un 1/4 des demandes en oncologie, concentrées sur un faible nombre de cancers rares, demandes faites par les start-up, mais exploitées par les big-pharma, avec une régulation peu sélective par les agences (FDA, EMA), pour des coût de traitement beaucoup plus élevé, avec une forte croissance annuelle, responsable de 2/3 des remboursement d'anticancéreux, pour des molécules au SMR très moyen, impactant le budget des établissements hospitaliers.

Nous proposons de réfléchir, en nous appuyant sur une modélisation microéconomique, à l'impact de la législation des OD, à la stratégie des firmes, et au mode de fixation des prix des médicaments.

P403

E-santé Tabac

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Problématique :
La communication sur le changement social est un élément essentiel des efforts de prévention portés historiquement sur le contenu des messages transmis, sur la façon de se comporter, ou sur le mode de transmission (Courbet, 2014). Ainsi en tenant compte du contexte communicationnel actuel et de la «génération digital native », comment un serious game qui est un jeu combinant une intention sérieuse (pédagogique, communicationnelle…) avec des ressorts ludiques sur le tabac, pourrait-il représenter une stratégie de communication utile à la prévention des cancers ?

Méthodologie :
A partir de l'analyse du discours lors de focus groupe réalisés auprès de 57 jeunes, un prototype de « serious game » a été développé en collaboration avec une société spécialiste en e-santé, le groupe Genious.
Des jeunes scolarisés de la 6ème à la terminale en Languedoc-Roussillon l'ont testé durant l'année scolaire 2015-2016. 6 focus groupes ont été réalisés auprès de 55 élèves (30 filles, 25 garçons), afin d'évaluer la pertinence du jeu et la compréhension du message préventif.
Un questionnaire a été proposé auprès de 183 élèves (93 filles et 90 garçons, moy = 14,12 ans ; écart-type de 2,19) et a permis de recueillir leurs avis sur les dimensions ludique, pédagogique et ergonomique du jeu.
Résultats :
Le test du chi2 croisant le statut tabagique et l'apport de connaissances sur le tabac grâce au jeu, montre que l'apport de connaissances sur le tabac est moins affirmé pour les fumeurs quotidiens (p=0.039). En effet, 24 % des fumeurs quotidiens ont acquis des connaissances, versus 59 % pour les fumeurs occasionnel, 40% pour ceux qui ont essayé mais ne sont jamais devenus fumeurs, et enfin 61% pour ceux qui n'ont jamais fumé.

Conclusion :
Il apparaît ainsi que ce prototype de serious game pourrait être développé vers un outil de communication destiné à une population de jeunes non initiée au tabac comme outil de prévention précoce du tabagisme.

P404

Quels sont les freins et les facilitateurs à la participation au dépistage organisé du cancer colorectal ? Une étude qualitative par focus groups.

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Détecté à temps, le cancer colorectal se guérit dans 9 cas sur 10. Pourtant, il reste la 2ème cause de mortalité par cancer en France (HAS, 2013). Dans ce contexte, la participation au dépistage organisé doit être améliorée. Suite au récent changement de test de dépistage (passage du test Hémoccult II au nouveau test immunologique) il semble important de s'intéresser au changement de pratiques des usagers. Ainsi, cette étude vise à identifier les représentations sociales (Jodelet, 1984) de la population cible envers le dépistage du cancer colorectal et envers le nouveau test immunologique.

Six focus groups ont été menés avec des personnes issues de la population générale, dans la tranche d'âge concernée par le dépistage organisé (29 participants, 13 hommes et 16 femmes). Les supports utilisés portaient sur les connaissances sur ce cancer, le risque perçu, la participation au dépistage et l'arrivée du nouveau test, le rapport au médecin généraliste et les messages de sensibilisation.

Une analyse de contenu thématique a ensuite été réalisée (Bardin, 1993). Les principaux freins à la participation au dépistage sont : l'absence de symptômes, la procrastination et le manque de temps (nécessité de prendre rendez-vous chez le médecin généraliste), mais également le fait que ce cancer concerne une partie du corps considérée comme sale, liée à un sujet tabou. A l'inverse, les principaux facilitateurs sont : la simplicité pratique du nouveau test, les encouragements de l'entourage (médecin et proches), ainsi que le fait de recevoir un coup de pouce (« nudge »), comme l'invitation à se faire dépister envoyée tous les deux ans. Durant les focus groups, les échanges ont été enrichis par les expériences de cancer relatées, vécues par les participants eux-mêmes ou par leurs proches, et participant au processus de formation des représentations sociales.

Cette étude a permis d'avoir une meilleure compréhension de l'adhérence au dépistage.

P405

Posttraumatic stress disorder after lymphoma diagnosis: a prospective study

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Background:
For a number of years investigators have reported trauma-related symptoms such as intrusive memories, avoidant behaviors, and heightened arousal in survivors of cancer. More than one-third of long-term non-Hodgkin's lymphoma (NHL) survivors experienced posttraumatic stress disorder (PTSD) symptoms. Nevertheless, only a few prospective researches showed the development context of PTSD symptoms. The aim of our study was to assess the relation between emotional and cognitive impact of the news of a lymphoma diagnosis and the development of subsequent PTSD symptoms.

Methods:
About 15 days after receiving the lymphoma diagnosis subjects were asked to complete the emotional distress (fear, helplessness, etc) and cognitive dissociation (stunning, disorientation, etc.) peritraumatic questionnaires (at the time of the news or immediately after); 5 weeks after receiving the diagnosis participants completed measures of PTSD (PTSD CheckList-Specific), depression (BDI) and anxiety (HAD) symptoms, and the quality of life questionnaire (SF-36) and coping strategy (WCC).

Results:
Of the 92 participants (55% men, mean aged 46 years), 68.6% had a NHL and 31.4% had a HL. Among them 49% reported a significant emotional distress and 16% a significant cognitive dissociation during or immediately after receiving the lymphoma diagnosis. Five weeks after 43% reported a partial PTSD diagnosis. In a logistic regression model to predict partial PTSD, significant peritraumatic emotional distress and a low level of "mental health" for the quality of life felt were the best predictors.

Conclusion:
This study objectively demonstrates the importance of the emotional impact of the news of a lymphoma diagnosis for the development of cancer-related PTSD symptoms.

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Identification des principaux déterminants psychosociaux du maintien en emploi des femmes ayant un cancer du sein : une revue de la littérature

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Introduction : Le maintien en emploi suite au diagnostic de cancer du sein englobe à la fois : le retour au travail et ses délais, et, le quota horaire hebdomadaire. Si les facteurs sociodémographiques, médicaux et professionnels du maintien en emploi ont fait l'objet de nombreuses investigations, les principaux déterminants psychosociaux, sont à notre connaissance peu abordés.
Méthode : Une revue de la littérature (RDL) publiée jusqu'à Juin 2016 a été réalisée sur : Medline, Psycinfo, Psycho & Behavioral Sciences, et SocIndex. Les termes utilisés ont été définis en Mesh et Thesaurus. Une formule booléenne a été constituée. La littérature grise et les bibliographies des articles identifiés ont fait l'objet d'un complément de recherche.
Les études sélectionnées devaient être publiées en langue française ou anglaise et évaluer quantitativement un ou plusieurs déterminants psychosociaux du maintien en emploi des femmes ayant un cancer du sein.
Les niveaux d'évidence ont été évalués à l'aveugle par trois auteurs avant d'établir un niveau final par consensus.
Résultats : Au total, 8132 articles ont été identifiés, dont 17 ont répondu aux critères d'inclusion. Deux articles ont complété notre recherche après vérification des bibliographies de Vidor et al. (2014), et Van Muijen et al. (2013). L'échantillon total est composé de 19 articles.
Les principaux déterminants du maintien en emploi sont : une bonne qualité de vie mentale et physique, une bonne satisfaction de vie et une forte perception de soutien professionnel à toutes les étapes de la maladie. La fatigue semble ne pas avoir d'impact significatif.
Discussion : Les aspects méthodologiques seront discutés. Nos résultats concordent avec les études qualitatives, ainsi que des RDL menées sur la pathologie cancéreuse en général. L'absence de significativité de la fatigue est notamment dû à sa forte colinéarité avec les traitements qui sont prépondérants dans le maintien en emploi.

P407

Présentation du protocole de l'essai randomisé contrôlé international évaluant l'impact sur la survie d'un programme d'activités physiques adaptées chez des patients atteints d'un cancer du côlon de stade II ou III : Etude CHALLENGE.

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Introduction : L'étude interventionnelle internationale CHALLENGE dirigée par Kerry Courneya (Canada) évalue l'efficacité d'un programme supervisé d'activités physiques adaptées sur la survie sans maladie chez des patients atteints d'un cancer du côlon de stade II ou III.
Objectif : L'objectif de ce poster est de présenter le protocole de l'étude internationale CHALLENGE conçu par Kerry Courneya (Edmonton, Canada).
Méthodes : Les patients sont répartis aléatoirement, soit dans le groupe expérimental qui bénéficie d'un programme combinant activité physique et soutien comportemental pendant 3 ans, soit dans le groupe contrôle qui ne bénéficie pas de ce programme. Le critère de jugement principal est la survie sans maladie évaluée pendant 10 ans.
Résultats attendus : Le taux de survie sans maladie devrait être plus élevé dans le groupe expérimental que dans le groupe contrôle sur les 10 années de suivi.
Discussion : 962 patients seront inclus dans l'étude afin d'obtenir une grande précision sur l'estimation de l'effet de l'activité physique sur la survie. Au 31 décembre 2013, 250 patients ont été randomisés dans 20 centres canadiens et dans 26 centres australiens. Le Comité de Protection des Personnes (CPP) de l'ICM de Montpellier a validé la pertinence du projet au niveau scientifique et médical et la valeur éthique vis-à-vis des personnes qui vont participer à cet essai. L'objectif pour l'ICM de Montpellier est d'inclure 30 patients.
Conclusion : Il s'agit de la première étude clinique désignée pour véritablement répondre à l'effet de l'activité physique sur la survie. Cela pourrait signifier que l'activité physique n'a pas qu'un effet strictement adjuvant (qualité de vie), d'atténuation des effets secondaires des traitements, mais sur l'évolution tumorale.

P408

Time perspective: a main predictor of quality of life in patients with brain metastasis

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BACKGROUND

Brain metastases (BM) are known to impact health related quality of life (QOL). Time perspective (how an individual partitions his/her past, present and future timeframes) has historically been a critical component of psychological adjustment in several disease contexts. No study has examined the role of time perspective on the QOL in patients with BM. We suppose that depressive symptoms mediate the relationship between past-negative time perspective and QOL in BM patients.

METHOD

48 participants were recruited (56% females; 56.7 years ± 12.4) in a consecutive inclusion cohort study called CEREMET-LR and supported by the SIRIC Montpellier Cancer. Participants completed 3 questionnaires, EORTC QLQ-C30 3.0, Zimbardo Time Perspective Inventory (ZTPI), and the Beck Depression Inventory-II (BDI-II). Analyses explored the mediation effects of their depressive symptomology on QOL. Independent variable included past-negative time perspective. Bootstrapping approach and path analysis was used to test the mediation model.

RESULTS

Preliminary analyses: The independent-t and Mann-Whitney tests showed that age, genre, marital status and level of study, had no significant statistically difference on QOL and depressive symptomology, and past-negative time perspective ($p > .05$). Path analysis: Depressive symptomology significantly mediated the relationship between past-negative time perspective ($\beta = 5.08$, $p <.01$, CI = 2.39, 7.77) and QOL ($\beta = -2.16$, $p <.01$, CI = -2.96, -1.36). There was a negative indirect association of past negative time perspective on QOL through the depressive symptomatology (-10.98, IC = -17.37, -5.79).

DISCUSSION

The results suggest the past-negative time perspective as a predictor of QOL. Thus, psychological interventions that reframe time perspective could be an effective solution to decrease depressive symptoms and improve QOL in BM patients.

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Tell me how you eat, I will tell you how you are! Assessing the dietary intake in 1762 cancer patients with an ingesta-Verbal/Visual Analogue Scale

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***Purpose*:** Assessing the nutritional intake of cancer patients is a major challenge for the clinicians because weight loss contributes to cachexia, which is very common and leads to poor prognosis. The aim of this novel study was to validate a Visual/Verbal Analogue Scale of food *ingesta* (*ingesta*-VVAS) as a relevant and quick measure of clinical food intake in cancer patients.

***Methods*:** Between January 2009 and December 2011, five experimented dieticians gathered the data, performed the clinical exam and the *ingesta*-VVAS in 1762 oncology patients in the Cancer Institute of Montpellier (ICM) in France. The external validity of the *ingesta*-VVAS was mainly determinate using daily energy intake, based on a 1-day recall. Patients had to answer to "How much do you currently eat on a scale from 0 "*nothing at all*" to 10 "*as usual*". We focused on patients ingested less than 28 Kcal/Kg/day to determine the *ingesta*-VVAS accuracy for assessing the energy intake as a function of the median.

Results: The feasibility of the *ingesta*-VVAS was 97.7%. The scores were significantly correlated ($p<.05$) with energy intake, both in Kcal/day ($\rho = .72$) and in Kcal/Kg/day ($\rho = .67$), especially in undernourished patients ($\rho = .74$). Psychometric proprieties for ingesting less than 28 Kcal/Kg/day with a *ingesta*-VVAS score ≤ 6 were: specificity of 81.7%, positive predictive value of 92.2%, sensitivity of 62.9%, and negative predictive value 46%. The calculated Youden's index was J = 0.45 and the Yule's coefficient Q = 0.77.

Conclusions: A valid *ingesta*-VVAS may generate great interests in clinical practice both for professional - who could adjust their nutrition intervention and reduce cachexia - and cancer patients - who would be more involved in their own dietary management.

P410

Le rôle des sages-femmes dans le dépistage du cancer du col de l'utérus.

Sonia PURGUES

Centre Emile Durkheim

Cette étude financée par la Ligue Nationale contre le CAncer (2015-2017) a pour objectif d'étudier le rôle que la sage-femme prend désormais dans la prévention du cancer du col de l'utérus. Il n'existe pas en France de programme national de dépistage organisé (DO) du cancer du col utérin hormis dans quelques départements. La couverture réelle du dépistage n'est que de 58% (2014) avec une grande hétérogénéité des pratiques et nous savons que moins de 30% des jeunes filles sont vaccinées. Les sages-femmes ont reçu l'autorisation de pratiquer le suivi gynécologique de prévention depuis juillet 2009. Ainsi, dans ce cadre et sous réserve de contre-indications éventuelles, la pratique du frottis et de la vaccination par les sages-femmes ne se limite plus aux seules femmes enceintes. L'activité de prévention de ce cancer réalisée par les sages-femmes reste pourtant ignorée par une grande majorité de femmes. Nous nous questionnerons sur la place de ces professionnelles et leur légitimité vis à vis des femmes et des autres acteurs de santé habilités (gynécologues et médecins généralistes). Nous nous demanderons si les sages-femmes, souhaitent investir ce rôle. Nous cherchons à mesurer la connaissance des femmes en matière de prévention en gynécologie. Du côté des autres professionnels, nous chercherons à comprendre comment ils reçoivent l'action des maïeuticiennes. Deux terrains d'enquête sont investigués : la Gironde (33) et le Bas-Rhin (67). Comme ce dernier dispose d'un DO, nous voulons savoir si cela favorise une meilleure connaissance du rôle de la sage-femme et/ou une coopération avec les autres acteurs de prévention.

P411

Female lung cancer trends, staging and histology in Herault, France

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Objectives
In France, the incidence of lung cancer has decreased since 2000 in men, but remains strongly on the increase in women. Compared to other departments (administrative areas) in France, incidence of, and mortality from lung cancer in women were highest in the Hérault department.
The purpose of this study was to examine, using data from the cancer Registry of the Hérault, trends in lung cancer in women over a period of 17 years.
Material and Methods:
All invasive cases of lung cancer (ICD-O 3 : C33-C34) diagnosed in women between 1995 and 2012 in the Hérault Department were included. Incidence data, by age, stage and histology were derived from the cancer registry. Mortality data were derived from the National Institute of Medical Research (CépiDC-INSERM). Trends in incidence and mortality were estimated by modeling the log-incidence according to year of diagnosis.
Results
Among 9 675 invasive lung cancers recorded in the Hérault over 17 years, 2 950 were diagnosed in women, and 30.2% were aged less than 50 years old at diagnosis. The annual rate of change of incidence and mortality were respectively +7% and 4%, this rate increased particularly in the latter years of the study period. Breast cancer mortality - usually the primary cause of mortality in women - dropped below lung cancer mortality in 2012.
Increase in incidence was mainly constant and concerned all ages, stages and histology. The greatest increases rises were observed for women aged over 50 years and especially for adenocarcinoma and early stages (I-II).
Discussion and conclusions
In the Hérault department, a substantial increase in incidence and mortality was observed over the 17-year study period. This is mainly due to the high level of smoking in the female population, which may in turn be related to several factors, and particularly the high level of unemployment in this department.

P412

Exhaustivité du passage en réunion de concertation pluridisciplinaire. Etude dans un département de Midi-Pyrénées disposant d'un registre de cancer, le Tarn

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Le plan cancer a rendu obligatoire le passage en réunion de concertation pluridisciplinaire (RCP) de tous les dossiers de cas de cancer diagnostiqués. Cette exhaustivité n'est pas facile à atteindre.
L'exhaustivité a été estimée en comparant la base du registre des cancers du Tarn, qui recense tous les cas de cancers diagnostiqués chez des résidents du Tarn avec la base extraite du dossier communicant de cancérologie de la région Midi-Pyrénées qui comporte toutes les fiches patients correspondant à un passage en RCP. Tous les cas de tumeurs solides diagnostiqués durant la période 2010-2013 ont été inclus dans cette étude. Sont ici analysés différents facteurs pouvant être associés au fait de passer en RCP.
Sur les 11000 patients atteints d'un cancer diagnostiqué dans la période, nous avons retenu 9634 cas (exclusion des cancers cutanés non mélaniques, des hémopathies et des cas dont le domicile était imprécis). Dans 83% des cas ils étaient passés en RCP. On constate une augmentation du taux de passage entre 2010 (79%) et 2013 (86%). Le passage en RCP est plus fréquent pour les cancers du sein (95%), de la prostate (90%) et du colon-rectum (89%). Les cancers présentant une atteinte ganglionnaire sont plus fréquemment discutés en RCP. La fréquence de passage en RCP diminue au-delà de 75 ans. Pour les cancers présents chez les deux sexes, le passage est plus fréquent chez les hommes. Enfin les dossiers des patients résidants dans des zones éloignées des deux principales villes du Tarn, ainsi que ceux résidents dans les zones les plus défavorisées, sont moins souvent soumis à la RCP que les autres.
Nous observons une augmentation régulière de la fréquence des soumissions. Si l'obligation de passage en RCP peut être discutée, la sélection que nous observons ne relève pas d'une sélection raisonnée. Il semble plutôt que les cas qui ne passent pas en RCP sont ceux qui en auraient le plus besoin.

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Méthodologie des essais dans le domaine des Soins de Support : Présentation des activités du groupe méthodologie au sein de l'intergroupe UNICANCER-AFSOS

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Objectifs : UNICANCER et AFSOS se sont rapprochés pour mutualiser leurs compétences afin de mener des études cliniques dans le domaine des Soins de Support (SdS) en cancérologie. L'intergroupe UNICANCER-AFSOS a pour ambition que ces études soient réalisées selon un cadre méthodologique strict : études multicentriques, randomisées, avec des critères de jugement appropriés à l'évaluation du SdS. C'est dans ce contexte que le groupe méthodologie a été créé au sein de l'intergroupe, avec pour objectif 1) de définir les spécificités des essais cliniques pour l'évaluation des SdS 2) de proposer des recommandations méthodologiques pour à terme développer des essais 3) d'apporter son expertise dans la conception des études de l'intergroupe.
Méthodes : Parmi les problématiques soulevées, deux thématiques de travail ont été priorisées : la méthodologie des essais de développement des SdS non médicamenteux et la méthodologie des essais testant les SdS lors d'études évaluant l'efficacité d'un traitement/stratégie thérapeutique. Pour répondre aux objectifs, il est prévu de définir des algorithmes de recherche dans la base de données PUBMED et de faire une synthèse critique de la littérature afin de rédiger des recommandations méthodologiques.
Résultats : Une première recherche documentaire sur les essais évaluant les SdS non médicamenteux a été menée. Un total de 8000 articles a été retrouvé, un tri de ces articles est en cours et la synthèse critique sera faite après élaboration d'une grille de relecture. La même démarche sera appliquée aux essais évaluant conjointement SdS et traitement curatif. Aussi, une revue bibliographique sur l'existence de recommandations méthodologiques pour l'évaluation des SdS a été conduite montrant un manque avéré de recommandations dans ce domaine.
Conclusion : Le travail de recherche bibliographique est en cours et le groupe de travail réfléchit en parallèle à de nouvelles problématiques pour l'évaluation des SdS en oncologie.

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Unité d'oncoréhabilitation - bilan d'activité et perspectives

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L'institut universitaire du Cancer de Toulouse a ouvert au sein du département des soins de support, une unité dédiée à la prise en charge des déficits liés au cancer afin de réduire leur conséquence dans la vie quotidienne du patient. L'objectif de cette unité est d'évaluer les besoins et de proposer un projet personnalisé de réhabilitation pour tous les patients atteints de cancer sur un modèle préexistant pour les cancers des voies aéro-digestives supérieures (VADS).
L'objectif de ce travail est de présenter l'activité de cette unité 1 an après son ouverture en décrivant la population prise en charge, les types de bilan, les modalités de prises en charge proposées sur la période des 6 premiers mois de l'année 2016.
L'activité réalisée en hospitalisation de jour correspond à une file active de 265 patients. Les patients présentent dans 60% des cancers des voies aérodigestives, 20 % des hémopathies, 10% des cancers du sein. Les prises en charge concernent les déficits du carrefour (voix, parole, déglutition), la désadaptation à l'activité physique, les déficits neurologiques.
Ces résultats sont discutés en analysant les parcours patients, les leviers et les freins rencontrés pour l'organisation de cette nouvelle activité en cancérologie.

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Améliorer la prise en charge des cancers des personnes déficientes intellectuelles. Étude interventionnelle en Hérault, bilan à trois ans et demi.

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Situation: Les cancers des personnes déficientes intellectuelles (PDI) (2.5% de la population) sont aussi fréquents que dans la population générale (PG), différents, mal connus, diagnostiqués tardivement et difficiles à traiter. L'étude les compare à ceux de la PG, et alerte familles, professionnels de la DI et le corps médical sur ce risque.
Méthode: Croisement d'une liste des PDI avec la base du Registre des Tumeurs de l'Hérault, avant et après information des familles, professionnels du handicap et médecins pour évaluer l'efficacité de l'intervention.
Résultats: Le recueil de 100% des 120 établissements et dispositifs destinés aux PDI, de 76% des 158 EHPADs et des PDI hors établissement a trouvé parmi 3465 adultes, 167 cancers chez 159 personnes. Seins 28, autres organes féminins 12, prostate 19, testicules 7, cancers digestifs 16, poumons 9, bouche et ORL 7, peau 18, leucémies et lymphomes 23, SNC 5, cancers de lieu primitif inconnu 2. A côté de DI de causes génétiques, les tumeurs ont été trouvées avec DI post-traumatique, infectieuse ou associées à des troubles psychiatriques. Les traitements, ont souvent dû être modifiés, du fait de difficultés de réalisation (éloignement, nécessité de rester immobile) ou de refus des patients.
Discussion: La répartition des cancers est particulière: excès de tumeurs testiculaires, leucémies et lymphomes, et peu de cancers pulmonaires et ORL. Le risque tumoral n'est pas limité aux DI de causes génétiques. La comparaison avec la PG pour le stade au diagnostic et le résultat du traitement sont en cours.
Conclusion: Cette recherche unique à l'international confirme la distribution particulière des cancers, et le besoin d'accompagner des soins. L'impact de l'intervention nécessite une prolongation du suivi vu le faible nombre des tumeurs recueillies depuis l'intervention.
Remerciements: Etude soutenue par l'institut National du Cancer (INCa)

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La sage-femme comme nouvel acteur de prévention du cancer du col de l'utérus : Enjeux professionnels, identification par les femmes et partage des compétences

Béatrice JACQUES

Centre Emile Durkheim

Cette étude a pour objectif d'étudier le rôle que la sage-femme prend désormais dans la prévention du cancer du col de l'utérus. Il n'existe pas en France de programme national de dépistage organisé (DO) du cancer du col utérin hormis dans quelques départements. La couverture réelle du dépistage n'est que de 58% (2014) avec une grande hétérogénéité des pratiques et nous savons que moins de 30% des jeunes filles sont vaccinées. Les sages-femmes ont reçu l'autorisation de pratiquer le suivi gynécologique de prévention depuis juillet 2009. Ainsi, dans ce cadre et sous réserve de contre-indications éventuelles, la pratique du frottis et de la vaccination par les sages-femmes ne se limitent plus aux seules femmes enceintes. L'activité de prévention de ce cancer réalisée par les sages-femmes reste pourtant ignorée par une grande majorité de femmes. Nous nous questionnerons sur la place de ces professionnelles et leur légitimité vis à vis des femmes et des autres acteurs de santé habilités (gynécologues et médecins généralistes). Nous nous demanderons si les sages-femmes, elles-mêmes, souhaitent-elles investir ce rôle. Quelles conséquences cette nouvelle pratique peut-elle avoir sur le métier ? Nous cherchons à mesurer la connaissance des femmes en matière de gynécologie de prévention. Ont-elles un suivi gynécologique régulier ? Que représente à leurs yeux le dépistage par frottis ? Du côté des autres professionnels habilités, existe-t-il la crainte d'une déqualification de l'activité de prévention, si elle est confiée aux sages-femmes ? Deux terrains d'enquête sont investigués : la Gironde (33) et le Bas-Rhin (67). Comme ce dernier dispose d'un DO, nous voulons savoir si cela favorise une meilleure connaissance du rôle de la sage-femme et/ou une coopération avec les autres acteurs de prévention. A l'inverse, le territoire de la Gironde disposant d'un dépistage individuel, les enjeux sont-ils différents ?

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Individual socio-economic status and breast cancer diagnostic stages: a French case-controls study

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Objectives:
Health inequalities have increased over the last 30 years and represent a significant public health problem. We aimed to investigate whether the risk of having advanced stage breast cancer (BC) differed according to socio-economic status.
Material and methods:
We conducted a matched case-control study on 619 women with BC, living in the Hérault, a French administrative area. Both Cases and Controls were recruited among invasive cases diagnosed in 2011 and 2012 and treated in Hérault care centers. Cases were defined as patients with advanced stage BC at diagnosis. Controls were composed of early stage patients. Individual socio-economic status was assessed using a validated individual score adapted to the French population and health care system.
Results:
We observed that patients with low socio-economic status have a two-fold increase in the risk of having late stage BC, regardless of cancer characteristics and mode of detection (screening vs clinical signs). The association between the risk of having late stage BC and low socio-economic status was different depending on whether BC was diagnosed with or without mammography screening. For patients with BC detected by mammography screening, low socio-economic status was positively associated with the risk of late stage BC. We observed a positive association between risk of late stage BC and low socio-economic status among patients with no history family of BC. No differences according to socio-economic status were observed among patients diagnosed with clinical signs or with a history family of BC.
Discussion and conclusions:
One possible explanation for these results could be that low socio-economic status patients have less regular follow-up, which can lead to later and poorer diagnosis. Follow-up is improved in women with a better awareness of BC. Health policy makers could reduce health inequalities by reducing the delay in breast cancer diagnosis for women with low socio-economic status.

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MOOC/SPOC Parcours de soins des patients atteints de cancers

Anne-Laure FIZE, Pr Roland BUGAT

PHUC CAPTOR WP4

Dans le cadre du programme CAPTOR (http://www.captor-cancer.fr/), nous mettons actuellement en place un MOOC/SPOC intitulé « **Parcours de soins des patients atteints de cancers** ».
Cette formation 100% en ligne et gratuite sera proposée à partir du mois d'octobre prochain à l'ensemble des professionnels du parcours de soins et permettra de valider leur obligation DPC.
En particulier, nous ciblons les professionnels du parcours de soins "de ville" qui sont souvent en demande d'informations sur la prise hospitalière des patients atteints de cancers, mais considérons également que notre formation peut intéresser les chercheurs afin de découvrir la prise en charge médicale des patients qui concernent de près ou de loin leurs recherches.
Ainsi, nous considérons que l'avenir de la formation en oncohématologie - *et en matière de soins en général* - passe par des formations ouvertes à l'ensemble des professionnels et des bénévoles d'associations: "**Apprendre ensemble pour soigner ensemble**". Dans cette perspective, des exercices collaboratifs en ligne permettront de faire travailler des groupes multiprofessionnels sur des questions spécifiques au lien ville-hôpital, et peut-être même de faire émerger de nouvelles solutions pour accompagner l'évolution de la prise en charge des patients atteints de cancers, particulièrement impactée par l'augmentation des anticancéreux oraux et de la prise en charge à domicile.

Posters - Axis 5
« Health Technologies »

P501

Circulating microRNA detection using fluorescence-based nanofluidic platform for the early diagnosis of pancreatic cancer

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85% of patients affected by pancreatic adenocarcinoma (PDA) are diagnosed at an advanced stage, preventing effective care and curative treatments. Therefore, it is urgent to find reliable biomarkers to manage the early detection of this disease by means of appropriate tests. MicroRNAs (miRNA) have recently emerged as candidate biomarkers due to their early alteration during pancreatic carcinogenesis. Since these molecules can be quantified in biological fluids, miRNAs provide a new class of non-invasive biomarkers for PDA diagnosis.
We are currently studying miRNA/DNA hybridization using biofunctionalized nanoslits in combination with fluorescence microscopy. Fluorescently labeled target molecules are captured in specific locations within the nanochannel. Because of the reduced depth of the channel that turns into a reduced fluorescence background, the amount of hybridized targets can be directly correlated to the fluorescence signal on the sensor. As a result, this simple fluidic platform enables studies of the miRNA interaction with probe molecules, and allows us to investigate the influence of various hybridization parameters (probe design and temperature) in order to efficiently detect SNP (single-nucleotide polymorphism) between let7-b and let7-c targets.
On the other hand, detection in complex fluids, such as plasma, is being addressed. A special care is given to the sample preparation protocol and its consequences on the detection outcome. As a proof of concept, we have shown that miRNA spiked in 10% plasma solution could be detected easily into nanochannels without extra preparation. Experiments aimed at detecting endogenous miRNA are currently ongoing. This multidisciplinay project paves the way for the simple, reliable and cost-efficient detection of candidate miRNA biomarkers for the early-diagnosis of PDA, a disease with no cure when detected too late.

P502

Design of a nanostructured MRI contrast agent

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Magnetic nanoparticles (NPs) offer contrast enhancement for magnetic resonance imaging (MRI), which depends on their composition, size, surface properties, magnetization and aggregation state in the biological environment. These key parameters influence the longitudinal and transverse relaxivities, Ri (relaxation rate per unit concentration in mM) according to the Koening-Keller model.[1] A way toimprove relaxometric efficiency is to increase the magnetization per volume unit of the nanomaterial. Here we report our investigation of non-oxidized iron NPs as MRI contrast agents. The synthesis and surface coating of iron NPs is described as well as the stability of the colloidal aqueous solutions obtained, which is supported by Dynamic Light Scatterring studies. The measurement of their relaxivities clearly evidences their increased efficiency for MRI in comparison to iron oxide ones.[2] Preliminary evaluation of their cytotoxicity will also be reported.

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P503

177Lu-lilotomab versus 177Lu-rituximab in antibody radionuclide conjugate therapy of Non-Hodgkin lymphoma: a radiobiological approach

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We have developed a preclinical radiobiological approach to compare the new antibody radionuclide conjugate (ARC)^{177}lu-labelled lilotomab directed against CD37 receptor*versus* ^{177}Lu-labelled rituximab directed against CD20 receptor in the therapy of non-Hodgkin lymphoma.
DOHH2 and Ramos lymphoma cells were exposed *in vitro* to unlabeled or ^{177}Lu-radiolabelled lilotomab, rituximab, or non-specific cetuximab. A Bliss mathematical model was used to discriminate between immunological (mAb) and radiological (^{177}Lu) cytotoxic effects contributing to final ARC therapeutic efficacy. We investigated the biological (cell death, apoptosis, non-targeted effects, cell cycle arrest, protein expression) and physical (dosimetry) parameters that could affect these two components. *In vivo*, in mice bearing subcutaneous Ramos or DOHH2 tumour xenografts, survival and tumour growth were determined and dosimetry was performed according to MIRD formalism.
We showed in both cell lines that unlabeled rituximab was more cytotoxic than unlabeled lilotomab. However, per Gy, we showed that in the most radiosensitive cell line, the two ARC showed the same cytotoxic efficacy while ^{177}Lu-rituximab was still more efficient than ^{177}Lu-lilotomab in the most radioresistant cell line. These observations were supported by *in vivo* therapeutic efficacy of ^{177}Lu-lilotomab and ^{177}Lu-rituximab. In DOHH2 tumour xenograft model, although rituximab was shown to be more efficient than lilotomab, tumour uptake of the two antibodies was similar and led to the same final tumour growth delay. We hypothesized that in this radiosensitive model, irradiation could counterbalance for the lower efficacy of the lilotomab against rituximab. In the Ramos tumour xenograft model similar therapeutic efficacy could be obtained only if the tumour absorbed dose of^{177}Lu-lilotomab was increased.
We have developed a radiobiological model to compare and predict the therapeutic efficacy of ^{177}Lu-lilotomab versus^{177}Lu-rituximab

P504

Entropic Boltzmann Closure for Radiotherapy

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The majority of patients affected by cancer are nowadays treated by radiotherapy. The main goal of this technique is to target and destroy tumoral cells without damaging the surrounding tissue. On the last decades, a major effort was made to improve technologies involved in the development of this treatment.
Our work consists on the development and validation of a new model designed to simulate the energy deposition of the particles used in radiotherapy, within human tissues. This model is based on a kinetic entropic closure of the linearized Boltzmann equation [1]. This equation takes a lot of computation time to be resolved. To simplify this, we replace fluencies by angular moments, which allows us to get rid of the angular variables and improve the calculation time. We obtain a set of angular moments equations, and we close this set using the Boltzmann's principle of entropy maximization.
We show that this model has an accuracy comparable to references Monte-Carlo codes, and is less time-consuming than these ones. Moreover, we show that this method is applicable to MRI-guided radiotherapy which consists in irradiating a patient under the influence of a magnetic field. Thereby, we are able to highlight some effects that occur on the propagation of particles in the matter, which modify the dose distribution on the interface between materials of different densities. This has to be taken into account in order to prevent creation of hot spots or spread of energy distribution in a human body. Therefore, our model could be applied to future clinical cases and would allow a faster and more efficient way to plan a viable treatment for a patient.

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P505

Involvement of targeted and non-targeted effects during alpha or Auger RIT of small volume peritoneal carcinomatosis

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We investigated *in vitro* and *in vivo* the relative contribution of targeted and non-targeted effects in the therapeutic efficacy against tumours of antibodies radiolabeled with alpha particle (^{212}Pb, ^{213}Bi) or Auger electron (^{125}I) emitters. Targeted effects occur in cells directly crossed by ionising particles while non-targeted effects are measured in cells neighboring irradiated cells.
Targeted effects were measured *in vitro* in cells exposed to antibodies radiolabeled with alpha or Auger emitters (donor cells) while non-targeted effects were investigated in recipient cells. Recipient cells consisted of cells not exposed to radiolabeled-mAbs, but grown in medium previously incubated for 2h with donor cells. We showed that the relative contribution of targeted effects *versus* non-targeted effects was higher during alpha RIT than Auger RIT. Alpha particles produced 53BP1 and gamma-H2AX foci in donor cells that could be differentiated in large, medium and small foci, while only small foci were observed in recipient cells. We assumed that large foci would correspond to locally multiply damage sites in DNA. Conversely, Auger RIT led predominantly to non-targeted effects compared with targeted effects. Use of radical scavengers showed that oxidative stress was involved in non-targeted effects. *In vivo*, we showed in athymic nude mice bearing tumor xenograft that non-targeted effects were also involved and participated to therapeutic efficacy of radiolabeled antibodies.
These results indicate that although producing single DNA lesion, non-targeted effects can contribute to the therapeutic efficacy of mAbs radiolabeled with alpha particle or Auger electron emitters. These findings are particularly relevant for targeted therapy in which vectors cannot gain access to every tumor cell. One of the issues raised by these results is also related to radiation protection since non-irradiated tissues can show DNA damage and subsequent possible cell death or cell transformation.

P506

High performance modelling of the transport of energetic particles for radiotherapy.

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This work is focused on the study and validation of an algorithm dedicated to the description of the transport and energy deposition by energetic particles (photons, electrons and protons) for therapeutic purposes. It provides a good accuracy and is much less CPU time consuming than a reference Monte Carlo code. The algorithm can simulate different treatment techniques such as the external radiotherapy, brachytherapy or intra-operative radiation therapy.

The kinetic M_1 model is based on the spherical harmonic expansion of the distribution function, solution of the linear Boltzmann equation. The first two angular moments equations, combined with the Continuous Slowing Down Approximation, are closed by using the Boltzmann's principle of entropy maximization [1].

This method is validated by a comparison with standard Monte Carlo codes [2] and by assessment of experimental data obtained on a clinical accelerator at the comprehensive cancer center Institut Bergonié in Bordeaux.

A protocol of validation with a large number of heterogeneity shapes has been defined for various complex phantoms both for electron and photon sources. Depth-dose curves and profiles of the beam at different depths have been measured in water phantoms including inhomogeneity of bone and lung.

A comparison with experimental data demonstrates the good efficiency of M_1 model, both considering the computational cost and the accuracy of the calculations. Indeed, the M_1 code calculates the reference dose deposition in a few seconds whereas a full Monte Carlo code needs hours or even days. M_1 is a promising candidate for the development of Treatment Planning Software based on deterministic models.

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P507

Development of a high content screening approach on 3D human colon organoids to identify drug candidates against colon cancer

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Since few years, a technological breakthrough allows to re-create in vitro 3D intestinal epithelial mini-organs to study the intestinal stem cell (ISC) capacities and their ability to reconstitute a fully functional intestinal epithelium with the different cell populations (stem cells, transit-amplifying progenitors and differentiated cells-enterocytes, enteroendocrine, goblet cells). This 3D colon organoid model represents undoubtedly a good tool to study the ISCs roles and the cellular and molecular mechanisms involved in proliferation and differentiation processes under physiological and pathophysiological conditions.

As a matter of fact, we are also able to establish 3D colon organoids from epithelial cells isolated from either normal or tumoral tissues from colorectal cancer (CRC) patients as well as crypts from inflammatory bowel disease resections or biopsies. Indeed, in the colon, recent studies have shown that cancer originates from the colon crypt stem cells, and it is well established that IBD patients have an increased risk to develop CRC.

Here, our aim was to develop a high content screening (HCS) approach on 3D human colon organoids in order to identify drug candidates against colon cancer stem cells.

We optimized the 3D organoid culture in order to obtain a more robust and cost effective culture condition regarding the screening objectives. We then developed a program allowing the recognition, the counting and the follow-up of the organoid structures by high-content-analysis. Finally, we also used the machine-learning capacity of the HCS software to standardize the survival/apoptosis rate of our 3D colon organoid cultures.

This approach is now used in our laboratory to screen the impact of cytokines, growth factors, inhibitors… on the patient colon organoids (CRC and IBD). This will lead to a better understanding of the colon pathophysiology as well as the identification of new drug candidates in CRC and IBD.

P508

Glioma stem cells mechanoreception in new 3D matrix.

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Current standard of care against glioblastoma (GBM) including surgery, chemotherapy and radiotherapy have limited efficiency. Invasive Glioblastoma stem cells (GSC) disseminate within the normal brain parenchyma and are responsible for the fatal outcome. Clinical observations demonstrate that GSC preferential migration areas are fibrous in nature. However, to date little is known about the perception of physical stimuli to induce invasion. GSC are sensitive to the mechanical properties of the surrounding tissue (pressure, confinement, fiber diameter and tissue rigidity) and use the microenvironment stiffness to enhance invasion. GSC can thus perceive their physical microenvironment and translate it into mechanical membrane deformation by mechanotransduction.
Piezo1 is a stretch-activating ion channel mediating mechanosensory transduction. It is activated by traction forces and its activation causes transient Ca2+ influx in a substrate stiffness- and confinement- dependent manner. Piezo1 has been reported to be involved in cell motility and adherence in CSC and it is highly expressed in GSC. Further, it is an important determinant of mechanosensitive lineage choice in neural stem cells and may play similar roles in other multipotent stem cells. Piezo1 seems to be a promising candidate to observe the mechanoreception in GSC.
In this context, our objective is on the first hand to develop a 3D artificial fibrillary tissue which can allow *in vitro* recapitulation of the migration behavior observed *in vivo*. We designed a 3D electrospun fibers to study the influence of the morphological and mechanical properties of the support on GSCs migration. This 3D matrix is highly plastic as key physical parameters can be modulated including stiffness, confinement, as well as alignment of the fibers.
On the other hand, this support will allow us to describe the correlation between physical parameters, calcium influx through Piezo1 expression and the migratory behavior of GSCs.

P509

Synthesis of new Imidazo[1,2-a]quinoxaline and Pyrazolo[1,5-a]quinoxaline derivatives as IKK inhibitors

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IκB kinases(IKK) play critical roles in regulating the immune response through nuclear factor-κB and IFN regulatory factor - dependent signaling transduction cascades. These kinases have been implicated in the pathogenesis of many human diseases,including cancer[1] . In fact, dysregulation of IKK activities promotes tumor survival, proliferation, migration, metastasis, and angiogenesis - common characteristics of many types of human cancers.[2,3]Targeting IKK is becoming an increasingly popular avenue for the development of novel therapeutic interventions for cancer and many pharmaceutical companies are developing inhibitors that target IKK. BMS-345541(4(2'-aminoethyl)amino-1,8-dimethylimidazo(1,2-a)quinoxaline) was identified as a selective inhibitor of the catalytic subunits of IKK (IKK2 IC(50) = 0.3 µM, IKK1 IC(50) = 4 µM)[4]. The aim of this study is to obtain new IKKinhibitors, analogues of BMS-345541. For this purpose, we have synthesized a variety of compounds diversely substituted belonging to two chemical series: imidazo[1,2-*a*]quinoxaline and pyrazolo[1,5-*a*]quinoxaline. Their biological activities as potential IKK1 and IKK2 inhibitors are described[5].Two strategies of synthesis are developed to obtain a variety of compounds with short reaction times by using micro-wave assistance. The preparation of these compounds is particularly simple and is carried out in good yields.

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P510

Human dermal substitute to decipher gene electrotransfer mechanisms on skin

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The skin is an attractive target for gene therapy and vaccination due to its large surface, its accessibility and its richness in dendritic cells. Gene electrotransfer is an emerging skin-directed therapy which is a safe and efficient non-viral gene delivery method based on local electric field application.
Electric field application results in transient cell membranes permeabilization, allowing therapeutic molecules penetration. Due to the increasing use of gene electrotransfer, a better understanding of DNA electro delivery mechanisms at tissue scale could help to make it an attractive approach for the treatment of skin pathologies in general.
The mechanisms of gene electrotransfer remain a fragmented knowledge *in vivo*. Indeed, although electrotransfer of genes is highly effective on 2D cell culture *in vitro*, it is much less efficient *in vivo*. Tissue organization is more complicated than *in vitro*, since cells develop intercellular junctions and extracellular matrix (ECM). The development of three-dimensional (3D) human tissue models helps to mimic and predict *in vivo* situations. In order to study skin DNA electrotransfer mechanisms, we developed by tissue engineering an innovative 3D reconstructed human dermal substitute based on self-assembly approach which is a representative model of *in vivo* tissue organization.
Our study shows that the cells within this 3D tissue can be efficiently electropermeabilized with electric field parameters classically used *in vivo* for gene delivery. A reporter gene was successfully electrotransfered into this human tissue with gene expression. We also reported evidences that electrotransfection success depends on plasmid mobility within tissue rich in collagens, but not on cell proliferation status (Madi et al 2016; Curr Gene Ther).
In addition to proposing a reliable alternative to animal experiments, tissue engineering produces valid biological tool for the *in vitro* study of gene electrotransfer mechanisms in human skin.

P511

Lipid nanocapsules formulation and cellular activities evaluation of a promising anticancer agent: EAPB0503

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Context: EAPB0503, lead compound of Imiqualinesa-b, presented high antitumor activities c-d but also a very low water-solubility which was critical for further preclinical studies.
Objective: To apply to EAPB0503 a robust and safe lipid formulation already used for poor soluble anticancer agents for injectable administration at a concentration higher than 1 mg/ml.
Materials and methods: Physicochemical properties of EAPB0503 were determined to consider an adapted formulation. In a second time, lipid nanocapsules (LNC) formulations described in the patent developed by Heurtault et al. and based on the phase-inversion process were developed for EAPB0503 encapsulation. Then, EAPB0503 loaded-LNC were tested in vitro on different cell lines and compared to standard EAPB0503 solutions.
Results: Optimized EAPB0503 LNC displayed an average size of 111.7 ± 0.9 nm and a low polydispersity index of 0.059 ± 0.002. The obtained loading efficiency was higher than 96 % with a drug loading of 1.7 mg/mL. A stability study showed stability during 4 weeks stored at 25°C. In vitro results highlighted similar efficiencies between LNC and standard EAPB0503 solutions prepared in DMSO.
Discussion: In view of results obtained for loading efficiency and drug loading, the use of a LNC formulation is very interesting to permit the solubilization of a lipophilic drug and to improve its biodisponibility.
Conclusion: Preliminary tested pharmaceutical formulation applied to EAPB0503 significantly improved its water-solubility and will be soon considered for future preclinical in vivo studies.

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P512

Analysis of the in vitro and in vivo effects of photodynamic therapy on prostate cancer by using protoporphyrin ix-polyamine derivatives

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Photodynamic therapy (PDT), using porphyrins as photosensitizers (PS), has been approved for the treatment of several solid tumors. We developed a new vectorization strategy based upon the chemical derivatization of Protoporphyrin IX (PpIX) with the two polyamines (PA), spermidine (PpIX-dSd) and spermine (PpIX-dSm). PA, as well as their porphyrin derivatives (PpIX-PA), are actively transported and accumulated into cancer cells by the Polyamine Transport System (PTS). Phototoxicities of PpIX-PA have been assessed after red light irradiation of two Chinese hamster ovarian cell lines, CHO and CHO-MG (which differ from each other by their PTS activity), along with the human healthy prostate cell line RWPE-1 and three human prostate cancer cell lines, PC-3, DU 145 and LNCaP. We showed PA derivatization increased PS efficiency. Photoactivation of PpIX-PA triggered the intrinsic apoptotic pathway and also activated the COX-2/PGE2 pathway, known as an inducer of apoptosis resistance (through the p38/MAPK protein which is pro-apoptotic but also a positive regulator of COX-2). However, inhibition of COX-2 did not increase PDT efficiency and inhibition of p38/MAPK resulted in increased PDT-induced apoptosis. These PS also induced a reduction in expression of NF-κB, a pro-survival factor. In vivo phototoxicities of PS have been tested on PC-3 subcutaneous xenografts performed in nude mice. Tumor irradiation by red light of PpIX-dSd treated mice resulted in growth slowing and histological studies showed a drop in both the proliferative marker Ki67, and the anti-apoptotic protein Bcl-2 levels. Nevertheless, in vitro PpIX-dSm efficiency failed to be confirmed in vivo. So, PA-derivatization increased PpIX in vitro phototoxicity. Activation of the COX-2/PGE2 pathway did not seem to reduce PDT efficiency. Only PpIX-dSd, was found somewhat active on a murine model. These data showed that these new PS could be good candidates in the context of prostate cancer treatment by PDT.

P513

Targeting Glioblastoma with Nanoparticles

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Glioblastoma (GB) is the most common devastating type of primary malignant tumor of the CNS. Current therapy has done very little in extending the life expectancies of GB patients and these tumors inevitably recur with no effective treatment. Therefore, the development of more effective treatments is urgently needed.
The siRNA technology has become a promising method for inactivating essential proteins required for cancer cell survival without hazards to normal cells. Although their efficacy is well proven in vitro, the therapeutic use of siRNA is limited by their pharmacokinetic properties and their inability to cross biological and intracellular barriers. Therefore, delivery systems that can improve siRNA efficacy *in vivo* need to be developed.
This project aims to evaluate the efficacy of peptide-based nanoparticles (PBN) carrying siRNAs to target GB *in vivo*. Different PBN are being tested *in vitro* using GB cell lines genetically modified to express 2 bioluminescent reporter genes: Fluc (siRNA target) and Nluc (internal control). These cell lines are also being used to generate mice subcutaneous and intracranial tumors to test the PBN in vivo. Optical imaging will be used to determine the specific siRNA targeting and efficiency. Finally, histological studies will show the cellular and subcellular location of the PBN.
The setting-up and validation of this system will have large implications in the study of PBN carrying siRNA for different targets or other therapeutic agents to tumor cells.

P514

Conception et synthèse de "mimobodies" thérapeutiques par ingénierie chimique

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Pour profiter de la grande spécificité des anticorps (Ab) monoclonaux dans les traitements anticancéreux nous proposons la sélection d'éléments de liaison dans les régions variables des Ab pour une analyse combinée structurale et fonctionnelle. Notre modèle d'étude concerne l'interaction Rituximab-CD20. Cette interaction antigène-Ab se fait *via* des séquences précises du domaine variable CDR. Pour mimer les domaines de reconnaissance de l'Ab nous avons analysé d'un côté les paratopes issus de l'analyse structurale 3D ainsi que l'affinité pour CD20 de courts fragments peptidiques balayant l'ensemble du CDR. Ceci dans le but de designer un mime d'Ab composé des fragments peptidiques nécessaires à l'interaction. La synthèse de peptides par la méthode spot nous a permis d'obtenir une banque de 800 peptides issus de la séquence du domaine hypervariable de la chaine lourde et la chaîne légère du Rituximab. Cette synthèse est rendu possible grâce à la technique SPOT® qui permet de préparer simultanément un grand nombre de différents peptides immobilisés sur membrane de cellulose. Après avoir effectué un test d'affinité avec l'antigène marqué à la cyanine5, plusieurs peptides interagissant avec la cible ont pu être identifiés, provenant des boucles du paratope de CDR. Afin d'identifier les résidus critique pour maintenir l'interaction nous avons dans un premier temps effectué une analyse Ala-scan des fragments peptidiques. Ensuite une analyse mutationnelle permettra le design de nouveaux peptides avec une sélectivité accrue.

Ces différents peptides seront ensuite synthétisés par SPPS afin de permettre leur greffage sur un scaffold peptidique permettant plusieurs synthèses orthogonales.

La combinaison de l'analyse cristallographique, la modélisation moléculaire et l'identification de zones d'interaction par analyse de banques de peptides sur membrane nous permet de proposer une nouvelle voie chimique pour concevoir des mimes d'Ab pour le diagnostic et/ou la thérapie.

P515

Nanoparticles for cancer theranostic: targeting, imaging, and photodynamic therapy

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Cancers are usually treated by surgery, radiotherapy, and chemotherapy. Some of them with weak aggressive potential in the short term do not justify these heavy treatments, and prompt the consideration of minimally invasive treatments. Photodynamic therapy (PDT) is considered as an alternative treatment due to its noninvasive nature and minimal cumulative side effects even after repetitive treatments. Recently, there is considerable research effort in developing nanoscale systems in the fight against cancer, particularly for use in cancer imaging and therapy. In this context, the development of biodegradable and biocompatible drug delivery system based on nanoparticle technology could be of particular interest to achieve the combination of targeting, imaging, drug delivery and photodynamic therapy of cancers. In our laboratory, we have already identified the membrane receptors overexpressed by cancer cells and we have used mesoporous silica nanoparticles carrying 2-photon photosentisizers (2 PS) grafted with ligands specific of these receptors for imaging and therapy. In this study, we used the zebrafish (*Danio rerio*) to develop an integrated model for *in vivo* investigations on new nanotools. The two-photon PDT was applied to the 48 hours post-fecondation (hpf) zebrafish embryos injected with cancer cells previously loaded with Periodic Mesoporous Organosilica (PMO) nanoparticles functionalized with 2 PS (PMO-2PS). The confocal fluorescence microscopy showed the reduction of the xenograft mass after two-photon irradiation. The xenograft reduction was confirmed by cell viability measurement with acridine orange and activated caspase-3 assays.
This work at the interface between fundamental and applied research could lead to the design of effective and biocompatible prototypes for personalized medicine.

P516

Polymeric self-assemblies for photodynamic therapy: a critical approach

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The work presented here suggests a new approach in the critical development of polymeric nanovectors for photodynamic therapy (PDT) against cancer. Whereas hundreds of studies quickly jump forward from formation of self-assemblies to biological application without having a thorough examination of the vector solution, we suggest having a parallel assessment of formation/characterization of the nanovectors and biological activity. This is possible by first using a careful physical chemistry characterization of the vectors by both batch techniques (light and neutron scattering, electron microscopy, atomic force microscopy) and Asymmetrical Flow Field-Flow Fractionation (AsFlFFF) coupled to adequate detectors (refractometry, light scattering). This enables us to fully characterize the vectors regarding purity, size and zeta potential.
Data on both polymeric micelles and polymersomes are presented here, using poly(ethyleneoxide-b-e-caprolactone), poly(ethyleneoxide-b-D,L-lactide) and poly(ethyleneoxide-b-styrene). Self-assemblies exhibiting size range of 20-200 nm are presented and reveal the possible presence of different populations of nanovectors in some cases. Controlled mixtures of different nano-objects are also studied, as well as crosslinked systems. For each new vector, its ability to carry a photosensitizer (Pheophorbide a) for PDT is examined. The activity in PDT either in 2D and 3D cell culture is presented and compared on different batches, in link with the purity analysis. Here again, it becomes highly recommended to develop a critical approach considering *in vitro* analyses, since different efficiencies are clearly observed depending on the vectors and the 2D or 3D culture type.
The work shows that selected mixtures of different vectors with different morphologies or sizes may lead to synergetic effects. Also, a strong influence of the crosslinking of the vector has been observed and will be presented.

P517

µLAS, a disruptive technology for size analysis of DNA with unrivalled sensitivity: application for circulating cell free DNA analysis

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Circulating Cell-free DNA (ccfDNA) is now recognized as a potential biomarker enabling personalized medicine for a wide range of pathologies. ccfDNA analysis is still limited by low concentration and complex, costly and time consuming methods. µLAS technology was used to concentrate and separate on-line DNA molecules.
When DNA is carried away in a laminar, viscoelastic flow in a capillary, and when a counter-electrophoresis is applied, transverse forces appear which drive DNA molecules towards channel walls. The force intensity depends on shear stress, and on the charge and size of the molecule. DNA molecules are axially distributed in the flow according to their size, and, therefore, migrate at different speed due to their different positions in the parabolic speed profile of the laminar flow. When transverse forces are very high, DNA molecules are no longer carried away by the flow, but crawl backward along the walls where electrophoresis is dominating.
We have used this unique technique to concentrate DNA at the junction of two capillaries of different diameters, and then to separate the molecules according to their size.
Two capillaries of different diameters were welded end-to-end, and implemented on a capillary electrophoresis instrument. A Picometrics LIF detector was placed 7 cm downstream the junction, to detect fluorescent molecules. The system was conditioned with a solution of PVP. DNA was injected in the large diameter capillary. When the injected DNA was totally concentrated at the junction, the electric field was lowered, and DNA molecules were then separated by size and detected in the smaller capillary.
This technology can easily get profile circulating cell-free DNA (ccfDNA) with a 100-1000x gain of sensitivity compared to the best electrophoresis technique and get the mass distribution of ccfDNA according to size.
The size profile obtained is insensitive to the sample volume injected, as well as insensitive to the presence of salts.

P518

Small animal non-invasive exploration: CREFRE-ENI department

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Small animal Non-Invasive Exploration (ENI) preclinical facility belongs to the Inserm unit UMS006/CREFRE. This unit aims at providing a continuum of services ranging from the creation of mice models to their phenotypic characterization with priority given to welfare of animals and conservation of their health status. ENI department combines state-of-the-art imaging technologies and high level data analyses expertise for the characterization of small animal models (mice, rats, marmosets) of human disease, new tracers and drugs characterization/evaluation. Its activity is spread over two locations in Toulouse:

- CREFRE-ENI / Oncopôle specifically dedicated to molecular imaging of small animals with **Single Photon Emission Computed Tomography** (nanoSPECT-CT), **Positron Emission Tomography** (nanoScan PET-CT), **Computed Tomography** (CT) and **Magnetic Resonance Imaging** (MRI) unit (coming soon).
- CREFRE-ENI / Rangueil providing a high-resolution**ultrasound imaging** facility with a high frequency unit (Vevo 2100), a **high spatial resolution 2-D X-ray** unit (Faxitron) and also a **gamma irradiator** totally dedicated to research (BIOBEAM 8000).

Each of these equipment can provide both a diagnostic tool and/or development aid of new therapies (biodistribution and/or therapeutic efficacy). The potential of small animal imaging in the field of translational research against cancer will be illustrated. Indeed, ENI works closely with (i) researchers in oncology (academic teams and private companies) who expose their problems and their needs for imaging, (ii) chemists and radiochemists able to develop new radiolabeling methods and (iii) radiopharmacists and doctors of the University Hospital of Toulouse and IUCT-O who ensure transfer of fundamental researches to clinic. Thus, ENI wants particularly to invest in the development and characterization of **new tracers** (possibly multimodal) for PET, SPECT, MRI and even optical imaging to meet the specific needs of each project.

P519

Image analysis in small animal models: CREFRE-ENI offer

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Small animal Non-Invasive Exploration (ENI) preclinical facility belongs to the Inserm unit UMS006/CREFRE. This unit aims at providing a continuum of services ranging from the creation of mice models to their phenotypic characterization with priority given to welfare of animals and conservation of their health status. ENI department proposes a huge panel of state-of-the-art imaging technologies:

- Single Photon Emission Computed Tomography (nanoSPECT-CT)
- Positron Emission Tomography (nanoScan PET-CT)
- Computed Tomography (CT)
- High-resolution ultrasound imaging (Vevo 2100)
- Magnetic Resonance Imaging (MRI 7 T) unit (coming soon)

To take the better advantage of these complementary technologies, ENI also provides high level data analyses tools and expertise.

Indeed, these equipments give access to precious data for characterization of small animal models (mice, rats, marmosets) of human disease, new tracers and drugs characterization/evaluation to improve diagnostic arsenal and/or providing development of new therapies (biodistribution and/or therapeutic efficacy). But, to take the better profit of this, the way one will analyze, construe them, is crucial.

ENI's team proposes to adapt data analysis methodology to the specificity of each imaging project. To allow this, the way we work is based on close collaboration between our team and, on the one hand, each user expertise and, on the second hand, on our scientific network of expert from complementary fields of research: data analysis/post treatment, statistics, biology, medicine, radiochemistry, physics….

In this presentation, we will illustrate, by taking some examples, how we use the different analysis softwares that we possess (PMOD, Interview Fusion, Vevolab, Matlab, Fiji, ICY, SPM, python packages, R…) for better quantification (ROI definition, image segmentation, brain atlas PET/SPECT/MRI coregistration) and multimodal image fusion.

P520

Electrochemotherapy guided by intraoperative fluorescence imaging for the treatment of inoperable peritoneal micro-metastases

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Surgery is often the first therapeutic indication in cancer. Patient survival essentially depends on the completeness of tumor resection. This is a major challenge, particularly for peritoneal carcinomatosis (PC) tumors widely disseminated in the large peritoneal cavity. These small tumors can be difficult to visualize and are often positioned in delicate locations. We propose an innovative therapeutic approach based on intraoperative fluorescence (IF) guided electrochemotherapy (ECT) for the treatment of peritoneal micro-metastases. ECT is clinically validated for the treatment of cutaneous tumors in animals and humans, but this is the first time that it has been used along with IF imaging for the targeted treatment of peritoneal metastases in a preclinical model. We set up a murine model of PC that develops secondarily to the resection of a distant primary tumor. Tumor growth and metastasis were monitored by non-invasive multimodal imaging. Mice were randomized into three groups: ECT group (bleomycin injected intravenously + EP) and 2 control groups (bleomycin alone and EP alone). 24hours after the intravenous injection of the tumor targeting agent Angiostamp™700, mice in all groups underwent an abdominal surgery for metastases exploration assisted by fluorescence imaging with the Fluobeam®700 portative device. EP was applied to every nodule detected by IF, except in the bleomycin control group. After surgery, the metastatic invasion was tracked by bioluminescence imaging. In mice treated with bleomycin or EP alone, the metastatic load progressed very rapidly and mice showed no significant difference in lifespan compared to non-operated mice. In contrast, the mice treated with ECT displayed a decreased metastatic load and an increased survival rate. These results provide evidence that IF guided ECT is an effective approach for the treatment of inoperable intraperitoneal micro-metastases.

Posters - Industrial Partnership & Technology Platforms

P601

DiaDx, liquid biopsy for personalized medicine in Oncology: New Research Use Only Services and Diagnostic Kits for Companion Diagnostics.

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Background: Spatial and temporal clonal tumor heterogeneity limits accuracy of mutations identification when tumor molecular characterization is conventionally performed from tumor tissue (TT) specimen or biopsy.
Activities: By using its proprietary IntPlex® technology, DiaDx offers RUO services and assays for a pro-active diagnosis with a simple blood sample allowing whole and real-time molecular tumor characterization. IntPlex® provides unique multiparametric analysis of circulating DNA with unprecedented sensitivity level for mutation detection < 0.005% (*KRAS, NRAS, EGFR, PIK3CA*…).
Clinical validation through peer-reviewed publications in metastatic colorectal cancer: IntPlex® could replace TT analysis. A global concordance rate of 96% for *KRAS* exon 2 and *BRAF* V600E mutations between both approaches was found in a blinded study (n=106 patients). A retrospective blinded clinical study (n=48) showed that IntPlex® allowed to track acquired resistance conferring mutations in the course of treatment enabling prediction of relapse earlier than CT-Scan. Mutant allele frequencies < 0.01% were found responsible for acquired resistance highlighting the crucial need of high sensitive method such as IntPlex® as compared to other technical such as NGS. Recently, a real-time, blinded, multicenter and prospective clinical study (n=140) revealed clinical utility of IntPlex® under standard management care: the data turnaround time was 2 days while being 16 days for TT analysis; 25% of samples scored WT by TT analysis were found mutant by IntPlex® illustrating the fact that tumor-tissue analysis cannot provide a global spatial and temporal snapshot of the tumor as can do IntPlex®. In addition, mutant status as determined by IntPlex® was better correlated with clinical outcomes than TT analysis.
Conclusion: Ultrasensitive IntPlex® technology provides optimal mutation profile and offers to physicians a best-in-class assay.

P602

13C-Fluxomic and Isotopic Profiling - Powerful tools for metabolism investigation

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MetaToul Platform, LISBP

The study of metabolism in cancer cells has become a major research challenge with two main objectives: to characterize the metabolic dysregulations associated with cancer and to assist in the diagnosis and treatment of patients. As part of a partnership with the «Canceropôle Grand Sud-Ouest», the MetaToul-MetaboHUB platform (Toulouse, France) has developed ^{13}C-fluxomics approaches to characterize the unique metabolic features of cancer cells. Metabolic fluxes -*i.e.* the actual *in vivo* rates of biochemical reactions - represent the most accurate parameter for characterizing the actual operation of metabolic networks under specific physiological conditions. Intracellular metabolic fluxes are not measurable directly but can be accessed experimentally using ^{13}C-labeling strategies (^{13}C-fluxomics). The labeling patterns of metabolites (or end-products), measured by either MS or NMR, allows the calculation of intracellular fluxes from thanks to mathematical models describing the transition of single atoms in biochemical reactions as well as mass balances (Portais 1993, Szyperski, 1995; Wittmann, 2007). These methods are now well established for steady-state conditions, *i.e.* conditions where both the metabolism and the label incorporation have reached equilibrium, and have been successfully applied to the investigation of common microorganisms.
In this context, the platform offers a broad range of services, including the design of isotope-labelling experiments, protocols for sampling of labelled material, the isotopic profiling of metabolites using NMR or mass spectrometry, the processing and interpretation of isotopic data, and the calculation of metabolic fluxes. MetaToul-MetaboHUB is also providing support and expertise to interpret the data in a biological context.

P603

MPCC Platform: Preclinical models of Digestive Cancers

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The Montpellier scientific community felt the need to set up a platform dedicated to *in vivo* studies in oncology, more precisely for digestive cancers. In this context, the SIRIC Montpellier Cancer helped created, two years ago, the MPCC platform « Modèles Précliniques de Cancers Colorectaux ». Lucile Canterel-Thouennon has been recruited to develop and perform the preclinical experiments. MPCC's aim is to help researchers to better understand the processes behind tumor growth and metastases dissemination, as well as to test new molecules or drug combination to better predict human's response. MPCC's services may include in vivo study design, surgery, treatment, blood collection, tumor growth follow up by imaging, tissues sampling and data analyses.
As of today, we offer three types of surgery: intrasplenic, intracaecal and intrapancreatic grafts. In order to be as close as possible to the human pathology, the intrasplenic graft which gives hepatic metastases has been developed. This model mimics the hepatic metastases observed in colorectal cancers patients.
Intracaecal and Intrapancreatic grafts are two orthotopic models also available. All these surgeries can be performed on immunocompetent mice or on various immunodeficient mice. Working with luciferase transfected cells help to follow tumor localization, tumoral growth through time as well as the tumoral dissemination cell tracking. A panel of colorectal cancer cell lines has already been tested: SW620-luc, HCT116-luc, HT29-luc, CT26-luc… For pancreatic cancer grafts, cell lines already tested include BxPC3.
MPCC closely interacts with various platforms in Montpellier, *i.e.* the Animal, Living animal imaging and Histology facilities, respectively RAM, IPAM & RHEM.

P604

Development of a combined laser microdissection and proteomic analysis method, for identification of tumor signatures and targeted biomarkers quantification.

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Currently, the identification of genomic abnormalities in tumors allows to establish prognosis and to predict the susceptibility or resistance to some chemotherapies raising the possibility in the near future of individualized therapeutic approaches and thus better management of patients. Proteins expression is the downstream result of these combined genomic anomalies in tumoral cells and is essential for a better understanding of the mechanisms of cancer initiation, tumoral progression and metastatic scattering and to identify new biomarkers and pharmacological targets.

Mass spectrometry is the method of choice to identify, characterize and quantify the proteins in a complex sample. We have developed a method combining laser microdissection and mass spectrometry analysis to compare the levels of protein expression between tumoral and non tumoral tissue derived from the same patient on formalin fixed paraffin embedded tissue sections. After selection and cut of the areas of interest, proteins were extracted and the fixation reversed. Proteins were then digested by trypsin and the peptides analyzed by LC-MS/MS. The protein amounts between non tumoral and tumoral cells were finally compared by a label free approach. This procedure has been optimized for the study of several tumor types even on small material obtained by biopsy.

We focused here on Hepatocellular adenomas (HCA), rare benign tumors that constitute a heterogeneous entity, divided into several groups based on patho-molecular features ((1) HCA HNF1A mutated, (2) Inflammatory HCA, (3) HCA beta-catenin mutated (4) and finally, the unclassified HCA without known mutation or biomarker identified. We analyzed with our method this unclassified HCA group that allowed us to reveal deregulations of protein expression.

In conclusion, with this method we can identify global protein signatures in tumors and thus provide a new tool for clinicians to identify new biomarkers.

P605

La Plateforme AAPRISS - Apprendre et Agir Pour Réduire les Inégalités Sociales de Santé - Méthodes et objectifs

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Les mécanismes de construction des Inégalités Sociales de Santé (ISS) mobilisent les Déterminants Sociaux de la Santé (DSS) qui s'accumulent tout au long de la vie. Pour les praticiens, les décideurs et les chercheurs, réduire les ISS nécessite d'apprendre et de travailler ensemble.
Faisant suite au programme de recherche AAPRISS, la Plateforme expérimente un modèle pour favoriser les partenariats avec les collectivités territoriales et des institutions de santé qui a pour but d'apporter les connaissances de la recherche aux programmes de santé ou impactant la santé.
La Plateforme met à disposition des acteurs en charge des politiques publiques et des équipes de recherche l'expertise nécessaire à la prise en compte de la santé et à l'étude des ISS dans les interventions.
La Plateforme travaille soit en partenariat (recherche commune de financements avec les partenaires), soit en mettant à disposition ses compétences et par une offre des formations. Son socle scientifique repose sur l'IFERISS (18 équipes de 12 laboratoires de disciplines diverses).
La démarche de la Plateforme s'appuie sur des méthodes de travail interdisciplinaires expérimentées au sein de l'IFERISS et intersectorielles expérimentées dans le programme AAPRISS.
La Plateforme a co-construit par exemple avec l'agence d'urbanisme et d'aménagement Toulouse aire métropolitaine et Toulouse Métropole une grille d'évaluation introduisant une préoccupation pour la santé dans les choix d'urbanisme.
Différents partenariats, avec la CPAM 31, l'ARS LRMP, le Ministère de la Justice, ou encore le Pôle régional de compétences, la Plateforme EPIDAURE sont en cours.
La Plateforme bénéficie du soutien de la LNCC et du Cancéropôle Grand Sud-ouest
Les connaissances issues de la recherche deviennent des outils d'aide à la décision pour tous les acteurs en charge des politiques publiques. La plateforme contribue ainsi au rapprochement de la recherche et de la décision.

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Plateforme nationale au service de l'innovation et du transfert de technologie en cancérologie

MATWIN s'inscrit dans une démarche d'open-innovation pour développer la recherche translationnelle en cancérologie et raccourcir les délais de transfert des innovations vers les patients. Son objectif principal est d'accompagner des projets innovants à potentiel de développement industriel en favorisant des partenariats industriels précoces.

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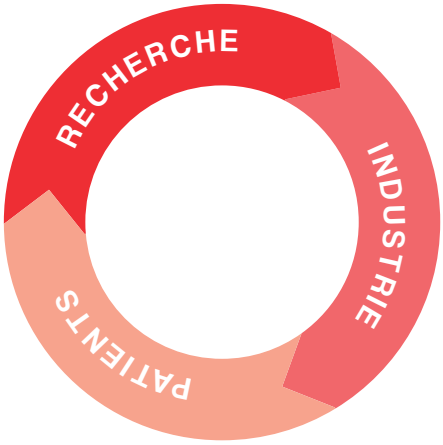

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Journées Cancéropôle Grand Sud-Ouest

23 au 25 Novembre 2016

Ces journées bénéficient du soutien de :

LA RÉGION OCCITANIE Pyrénées-Méditerranée

AstraZeneca

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