15èmes

Journées Cancéropôle Grand Sud-Ouest

20 au 22 Novembre 2019

Palais des Congrès / Arcachon

SEMINAR BOOKLET

Cancéropôle Grand Sud-Ouest

www.canceropole-gso.org

INSTITUT NATIONAL DU CANCER

L'équipe du Cancéropôle Grand Sud-Ouest remercie vivement

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

les membres du Comité de Pilotage Scientifique,

pour leur participation et leur implication dans l'élaboration du programme

de ces 15èmes Journées.

Comité de Pilotage Scientifique

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

Comités de pilotage des Axes

Axe 1 - Signalisation cellulaire et Cibles thérapeutiques
N. Bourmeyster, S. Britton, O. Coux, Y. Denizot, V. D'Hondt, K. Durand, L. Karayan-Tapon, C. Laurent, N. Larmonier, **J. Pannequin**, D. Santamaria

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

Axe 3 - Recherche translationnelle, de la biologie à la clinique
E. Assenat, N. Bakalara, P. Barthélémy, JP. Brouillet, T. Chardès, E. Chatelut, M. Dufresne, A. Evrard, V. Gigoux, N. Houédé, **AM. Khatib**, F. Lalloué, MA. Poul, I. Soubeyran, D. Tougeron, N. Tubiana-Mathieu

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

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

En tant que nouvelle Directrice du Cancéropôle Grand Sud-Ouest, je suis très heureuse de vous accueillir à Arcachon pour la 15ème édition de nos Journées Annuelles.

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

Ce programme est riche en interventions, de la part des chercheurs et des cliniciens de notre inter-région. Nos Journées sont aussi comme chaque année l'occasion d'accueillir des conférenciers invités de grande qualité que nous remercions vivement.

Nos Journées Annuelles reflètent ainsi le dynamisme de la recherche sur le cancer dans le Grand Sud-Ouest et le tissu dense de relations, de collaborations et de projets, créé depuis plus de 15 ans par notre communauté. C'est ce dynamisme que je souhaite renforcer grâce à des perspectives d'une meilleure intégration régionale des actions du Cancéropôle

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

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

Muriel Mathonnet
Directeur du Cancéropôle Grand Sud-Ouest

LE PROGRAMME DE SOUTIEN A L'EMERGENCE DU CANCEROPOLE GSO

NOUVEAU CALENDRIER : AAP OUVERT DU 27 JANVIER AU 6 MARS 2020 – SOUMISSION EN LIGNE

EMERGENCE DE PROJETS

OBJECTIFS Valider les premières étapes d'un projet ou une étude de faisabilité indispensables pour une soumission à un AAP national

CRITERES Approche nouvelle et originale, nouvelle voie d'exploration ou arrivée d'une équipe dans un nouveau champ disciplinaire

FINANCEMENT 20 k€ par projet (maximum)

EMERGENCE DE MODELES ET OUTILS

OBJECTIF Soutenir la mise en place de modèles et outils innovants avec une visée technique, allant des modèles biologiques à la modélisation et au traitement des données en lien avec le cancer, afin de favoriser la mise à disposition de nouveaux modèles pour la communauté du GSO et servir de tremplin pour l'obtention de financements plus importants

CRITERES Approche nouvelle et originale, impact du développement d'un tel modèle/outil en cancérologie

FINANCEMENT 20 k€ par projet (maximum)

EMERGENCE DE CONSORTIUM

OBJECTIFS Soutenir le développement de projets pluri-équipes au sein du GSO qui, avant de postuler à des appels à projets nationaux, doivent disposer de données préliminaires qui valorisent la complémentarité de leurs compétences

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

FINANCEMENT 20 k€ par projet (maximum)

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

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

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

FINANCEMENT 3 k€ par projet (maximum)

LES PROGRAMMES DE SOUTIEN DU CANCEROPOLE GRAND SUD-OUEST

MOBILITE TECHNOLOGIQUE

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

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

SEJOUR 3 mois maximum **FINANCEMENT** 4 k€ 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 2 k€ 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 20 k€ (maximum) destinés à financer des travaux ou de la mobilité

SOUMISSION EN LIGNE AU FIL DE L'EAU

NOUVEAUTE : COLLABORATION TRANSFRONTALIERE

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

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

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

SOUMISSION EN LIGNE AU FIL DE L'EAU

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

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

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

FINANCEMENT 40 k€ par projet (maximum)

SOUMISSION A L'AUTOMNE AUPRES DE LA DRCI DE L'ETABLISSEMENT PARTENAIRE

LES FORMATIONS DU CANCEROPOLE GRAND SUD-OUEST

LES TRANSLATIONNELLES DU GSO

Les Translationnelles réunissent de **jeunes médecins** (internes 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.

PRECEDENTES EDITIONS :

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

*PROCHAINE EDITION LE 13 DECEMBRE 2019 A TOULOUSE : CANCER DU POUMON. INFOS SUR **transla2019.canceropole-gso.org***

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

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

OBJECTIFS :

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

*PROCHAINE EDITION DU 14 AU 18 JUIN 2020 A TOULOUSE. INSCRIPTIONS SUR **imagerie.canceropole-gso.org***

DEVELOPPEMENT D'UN MEDICAMENT

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

PRECEDENTES EDITIONS :

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

WORKSHOP JEUNES CHERCHEURS

Le Workshop Jeunes Chercheurs a objectif d'améliorer la qualité des travaux et des publications de jeunes chercheurs. Il réunit des experts de renom et des jeunes chercheurs (post-doctorants seniors et jeunes titulaires) sélectionnés sur leurs travaux, en format résidentiel, afin de favoriser les échanges et de permettre aux jeunes chercheurs de bénéficier d'un coaching de qualité.

PRECEDENTES EDITIONS :

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

*PROCHAINE EDITION DU 13 AU 14 JANVIER 2020 A CARCASSONNE. INSCRIPTIONS SUR **yswbiofab.canceropole-gso.org***

PROCHAINEMENT

13 DECEMBRE 2019 : CANCER DU POUMON

La prochaine édition des **Translationnelles du GSO**, portant sur le cancer du poumon, aura lieu à Toulouse le 13 décembre. Cette journée est construite autour de sessions thématiques abordant tous les aspects de recherche, du fondamental à la clinique, suivie d'une table-ronde permettant aux participant d'échanger avec des experts du domaine. Les thèmes de cette édition : **Immunothérapie** ; **Thérapies Ciblées** ; **Nouveaux outils diagnostiques et thérapeutiques.** *Participation gratuite et hébergement offert pour les jeunes chercheurs et jeunes cliniciens (dates limites 22/11/2019 pour l'hébergement et 29/11/2019 pour l'inscription)*

Toutes les informations sur *transla2019.canceropole-gso.org*

Contact GSO : Alice BEIGBEDER

13 & 14 JANVIER 2020: YOUNG SCIENTISTS WORKSHOP « BIOFABRICATION & CANCER, FROM ORGANOIDS TO 3D PRINTING OF CANCER CELLS »

The 7th edition of the Young Scientis Workshop will be held in **Carcassonne**, January 13rd-14th. This workshop aims to allow young researchers to improve their ongoing projects and to enhance the quality of their future publications. Selected candidates will have the opportunity to present and discuss their work with keys opinion leaders in the field: Nathalie Vergnolle (Digestive Health Research Institute, Toulouse), Nicolas L'Heureux (BioTis, Bordeaux) and Fabien Guillemot (Poietis, Bordeaux). A training session on publication strategies will be provided by Abhay Pandit, senior associate editor at Biomaterials Journal (Elsevier, 2018 IF 10,273)

Contact GSO : Jean-Philippe BORGES

12-13 MARS 2020 : 9EMES JOURNEES DU CLUB SMAC « PHASES PRECOCES, TOXICITES, RISQUES COMPETITIFS »

Les 9èmes journées du club SMAC (statistiques et mathématiques appliquées à la cancérologie) se tiendront à Montpellier les 12 et 13 mars 2020. Deux journées ont été construites autour des thèmes **phases précoces, toxicités, risques compétitifs** : La première journée sera consacrée aux **nouveaux designs pour les essais de phase précoce**, la seconde à l'**analyse et au report des toxicités**.
Bien que relevant du Cancéropôle GSO, le comité scientifique du club s'ouvre progressivement aux chercheurs d'autres cancéropôles, cette année à PACA, afin de refléter la grande visibilité des conférences organisées par le club.

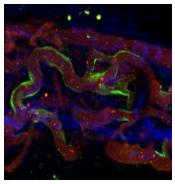
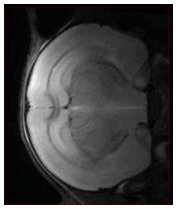
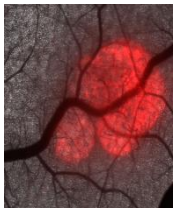
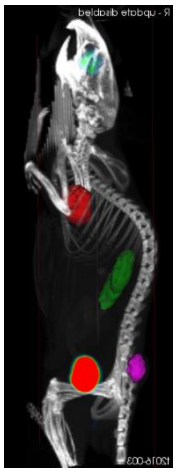
PRECEDENTES EDITIONS :

Le Club SMAC rassemble les chercheurs en statistiques et mathématiques autour d'un cycle de conférences visant trois objectifs abordés successivement :

- L'ouverture à des modèles encore peu utilisées en statistique en cancérologie
  - 2012 : Modèles de Markov cachés mixtes et traitement des données de cohortes de cancer
  - 2015 : Modélisation et simulation d'essais cliniques
  - 2018 : Médecine personnalisée, médecine de précision
- La présentation des développements de la recherche biostatistique en cancérologie à la communauté des chercheurs
  - 2013 : Dynamic predictions for repeated markers and repeated events
  - 2016 : Modélisation biostatistique et biomathématique des données d'imagerie
  - 2019 : Recent advances in joint models for cancer and the new statistical challenge of immunotherapy clinical studies
- La formation des jeunes et la diffusion des pratiques innovantes en biostatistique et méthodologie
  - 2014 : Évaluation et analyse de la qualité de vie en oncologie, nouveaux développements méthodologiques
  - 2017 : Actualité des critères de jugement en oncologie
  - 2020 : Phases précoces, toxicité, risques compétitifs

Contact GSO : Olivier CLAVERIE

6EME ECOLE D'IMAGERIE
DU PETIT ANIMAL APPLIQUEE AU CANCER
14 au 18 juin 2020, Toulouse

Lieu : Toulouse (Institut Universitaire du Cancer – Oncopole, CHU Purpan, CREFRE-Oncopole, IPBS)

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 6ème édition de cette école, organisée par le Cancéropôle Grand Sud-Ouest, le CREFRE et l'IPBS (plateformes GenoToul) 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 : Elisabeth BELLARD, Muriel GOLZIO, Carine PESTOURIE et Justin TEISSIE

Intervenants : Caroline DELMAS, Magali JACQUIER, Elisabeth MOYAL, Laure PARENT, Anne-Sophie SALABERT, Max BARDOTTI, Aymeric BLANC, Neal BURTON, Franck COUILLAUD, Frédéric COURBON, Philippe DAVAULT, Franck DESMOULIN, Tim DEVLING, Emmanuel GRAS, Renaud LEBRUN, Gilles RENAULT, Guillaume REVEILLON, Pierre SICARD, Philippe TROCHET

Conférencier invité : **Mickaël TANTER** (Institut Langevin, Paris) - « ***Nouvelles technologies d'imagerie en échographie*** »

Prérequis : Avoir un projet d'imagerie *in vivo*

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

Programme :

- **Formation théorique** : Optique, Bioluminescence, Fluorescence, Microscopie intravitale multiphotonique, Imagerie Nucléaire, Radiochimie et radiopharmacie, IRM, Echographie, Microtomographie Rayons-X, Irradiation guidée par imagerie, Endomicroscopie confocale laser, Anesthésies et confinement des animaux et des locaux, Règlementation et bien-être animal.
  Tables rondes, visite du cyclotron et du service de radiochimie PiR2.
- **Formation pratique** : des ateliers par petits groupes sur toutes les modalités d'imagerie avec des modèles murins.

Nombre de participants : 20

Tarifs (sans/avec hébergement) :
Académique : 700€ / 1100€
Privé : 1400€ / 1800€

Inscription avant le 15 avril 2020
Plus d'infos : http://imagerie.canceropole-gso.org

Le tarif « sans hébergement » inclut les repas du soir

*Prise en charge possible dans le cadre de la **formation professionnelle continue***

Validation d'unité de formation continue en expérimentation animale

Program

Wednesday 20nd November

13h45 – 14h00

Opening ceremony - Oncosphere presentation

Muriel MATHONNET, Cancéropôle Grand Sud-Ouest Scientific director

Pierre SOUBEYRAN, Inserm Actions for onCogenesis understanding and Target Identification in Oncology, Institut Bergonié (Bordeaux)

14h00 – 16h00

Chairs: Julie PANNEQUIN and Abdel-Majid KHATIB

Lecture: **Thomas HELLEDAY**, Weston Park Cancer Centre, Department of Oncology and Metabolism, University of Sheffield (United Kingdom) - **Targeting DNA repair: from basic biology to clinical trials**

- (Not) lost in translation: gene therapy for pancreatic cancer - **Pierre CORDELIER**, *Cancer Research Center of Toulouse*
- Smart-devices for the detection of circulating cancer biomarkers in clinical routine - **Aline CERF**, *LAAS-CNRS (Toulouse)*
- Mass spectrometry in clinical practice using hepatocellular adenomas as a proof of concept - **Frédéric SALTEL**, *Bordeaux Research in Translational Oncology*
- Glycosylation and cancer: the phostines window - **Norbert BAKALARA**, *Institute for Neurosciences of Montpellier*

16h00 – 17h00 Poster session & Coffee break

17h00 – 18h30

Chair: Olivier COUX

Lecture: **Sylvie URBE**, *Institute of Translational Medicine, University of Liverpool (United Kingdom)* - **Deubiquitylases (DUBs): druggable regulators of protein and organelle homeostasis**

- Targeting the ubiquitin-like molecule Nedd8 for therapeutic intervention - **Dimitris XIRODIMAS**, *Center for Biochemical and Macromolecular Research (Montpellier)*
- Hydrogen sulfide (H2S) signals through protein persulfidation - **Milos FILIPOVIC**, *Cellular Biochemistry and Genetics Institute (Bordeaux)*
- ER-resident oxidoreductase surfaces to promote liver tumor invasiveness - **Manon ROS**, *Bordeaux Research in Translational Oncology & Institute of Molecular and Cell Biology (Bordeaux)*
- The E3 ubiquitin ligase ASB2α in T helper 2 cells negatively regulates antitumor immunity in colorectal cancer - **Pierre LUTZ**, *Institute of Pharmacology and Structural Biology (Toulouse)*

Modération: Florence SORDES

Conférence: **Sandrine ROUSSEL**, *Université Catholique de Louvain (Belgique)* - **Education thérapeutique : constats, défis & applications en cancérologie**

- Programme ETP "GYN and Co LR": Evaluation d'une prise en charge précoce des troubles sexuels et fonctionnels pelviens chez les patientes traitées par curiethérapie utérovaginale ou intravaginale - **Anne STOEBNER**, *Département des soins de support, Institut du Cancer de Montpellier*
- Efficacité d'un programme d'ETP pour patients sous anticancéreux oraux - **Alice DHELLEMMES**, *Laboratoire CERPS (Toulouse)*

- Recrutement d'une patiente diplômée dans le cadre d'une UTEP rattachée à un Centre le lutte contre le cancer - **Emmanuelle ARFE**, *Institut Universitaire du Cancer Toulouse Oncopole*
- Effets de la réduction du stress basée sur la pleine conscience sur "l'empowerment" du patient atteint de cancer et sur la peur de la récidive - **Marion BARRAULT**, *Institut Bergonié (Bordeaux)*

Chairs : Marie-Piere ROLS and Hervé SEZNEC

Lectures: **Frédéric FRISCOURT**, *European Institute of Chemistry and Biology (Bordeaux)* - **Towards the Selective Tagging of the Sialome for Imaging Cancer Cells - A Chemical Biology Tale**

Véronique GIGOUX, *Laboratory of Physics and Chemistry of Nano-Objects (Toulouse)* - **Targeted magnetic nanoparticles remotely induced mechanical destruction of tumor microenvironment through rotating magnetic field**

6 selected talks for “Ma techno en 180 secondes” (flash-posters):

- Pulsed electric fields as key element overcoming cold-atmospheric plasma limits in cancer therapy - **Elena GRISETI**, *Laplace Lab & Institute of Pharmacology and Structural Biology (Toulouse)*
- Photodynamic therapy activity of new porphyrin-xylan-coated silica nanoparticles in a human colorectal cancer in vivo model - **Ludovic BRETIN**, *Peirene Lab, Limoges University*
- Detection of lipid droplets by MCARS microspectroscopy in cells expressing TrkB - **Tiffany GUERENNE-DEL BEN**, *Peirene Lab, Limoges University*
- Imaging of cancer cell death induced by magnetic hyperthermia - **Pauline JEANJEAN**, *IMOTION, Bordeaux University*
- Development of remotely controllable polymersomes for image guided drug-delivery - **Olivier SANDRE**, *Organic Polymers Chemistry Laboratory (Bordeaux)*
- Numerical investigation of the role of mechanical constraints on the growth of 3D tumour cells aggregates - **Vincent LE MAOUT**, *Institute of Mechanical Engineering (Bordeaux)*

18h30 – 19h30 Icebreaker & Poster session

Thursday 21st November

08h00 - 08h30 Welcome coffee

08h30 – 10h00

Chair: Malik LUTZMANN

Lecture: **Matthieu PIEL**, *Curie Institute (Paris)* - **Mechanisms and consequences of large nuclear deformation: from microchannels to breast tumors**

- A new way to escape: how structural centrosome aberrations promote invasive behaviors of epithelial cells - **Olivier GANIER**, *Institute of Human Genetics (Montpellier)*
- Making, watching and stressing tumor organoids in 3D - **Pierre NASSOY**, *Photonics, Numeric and Nanosciences Laboratory & Institut Optique Graduate School (Bordeaux)*
- MAGI1 suppresses luminal breast cancer through its interaction with AMOTs and the regulation of YAP signaling - **Alexandre DJIANE,** *Cancer Research Institute of Montpellier*

Modération : Louise POTVIN

Conférence: **Louise POTVIN**, *École de santé publique, Université de Montréal (Canada)* - **La recherche interventionnelle: science des solutions**

Table-ronde : Linda CAMBON *(UMR1212 Bordeaux Population Health)*, **Florence COUSSON-GELIE** *(Département Epidaure et Laboratoire Epsylon, Montpellier)*, **Cyrille DELPIERRE** *(UMR 1027 Epidémiologie et analyses en santé publique, risques, maladie chronique et handicap, équipe Equity, Toulouse)*, **Pierre INGRAND** *(Registre des cancers Poitou-Charentes, INSERM CIC 1402, Poitiers)*, **Grégory NINOT** *(Plateforme CEPS, Montpellier)*, **Philippe TERRAL** *(Centre de recherches sciences sociales sports et corps, Toulouse)*

10h00 – 11h00 Poster session & Coffee break

11h00 - 12h45

Chair: Sébastien BRITTON

Lecture: **Raphaël RODRIGUEZ**, *Curie Institute (Paris)* - **Prevalent roles of iron in cancer**

- Alternative therapeutic technologies to target undruggable proteins - **Muriel AMBLARD**, *Max Mousseron Biomolecules Institute (Montpellier)*
- Programming molecules for cancer therapy - **Sébastien PAPOT**, *Institute of Chemistry of Materials and Media of Poitiers*
- Targeting cancer stem cells with antibiotics - **Hélène GUILLORIT**, *Institute for Functional Genomics (Montpellier)*
- Oligo-urea foldamers used as tools to induce apoptosis: Study case of the death receptor DR5/TRAIL-R2 - **Benoit ODAERT**, *Institute of Chemistry and Biology of Membranes and Nano-objects (Bordeaux)*

Modération : Florence COUSSON-GELIE

Conférence: **Antoine DEUTSCH**, *Institut National du Cancer (Paris)* - **Les enjeux du déploiement national d'intervention probante**

- Transformer l'essai de l'expertise en recherche partenariale et interventionnelle : le rôle des plateformes d'expertise universitaire en Santé Publique - **Charlie MARQUIS**, *IFERISS (Toulouse)*
- Collaboration de recherche en ETP: retour d'expérience sur les freins et leviers - **Emilie GABORIT**, *IFERISS (Toulouse)*
- Pour des interventions justes nécessaires : élaboration d'un outil d'aide au repérage et de prise en charge du retour et/ou maintien en emploi pour des femmes diagnostiquées d'un cancer du sein. Projet REWORK-BC (SIRIC ILIAD) - **Bertrand PORRO**, *Université d'Angers et Université Paul Valéry (Montpellier)*

12h45 – 14h15 Lunch break

14h15 - 15h45

Chair: Malik LUTZMANN

Lecture: **Raphaël CECCALDI**, *Curie Institute (Paris)* - **How BRCA-deficient tumors ensure DNA replication and repair**

- New synthetic lethality approaches targeting DNA safeguard pathways and the mitochondrial step of nucleotide neosynthesis (pyrimidine) in breast cancer - **Stéphanie ARNOULD**, *Cancer Research Institute of Montpellier*
- Generation of cells resistant to tyrosine kinase inhibitors in chronic myeloid leukemia by a genome editing technique - **François-Xavier MAHON**, *CLCC Bordeaux & UMR1218 ACTION (Bordeaux)*
- Spatial distribution of FTO adjusts colorectal cancer stem-like properties through RNA modification - **Amandine BASTIDE**, *Institute for Functional Genomics (Montpellier)*

Chairs: Fabrice LALLOUE and Abdel-Majid KHATIB

Resistance of Melanoma to Immune Checkpoint Inhibitors is Overcome by Targeting the Sphingosine Kinase 1 - **Céline COLACIOS**, *Toulouse Cancer Research Centre*

Definition of new biomarkers of aggressiveness in glioma - **Elise DELUCHE**, *Limoges University Hospital*

Mutations of the B-cell receptor pathway confer chemoresistance in primary cutaneous diffuse large B-cell lymphoma leg-type - **Audrey GROS**, *Bordeaux Research in Translational Oncology and Bordeaux University Hospital*

7 selected talks (flash-posters):

- The endoplasmic reticulum resident-AGR2 protein: a novel secreted biomarker with pro-oncogenic properties - **Delphine FESSART**, *Actions for onCogenesis understanding and Target Identification in Oncology (Bordeaux)*
- Tumor antigen-specific CD8 T cells identified by TIM-3 expression predict response to PD-1 blockade in head and neck cancer - **Camille-Charlotte BALANÇA**, *Toulouse Cancer Research Center*
- Epithelial to mesenchymal transition (EMT) is associated with attenuation of succinate deshyfrogenase (SDH) in breast cancer, through reduced expression of SDHC - **Gro ROSLAND**, *Cellular Genetic and Biochemistry Institute (Bordeaux)*
- Towards Precision Medicine using Tumor-adapted H-1PV oncolytic virus in Preclinical Models of PDAC - **Pierre CORDELIER**, *Toulouse Cancer Research Center*
- Targeting proteolytic notch activation inhibits PD-1 expression and improves cytotoxic T lymphocytes (CTL) cytotoxicity against MSI and MSS tumor cells and enhances tumor-infiltrated CTLs and tumor regression - **Fabienne SOULET**, *Angiogenesis and Cancer Microenvironment Laboratory (Bordeaux)*
- Preclinical xenograft and culture models of Sézary syndrome reveal cell of origin diversity and subclonal heterogeneity - **Sandrine POGLIO**, *Bordeaux Research in Translational Oncology*

- Expression by immunohistochemistry of Anaplastic Lymphoma Kinase (ALK) in Glioblastoma Multiforme: Foreshadow of clinical implications (GLIMAL1 study) - **Labib EL HAJJ**, *Poitiers University Hospital*

Lecture : **Géraldine SIEGFRIED**, *Angiogenesis and Cancer Microenvironment Laboratory (Bordeaux)*- **Targeting Apelin cleavage sites for colorectal cancer treatment**

Modération: Annie SASCO

Conférence: **Emmanuelle RIAL SEBBAG**, *Epidémiologie et analyses en santé publique, risques, maladie chronique et handicap, équipe BIOETHICS (Toulouse)* - **Penser l'éthique au-delà de l'individu : pour une éthique collective**

- Effet du dépistage basé sur le PSA sur la mortalité par cancer de la prostate: résultats dans deux départements avec registre de cancer - **Faiza BESSAOUD**, *Montpellier Cancer Institute*
- Etat des lieux de l'information relative à l'oncofertilité pour les femmes jeunes atteintes d'un cancer du sein en ex-région Midi-Pyrénées: approches épidémiologique et éthique - **Florian MARTINET**, *Epidémiologie et analyses en santé publique: risques, maladies chroniques et handicaps (Toulouse)*
- **Silviane DARQUY**, *Bordeaux Population Health*

15h45 – 16h45 Coffee break

16h45 - 18h15

Chair: Muriel MATHONNET

Lecture: **Patrick PESSAUX**, *Strasbourg University Hospital* - **Planification-simulation-navigation: toward a precise surgery**

- Digital innovations in liver surgery: toward the digital tween - **Eric VIBERT**, *APHP - Paul Brousse Hospital (Villejuif)*
- From the bench to the bedside: development of SGM-101, a CEA-targeting agent for intraoperative fluorescence imaging of colorectal carcinoma - **Françoise CAILLER**, *SurgiMab (Montpellier)*

18h15 - 19h00

Chair: Julie PANNEQUIN

Lecture: **Hervé CHNEIWEISS** – *Inserm Ethics Committee President & Hed of the Neuroscience Department (Paris)* - **What are the current challenging ethical issues in oncology research ?**

Friday 22nd November

08h30 – 10h15

Chair: Violaine MOREAU

Lecture: **Martin HUMPHRIES**, *Wellcome Center for Cell-Matrix Research, University of Manchester (United Kingdom)* - **Mechanisms of extracellular rigidity sensing via the adhesion nexus**

- Glioblastoma metabolism and microenvironment: putting tumor back in context - **Thomas DAUBON**, *Angiogenesis and Cancer Microenvironment Laboratory (Bordeaux)*
- Mechanosensitive TRP channels push cancer cells invasion and metastasis formation - **Aubin PENNA**, *Signalisation and Membrane Ionic Transports Laboratory (Poitiers)*
- Role of Leukaemia Inhibitory Factor (LIF) on the tumorigenic properties of Cancer Stem Cells in gastric adenocarcinoma - **Lornella SEENEEVASSEN**, *Bordeaux Research in Translational Oncology*
- Regulation of tumor-derived DNA potential to activate anti-tumor immune responses by extracellular DNases - **Vanja SISIRAK**, *ImmunoConcEpt : Immunology from Concept and Experiments to Translation (Bordeaux)*

Chairs: Romain LARIVE and Abdel-Majid KHATIB

Lecture: **Rosa HERNANSAIZ BALLESTEROS**, *Institute for Computational Biomedicine (Heidelberg, Germany)* - **Multi-omics contextualisation of signalling pathways to identify drug targets and essential genes in cancer**

- Early evaluation of cancer treatments using modeling and AI - **Olivier SAUT**, *Institute for Research in Computer Science and Automation (Bordeaux)*
- Tumor microenvironment cellular network inference and analysis from bulk and single cell transcriptomes - **Jacques COLINGE**, *Cancer Research Institute of Montpellier*
- Radio-genomics approach for therapy response prediction - **Thierry COLIN**, *SOPHiA Genetics (Bordeaux)*

10h15 – 11h00 Coffee break

11h00 – 12h30

Chair: David SANTAMARIA

Lecture: **Mariano BARBACID**, *Spanish National Cancer Research Center - CNIO (Madrid, Spain)* - **Targeting K-RAS mutant lung tumors: an unmet medical need**

- Understanding and overcoming resistance to targeted therapy in lung cancer - **Julien MAZIERES**, *Toulouse Oncopole Cancer University Institute*
- Targeting acquired vulnerabilities in drug resistant BRAFV600E lung adenocarcinoma patients - **Marie-Julie NOKIN**, *Actions for onCogenesis understanding and Target Identification in Oncology (Bordeaux)*
- Notch Inhibition Overcomes Resistance to Tyrosine Kinase Inhibitors Promoted by Gate-Keeper Mutations in EGFR-Driven Lung Adenocarcinoma - **Antonio MARAVER**, *Cancer Research Institute of Montpellier*

12h30 – 12h45 Poster award session

12h45 – 14h00 Lunch

Session 1 – Translational research: from biology to clinics

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1 / 1
Targeting DNA repair: from basic biology to clinical trials

Thomas HELLEDAY

Weston Park Cancer Centre, Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

DNA damaging agents, i.e., radio- and chemotherapy, constitute the backbone for treatment of a wide variety of cancers and may result in complete cure from the disease. Here, I will give an overview on how DNA repair can be targeted using completely novel inhibitors and more specifically how cancer cells may require a specific DNA repair pathway to mediate survival to the high load of endogenous DNA damage. DNA repair inhibitors can be exploited in treatment of mutated cancers and here, I will present our pioneering work on using PARP inhibitors to selectively kill homologous recombination defective cancers and how this has been translated into the clinic. Furthermore, I will cover how to we identify novel targets using CRISPR-Cas9 and the difficulties of that approach. Novel targets emerging from our laboratory such as OGG1 and MTHFD2 will be discussed in detail and the strategies to advance these as anti-cancer treatments in a precision medicine approach. Finally, I will discuss the complication of targeting DNA repair proteins with many functions.

1 / 2
(Not) lost in translation: gene therapy for pancreatic cancer

Pierre CORDELIER

Cancer Research Centre of Toulouse

The main focus of this lecture will be to describe how molecular investigation of pancreatic tumors, a disease with no cure, translates into first-in-man gene therapy clinical trial for patients with this disease. In greater details, following a brief description of the function and the role of the selected candidate therapeutic genes, I will share with the audience the important steps leading to the production and the qualification of an innovative, clinical grade drug, and how we selected preclinical models and methodologies to best predict gene therapy product efficacy and follow-up in patients. We will discuss the main results of the phase I clinical trial, including ancillary studies and I will comment on the multicentric phase-II that is currently ongoing. Last, I will elaborate on what should be the next generation of gene therapy products that may be used for PDAC treatment.

1 / 3

Smart-devices for the detection of circulating cancer biomarkers in clinical routine

Alejandro K. JIMÉNEZ-ZENTENO[1], Julia CHERIER[1], Elise BOU[1,2], David BOURRIER[2], Bernard MALAVAUD[3], Christophe VIEU[2], **Aline CERF[1,2,4]**

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Liquid biopsy has the potential to revolutionize the clinical management of cancer patients and improve disease outcome. In this framework, circulating tumor cells (CTCs) could increase the temporal and spatial representativeness of heterogeneous solid tumors, both in primary and metastatic sites. In addition, minimally invasive techniques could offer frequent sampling, and consequently, enable real-time treatment adaptation and monitoring of the disease.

Microfiltration for CTC isolation has been widely explored using different configurations, constriction geometries, and materials. Considerable effort, particularly in the microfluidics field, has been devoted to improve devices' sensitivity, aiming for early detection of cancer. Blood filtration through porous membranes has shown limitations due to membrane fouling phenomenon and high transmembrane pressure drops. The former makes the use of pre-processed blood samples (i.e., diluted or pre-fixed) indispensable, requiring custom-made pumping units and the use of high filtration pressures, both inducing changes in the morphology and viability of CTCs.
We introduce novel micro-engineered devices for the isolation of CTCs from whole blood based on their intrinsic physical properties. Our technological solutions, relying on cutting-edge microfabrication technologies and supported by advanced computational simulations, were conceived to meet clinical requirements in order to facilitate the isolation of a large number of CTCs with low contamination levels, under physiological flow conditions (low-pressure regimes) and no blood pre-processing required to preserve cellular integrity and provide high-quality information. Captured cells can then be easily characterized, or collected for downstream analysis. The versatility and portability of our solutions renders them compatible with clinical routine, a step forward towards the implementation of liquid biopsy in clinical settings to guide medical decisions and adapt treatment plans at the patient scale.

1 / 4

Mass spectrometry in clinical practice using hepatocellular adenomas as a proof of concept

Margaux SALA[1], Delphine GONZALES[2], Thierry LESTE-LASSERRE[2], Nathalie DUGOT-SENANT[3], Valérie PARADIS[4], Sylvaine DI TOMMASO[1,5], Jean-William DUPUY[6], Vincent PITARD[7], Cyril DOURTHE[1,5], Jean-Frédéric BLANC[1,8], Charles BALABAUD[1], Paulette BIOULAC-SAGE[1], Anne-Aurélie RAYMOND[1,5,9,10], **Frédéric SALTEL[1,5,9,10]**

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[10] Contributed equally

Background & Objective:
Hepatocellular Adenomas (HCAs) are rare benign liver tumors. Bleeding and malignant transformation into hepatocellular carcinoma (HCC) are the two major complications. Until recently, 10% of hepatocellular adenomas (HCA) remained unclassified (UHCA). Among the UHCA, the sonic hedgehog HCA (shHCA) was defined by focal deletions that fuse the promoter of Inhibin beta E chain (INHBE) with GLI1. Prostaglandin D2 synthase (PTGDS) was proposed as immunomarker. This subgroup was associated with a high rate of bleeding. In parallel, our previous work using proteomic analysis showed that most UHCAs constitute a homogeneous subtype associated with overexpression of argininosuccinate synthase (ASS1). To clarify the use of ASS1 in the HCA classification and avoid misinterpretations of the immunohistochemical staining, the aims of this work were to study (i) the link between shHCA and ASS1 overexpression (ii) the clinical relevance of ASS1 overexpression for diagnosis.
Design:
Molecular, proteomic and immunohistochemical analyses were performed in UHCA cases of Bordeaux series. The clinico-pathological features, including ASS1 immunohistochemical labeling were analyzed on a large international series of 67 cases.
Results:
ASS1 overexpression and shHCA subgroup were superimposed in 15 cases studied by molecular analysis, establishing ASS1 as a biomarker of shHCA. Moreover, ASS1 immunomarker was better than PTGDS only found positive in 7/22 shHCA. Of the 67 UHCA cases, 58 (85.3%) overexpressed ASS1, 4 cases were ASS1 negative, and in 5 cases ASS1 was non contributory. Proteomic analysis performed in case of doubtful interpretation of ASS1 overexpression, especially on biopsies, can be a support to interpret such cases.
Conclusion:
ASS1 overexpression is a specific hallmark of shHCA known to be at high risk of bleeding. Therefore, ASS1 is an additional tool for HCA classification and clinical diagnosis. Moreover, mass spectrometry consists in an innovative way for HCA diagnosis.

1 / 5
Glycosylation and cancer: the phostines window

Emilie MARHUENDA[1,2,3], Ali SALEH[1,2,3], Zahra HASSANI[1,2,3], Ludovic CLARION[1,2,3], David VIRIEUX[1,2,3], Jean-Luc PIRAT[1,2,3], Hugues DUFFAU[1,2,3], Luc BAUCHET[1,2,3], Jean-Philippe HUGNOT[1,2,3], Julien CAMBEDOUZOU[1,2,3], David CORNU[1,2,3], **Norbert BAKALARA[1,2,3]**

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[3] Institut Charles Gerhardt, Montpellier

Current standard of care against glioblastoma (GBM) including surgery, chemotherapy and radiotherapy have limited efficacy on the overall patient survival expectancy. Invasive tumor cells, called glioblastoma stem cells (GSC), disseminate within the normal brain parenchyma, escaping surgical resection, resisting localized radiation and chemo-therapies, and are responsible for the fatal outcome. Clinical observations demonstrate that glioma cells preferentially migrate in fibrous areas. Moreover, desmoplastic process in vivo during tumor progression promotes the orientation of Extra Cellular Matrix (ECM) fibers proteins, increases stiffness of microenvironment and organized ECM orientation characterizes the tumor environment and poor prognostic.

GSC are sensitive to the stiffness of their environment. They use mechanical properties of the microenvironment to optimize invasion and thus penetrate far into the brain parenchyma whereby they escape resection and localized radiation therapy. Since the invasive properties of GSCs are to a large extent determined by the rigidity of the 3-dimensional topography of their microenvironment, we developed an artificial in-vitro 3D fibrillary tissue mimicking the in-vivo conditions. We designed 3D electrospun nanofibers (NF) with different stiffnesses to study the influence of mechanical properties of the support on GSC migration. We determined that migration of GSCs was highest at an intermediate stiffness characterized by a Young's modulus of 166 kPa as compared to tissue with moduli of 3.2 kPa, 542kPa and 1260 kPa. Migration rate was correlated with cell shape (spindle vs spread-out), expression of proteins implied in the Epithelial to Mesenchymal Transition (EMT) as well as regulation of proteins of the adhesomes. Mannoside acetyl glucosaminyltransferase 5 (MGAT5) overexpression is a feature of malignant tumors. The enzyme is implied in the clustering of membrane proteins forming adhesomes, in cell migration and EMT. We demonstrate that knock-out of the MGAT5 gene causes a drastic reduction of migration on tissue with the intermediate stiffness of 166 kPa associated with a decrease in focal adhesion maturation and EMT, but not on other tissues. We argue that MGAT5-mediated glycosylation is at the heart of mechanotransduction by GSC.

We have established a strategy based on rational drug design to create glycomimetic compounds - phosphinosugars also called phostines - in which the hemiacetal group of an hexopyranose was replaced by a chemically and configurationally stable phosphinolactone group with the aim to interfere with glycosylation in cancer cells. In vitro phenotopic screening of several derivatives bearing this scaffold described by Clarion et al revealed potent antimigratory and NS formation of GSC activities. The in vivo pharmacological activity of PST**3.1a**, lead compound, was shown in orthotopic graft models of GSC.

Session 2A – Post-translational modifications and cancer

2A / 1

Deubiquitylases (DUBs): druggable regulators of protein and organelle homeostasis

Sylvie URBE[1], Erithelgi BERTSOULAKI[1], Jane JARDINE[1], Andreas KALLINOS[1], Anne CLANCY[1], Hannah ELCOCKS[1], Joana GOMEZ[1], Elena MARCASSA[2], Emma RUSILOWICZ[2], Michael CLAGUE[1]

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Deubiquitylases (DUBs) fulfill a plethora of functions ranging from infrastructural core tasks (eg maintaining ubiquitin homeostasis), to highly specialised roles in stabilising defined sets of substrates (including oncogenes) or regulating signalling networks, intracellular trafficking and DNA repair pathways1. DUBs are emerging as promising new drug targets in cancer therapy, with the recent description of highly selective inhibitors adding to the promise.

I will discuss our efforts in characterising the biology of DUBs that offer opportunities to establish this class of enzymes as actionable drug targets in these disease settings.

2A / 2
Targetting the ubiquitin-like molecule NEDD8 for therapeutic intervention

Dimitris XIRODIMAS

Centre de Recherche en Biologie cellulaire de Montpellier

A key characteristic of ubiquitin and ubiquitin-like (Ubl) molecules such as SUMO and NEDD8 is their ability to modify substrates as single moieties or in the form of polymeric chains. The extent and topology of polymeric chains is finely balanced by the coordinated action of conjugating and de-conjugating enzymes. The activity of these enzymes is altered as part of the cellular response to stress and is de-regulated in pathological conditions including cancer, immunological and neurodegenerative diseases. Hence, these enzymes are regarded as major targets for therapeutic intervention. We identify the deconjugating enzyme for NEDD8, NEDP1/SENP8 as potential tumour suppressor. We found decreased levels of NEDP1 levels in Hepatocellular Carcinoma with concomitant accumulation of poly-NEDD8 conjugates. Biochemical and genetic analysis in human tissue culture cells and in C. elegans shows that deletion of NEDP1 causes the accumulation of NEDD8 chains, which prevent the induction of apoptosis upon DNA damage. Mechanistically, we found that NEDD8 chains directly bind to the HSP70 chaperone and inhibit the HSP70 ATPase activity, which is required upon DNA damage for the formation of the APAF1 apoptosome and apoptosis induction. The studies identify HSP70 as sensor of changes in the balance between mono- and poly-NEDD8 chain formation controlled by NEDP1, with direct impact on DNA damage induced apoptosis. They also suggest that the reported upregulation of protein NEDDylation in several tumours maybe due to defects in the levels and/or activity of NEDP1/SENP8.

2A / 3
Hydrogen sulfide (H2S) signals through protein persulfidation

Emilia KOUROUSSIS, Jasmina ZIVANOVIC, Biljana BURSAC, **Milos FILIPOVIC**

IBGC UMR5095, CNRS, University of Bordeaux

Life emerged in hydrogen sulfide (H2S) environment eons ago, and even flourished in the same environment for billion years. Its role outside of sulfur metabolizing bacteria was, however, neglected but ever since the first report of H2S's potential physiological role, there has been a burgeoning literature on the subject of H2S signaling. Signaling by H2S is a new field of research and the exact mechanisms of H2S actions are still under active investigation but the evidence accumulates to suggest that H2S signals through protein persulfidation, a posttranslational modification of cysteine residue. To study this posttranslational modification, we have developed new tools which allow us to selectively label protein persulfides. Our data show that this modification is conserved through evolutions in all species and that it is the integral part of thiol-based redox signaling serving as a mechanism to protect cysteine residues. Receptor tyrosine kinase signaling seems to be particularly regulated by protein persulfidation. Persulfidation of epidermal growth factor (EGF) receptor decreases its phosphorylation and activation by EGF. EGF-induced cytoskeleton remodeling and proliferation are also affected by persulfidation. Our data suggest that this new posttranslational modification is of relevance for the regulation of basic cellular functions and that it may be a good therapeutic target for cancer treatment.

2A / 4

ER-resident oxidoreductase surfaces to promote liver tumor invasiveness

Manon ROS[1,2,3], Joanne CHIA[2], Anh Tuan NGUYEN[2], Xavier LE GUEZENNEC[2], Ruth MCDOWALL[2,4], Sergey VAKHRUSHEV[5], Henrik CLAUSEN[5], Martin HUMPHRIES[4], Frédéric SALTEL[1,3], Frederic BARD[2]

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Metastasis is a major driver of cancer morbidity; it requires metalloproteases (MMPs) cleaving peptidic bonds in collagen fibers. Whether other enzymatic collagen processing is required is unknown. Metastasis of liver tumors is strongly dependent on the GALA pathway, which induces protein O-glycosylation in the ER (Nguyen et al., 2017). Here, we show that GALA also leads to O-linked glycosylation of ER resident protein calnexin (cnx), which along with oxidoreductase ERp57, traffics to the cell surface and accumulates at sites of ECM degradation called invadosomes. We show that cnx/ERp57 complex in the presence of secreted glutathione reduces abundant disulfide bonds in the ECM, a process that is essential for collagen degradation. These findings uncover a moonlighting function or cnx/ERp57 essential for disulfide bond reduction during collagen degradation by metastasizing cancer cells.

2A / 5

The E3 ubiquitin ligase ASB2α in T helper 2 cells negatively regulates antitumor immunity in colorectal cancer

Camille SPINNER, Isabelle LAMSOUL, Arnaud MÉTAIS, Chanaëlle FÉBRISSY, Anne GONZALEZ DE PEREDO, Christel MOOG-LUTZ, **Pierre LUTZ**

Institut de Pharmacologie et de Biologie Structurale, Toulouse

The immune system plays major roles in the development, evolution, response to treatment and outcome of cancers. Notably, the quality of the immune response is an important prognostic factor for cancer patients and this is particularly true for patients with colorectal cancer (CRC), one of the most common malignant neoplasms with poor response to treatment and high mortality. The escape of cancer cells from host immunosurveillance involves a shift in immune responses, including an imbalance in T helper 1 (Th1) and Th2 cells. We here questioned whether the E3 ubiquitin ligase ASB2α has a role in T helper cells and in antitumor immunity.

We showed that ASB2α is expressed in the Th2 subset of CD4 positive T cells and that its expression is positively regulated by the master transcriptional regulator of Th2 cells, Gata3. Importantly, the production of Th2 cytokines is reduced following*ASB2* deletion in mice, indicating that ASB2α controls the effector functions of Th2 cells. We then questioned whether ASB2α has a role in Th2 cells and in the immune response to CRC. Consistent with the fact that a Th1-dominated immune response predicts positive outcome CRC, we found that high *ASB2* levels in CRC biopsies associated with poor outcome in CRC. To elucidate a potential functional relationship between *ASB2* expression and CRC, we subjected *ASB2* knockout and control mice to a model of colitis-associated tumorigenesis. Accordingly to the patient data, we found that loss of ASB2α in hematopoietic cells promoted a Th1 response and attenuated colitis-associated tumorigenesis in mice. Furthermore, diminished Th2 function correlated with increased IFN-γ production and an enhanced type 1 antitumor immune response in *ASB2*-deficient mice (Spinner et al., Cancer Immunology Research 2019).

At the molecular level, ASB2α is the specificity subunit of a Cullin 5-RING E3 ubiquitin ligase and is known to exert its effects through the polyubiquitylation of specific substrates leading to their degradation by the proteasome. To identify ASB2α substrates to be degraded in Th2 cells is critical to modulate ASB2α function for therapeutic means. We therefore performed an in-depth comparison of the proteome of Th2 cells from *ASB2*-deficient and control mice to identify proteins that accumulate in ASB2α-deficient cells but not in ASB2α-expressing cells. How ASB2α-mediated degradation of its specific substrates in Th2 cells drives an adaptive immune response that supports tumor development will be presented.

Our work suggests that ASB2α promotes a Th2 phenotype in vivo, which in turn is associated with tumor progression in a mouse model of colitis. Taken together, our results substantiate a pro-tumor activity of Th2 cells in CRC and suggest that ASB2α may serve as a therapeutic target in CRC.

Session 2B – Education thérapeutique

2B / 1
Education thérapeutique : constats, défis & applications en cancérologie

Sandrine ROUSSEL

Université Catholique de Louvain (Belgique)

L'Education Thérapeutique du Patient a été définie en 1998 par un groupe de travail de l'Organisation Mondiale de la Santé. Actuellement, les concepts-clés qui semblent faire consensus (santé globale, autonomie, participation, paternalisme, éducation thérapeutique…) recouvrent en réalité, dans les équipes de soins, des représentations variées. L'Education Thérapeutique prend aussi différentes formes. Cette « double » diversité est un constat qu'il importe de considérer tant sur le plan des pratiques professionnelles que sur le plan de la recherche et ce, afin de faire face aux défis que représentent la santé des populations, en général et les approches en cancérologie, en particulier.

Quelles sont les pratiques actuelles d'Education Thérapeutique ? Comment expliquer cette variété ? Quel éclairage peuvent nous apporter les représentations sociales ? Quelle est la diversité des représentations des concepts-clés en Education Thérapeutique ? Telles sont les interrogations que cette intervention se propose d'aborder.

La prise en considération de cette diversité est un premier pas. Il n'y a pas une mais des manières d'y répondre. Un minimum de consensus et dès lors, de dialogue, est néanmoins essentiel. La diversité actuelle de l'Education Thérapeutique ouvre en effet sur des réflexions telles que : les approches participatives doivent-elles être incarnées par toute l'équipe ou par certains soignants (plus à l'aise avec ce type d'approche) et soutenues par les autres soignants ? Les concepts-clés en Education Thérapeutique doivent également être clarifiés. En matière de recherches, cela permettra de ne pas en rester à des sous-entendus. En matière de pratiques professionnelles, tout l'enjeu consiste à assurer la cohérence de l'approche éducative auprès du patient.

2B / 2

Programme ETP « GYN and Co LR» : Evaluation d'une prise en charge précoce des troubles sexuels et fonctionnels pelviens chez les patientes traitées par curiethérapie utérovaginale ou intravaginale

Anne STOEBNER-DELBARRE[1], Marie-Eve HUTEAU[1], Martra JARLIER[2], Nabila BOUAZZA[3], Caroline PERRIER[4], Huguette GELY[5], Sophie BARDES[5], Hélène DE FORGES[5], Christine KERR[5]

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Contexte : L'annonce d'un cancer pelvien et ses traitements entrainent des souffrances physiques et psychiques qui altèrent la vie affective et sexuelle des patientes. Depuis 2011 un programme d'ETP « GYN and Co LR » est proposé à l'Institut régional du Cancer de Montpellier (ICM) aux patientes dès la consultation d'annonce en radiothérapie. Les soignants impliqués ont été formés en ETP (40h) et à l'abord des troubles de la sexualité.

Méthode : Début 2017, un auto-questionnaire anonyme a été envoyé aux 349 patientes traitées, de 2014 à décembre 2015, par curiethérapie utérovaginale (PDR) pour un cancer du col, ou curiethérapie du fond vaginal (HDR), pour un cancer de l'endomètre ou du col opéré, de stade I à III. L'auto-questionnaire comprenait des questions ouvertes favorisant la libre expression et des questions fermées pour recueillir des données : sociodémographiques, de qualité de vie (EORTC, QLQ-C30 et QLQ-CX24), d'utilisation des dispositifs de santé sexuelle et d'évaluation du programme ETP. Des données médicales ont été extraites à partir des dossiers informatisés. En fin de chaque année, l'équipe du programme a été réunie pour faire une auto-évaluation annuelle qualitative conformément aux directives de l'ARS Occitanie.

Résultats : 167 femmes (48%) ont répondu, 68 (41%) traitées par PDR, âge médian 56 ans (31-85), et 99 (59%) par HDR, âge médian 70 ans (44-96). 96,3% étaient ménopausées. Près de 2/3 des femmes (65%) étaient sans activité ou à la retraite et 12% ne travaillaient pas (en recherche d'emploi ou n'ont pas repris le travail). Plus de la moitié (56%) n'ont pas eu d'activité sexuelle les 12 derniers mois (49% et 60% des patientes traitées par PDR et HDR). Le programme ETP est « très apprécié » par plus de 70% des patientes. Elles considèrent avoir pu parler de leur sexualité avec un professionnel dans 76% des cas et avec leur partenaire dans 75% des cas. Un tiers des femmes s'inquiète de sa sexualité ; 69% ont utilisé les gels hydratants (78% et 63% des femmes traitées par PDR et HDR, p=0.036) et 57% les dilatateurs vaginaux, ces derniers ont été utilisés plus d'1 fois/semaine par 57% des femmes. 78% des femmes estiment que ces dispositifs font partie de leur traitement du cancer et 85% estiment avoir reçu les informations nécessaires pour les utiliser. 41% trouvent ces dispositifs chers et proposent qu'ils soient pris en charge par l'assurance maladie. Les auto-évaluations qualitatives de l'équipe objectivent une évolution du programme et des critères de l'ARS au cours du temps qui seront discutés.

Conclusion : Les résultats soulignent les difficultés sexuelles chez les patientes ayant un cancer pelvien et l'importance de faciliter leur expression sur ce sujet. Le programme « GYN and Co LR » est bien accepté et l'évaluation montre l'intérêt de co-construire, avec les patientes, un accompagnement éducatif personnalisé intégré aux parcours de soins dès l'annonce, et en lien avec la ville.

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Efficacité d'un programme d'ETP pour patients sous anticancéreux oraux

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La délocalisation de la chimiothérapie de l'hôpital vers le domicile et l'arrivée des anticancéreux oraux transforment radicalement le schéma thérapeutique des patients atteints de cancer. Ce dernier, inédit dans le domaine de l'oncologie, fait reposer l'efficacité du protocole sur la responsabilité entière du patient, de la délivrance du médicament à la gestion des effets secondaires. Cet éloignement de la sphère hospitalière et des soins de support amène les patients à gérer également seules les conséquences psychologiques de la maladie. Notre recherche consiste en l'élaboration d'un programme d'éducation thérapeutique et son évaluation. Une étude préliminaire de faisabilité auprès de patients testeurs est réalisée. La seconde partie de cette étude est exploratoire, l'objectif est de montrer les effets de l'éducation thérapeutique immédiats et/ou à long terme. Une méthodologie mixte permet d'explorer l'impact psychologique de l'annonce et de l'initiation du traitement oral, de cibler les besoins éducatifs des patients et préciser si ceux-ci sont en adéquation avec les recommandations de la littérature. De plus, les analyses statistiques évaluent l'évolution des représentations de la maladie et des traitements, le sentiment d'auto-efficacité et la qualité de vie des patients. Enfin, la comparaison des résultats des participants à l'éducation thérapeutique et ceux d'un groupe contrôle permet de rendre compte de l'efficacité du programme.

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Recrutement d'une patiente diplômée dans le cadre d'une UTEP rattachée à un Centre le lutte contre le cancer

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Un centre de lutte contre le cancer reconnaît l'expérience patient en salariant une patiente diplômée au service de la promotion d'un programme d'éducation thérapeutique. Positionner le patient diplômé dans un effectif de professionnels spécialisés en cancérologie, tel a été l'enjeu d'une réflexion pluridisciplinaire menée durant quelques mois à l'Institut Claudius Regaud à Toulouse. L'établissement coordonne un programme d'éducation thérapeutique au cœur des départements d'Occitanie Ouest en collaborant avec des professionnels libéraux. Riche de cette expérience et confronté à l'étendue de la nouvelle région Occitanie, l'établissement a recherché un professionnel en capacité de rendre opérationnel et de promouvoir le programme d'éducation thérapeutique « Cancer et traitement oral : je gère ! » sur l'ensemble des départements d'Occitanie Est.

La fiche de poste met en avant une bonne connaissance du territoire géographique et des structures sanitaires autorisées à la cancérologie. Elle plébiscite des compétences acquises par l'expérience des soins et met en avant les capacités d'adaptation, la volonté d'agir, de collaborer en équipe pluridisciplinaire et d'innover. Délocalisé au regard du site d'implantation de l'établissement recruteur, le poste implique une autonomie et une capacité d'initiative dans le domaine de l'éducation thérapeutique du patient. Une réflexion interne a permis d'envisager le recrutement d'un patient diplômé. Un déterminisme a concrétisé cette réflexion durant l'année 2019. L'intention de l'institution est de ne pas faire de la maladie un métier mais d'élargir la palette de compétences proposées aux patients atteints de cancer et aux professionnels partenaires. De ce fait, les compétences expérientielles, les compétences en lien avec une expérience professionnelle antérieure à la maladie se trouvent au service d'une relation de soin juste et humaine.

Le cadre de l'éducation thérapeutique a tout d'abord démontré sa justesse pour permettre à des personnes d'horizons différents de co-construire ensemble. Ensuite, il a été favorable à une collaboration entre « la ville » et « l'hôpital » pour présenter la maladie cancéreuse comme un vecteur d'apprentissage et développer la littératie en santé d'une population impactée par une pathologie grave et chronique. Passer de l'intention à la réalité d'embauche d'un patient diplômé dans le cadre de l'éducation thérapeutique du patient implique de répondre en amont à certaines questions. Au regard des réponses apportées, nous avons retenu 2 missions principales. Ces missions sont déclinées sous forme de connaissances, capacités et compétences requises à l'embauche. Une liste a été établie et permet une évaluation sérieuse.

Un patient diplômé, salarié au sein d'une équipe de professionnels de soins de support implique un élargissement des champs d'actions que nous pouvons maintenant préciser. Le statut de patient diplômé salarié permet une véritable crédibilité de ce dernier auprès des professionnels de santé et une pro-activité non remise en question. Après l'intégration de l'éducation thérapeutique dans les parcours de soins en cancérologie, le patient diplômé facilite sa promotion auprès des acteurs de « ville » et concrétise la continuité des soins entre l'hôpital et le domicile. Fort de son expérience de vie avec la maladie, le patient diplômé représente une ressource pour les professionnels de santé et fait bouger les lignes du partenariat en santé. Pour l'institution, il s'agit d'un acteur de santé qui intervient en éducation thérapeutique et porte des valeurs fortes de solidarité, d'engagement, et d'entraide. L'intervention d'un patient diplômé se révèle bénéfique pour envisager un partenariat soignant-soigné sur le long terme à travers un regard complémentaire et une logique de vie, d'autonomie voire d'économie.

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The effects of MBSR on "patient empowerment" and FCR in the context of oncology : a waitlist-control study

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[Titre français: Effets de la réduction du stress basée sur la pleine conscience sur "l'empowerment" du patient atteint de cancer et sur la peur de la récidive]

Introduction. As the cancer survival population is growing, "patient empowerment" has become a topical issue in health promoting intervention design emphasizing the active and informed role of the patient. However, most studies tend to focus specifically on medical-related issues neglecting therefore existential issues cancer patients might face following cancer diagnosis and treatment. Particularly, fear of cancer recurrence (FCR) is currently considered one of the most distressing consequences of cancer among cancer survivors. However, it has also been identified as one of the most prevalent unmet needs among cancer patients. The aim of the present study was to explore Mindfulness-Based Stress reduction (MBSR) as an empowerment-based approach for cancer patients (receiving curative treatment).

Methods. A waitlist-controlled trial design was used. Patients were invited to participate in the study following 8-week Mindfulness-Based Stress Reduction program. Empowerment (HEIQ), fear for cancer recurrence (IPRC) and mindfulness (FFMQ) were primary outcomes. Assessments were completed at Time 1 (pretreatment), Time 2 (posttreatment/post-waitlist).

Results. In total, 27 cancer patients receiving curative treatment were included in the study (26 women; 1 man; age_m=51.21; rang=32-75). Overall, 70.83% of the population reported clinical levels of PRC (scores IPRC: dimension "severity" >13) before and after MBSR. However, psychological distress regarding PRC decreased significantly among MBSR participants (*N*=21) when compared with waitlist participants (*N*= 8). At time 2, patients who received MBSR reported greater FFMQ and HEIQ scores than Waitlist participants and these effects were significant. In addition, results demonstrated significant correlations between scores from FFMQ, HEIQ, and psychological distress regarding PRC: higher levels of mindfulness and empowerment correlated with lower levels of psychological distress regarding PRC.

Discussion. MBSR appears to be an efficacious and empowerment-based treatment approach for cancer patients suffering from FCR. Limits of current conceptualizations of patient empowerment are outlined. However, further controlled trials with larger numbers of participants are required.

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Towards the Selective Tagging of the Sialome for Imaging Cancer Cells - A Chemical Biology Tale

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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 [1]. However, the azido-reporter is not completely biologically inert as it can react with biological functionalities such as thiols.[2] This inherent instability makes the azide functionality a precursor for the potential accumulation of secondary metabolites with unknown biological effects, ultimately raising some concerns about its application for in vivo imaging.

To address this limitation, we decided to investigate the utilization of 3,4-disubstituted sydnones, a singular class of highly stable mesoionic dipoles, as novel chemical reporters [3] for the metabolic oligosaccharide engineering of sialoconjugates in living cancer cells [4].

The positioning of the reporter on the sialic acid was found to significantly alter its metabolic fate, leading to the favored incorporation of the reporter into specific class of sialoproteins, bringing imaging of glyco-biomarkers one step closer to novel exciting cancer diagnostics.

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Targeted magnetic nanoparticles induced mechanical destruction of tumor microenvironment through rotating magnetic field

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

Cancer-associated fibroblasts (CAFs) secrete collagen increasing ECM density and factors promoting tumor growth and resistance acquisition of cancer cells. Thus, CAFs eradication constitutes an interesting strategy to disrupt tumor microenvironment and inhibit cancer progression. In this context, the development of targeted nanotherapy represents a real opportunity to propose new therapeutic solutions. Alternatively to local heat release upon a high frequency alternating magnetic field exposure, magnetic nanoparticles (MNPs) generate torque or mechanical forces in response to a rotating low frequency magnetic field (RMF).

Here, we chose this last property to elaborate a nano-therapeutic strategy directed against CAFs. The main objectives were to develop MNPs targeting pancreatic CAFs, chosen as a model, and to evaluate whether mechanical forces generated by targeted MNPs and RMF exposure could induce CAFs death.

To target pancreatic CAFs that express the type 2 cholecystokinin/gastrin receptor (CCK2R), we synthesized MNPs decorated with its agonist gastrin (MNP@Gastrin). We showed that MNP@Gastrin bind to the CCK2R, internalize and accumulate in the lysosomes of CAFs expressing the CCK2R. Then, we screened different amplitudes and frequencies of RMF and demonstrated that RMF exposure induces the death of CAFs having accumulated MNP@Gastrin into their lysosomes. The optimal condition was obtained with a 40 mT and 1 Hz RMF that causes the death of ~40% of CAFs. Finally, we showed that cell death occurs through a lysosomal pathway.

This study establish the proof-of-concept that targeted MNPs can cell death and disrupt tumor microenvironment through mechanical forces upon RMF exposure and open new opportunities for cancer therapy.

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Pulsed electric fields as key element overcoming cold-atmospheric plasma limits in cancer therapy

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This last decade, **cold atmospheric plasma** (CAP), an ionized gas composed of heat, reactive species, charged particles and photons, has been proposed as a new tool for several biomedical applications. Among them, the anti-cancer effect of CAP and more recently, **plasma-activated liquids** (PALs), such as culture media, water or buffered saline solutions, previously exposed to plasma has been reported on different types of cancer *in vitro* and *in vivo*. Nevertheless, in vitro tests show that this novel approach is sometimes less efficient than expected and displays penetration limits when tested on **three-dimensional multicellular tumor spheroids** (MCTS) that mimic small avascular tumors architecture.

In parallel, **pulsed electric fields** (PEF) are well-known in the literature for their potential to reversibly or irreversibly permeabilize the cell membrane. This technique is based on the capacity of PEF to modulate the cell electric transmembrane potential inducing transient pores at the cell membranes without disturbing cellular homeostasis. Interestingly, cell electropermeabilization (EP) is used in clinics for either anti-cancer drugs delivery (electrochemotherapy) or gene electrotransfer (electrogenotherapy). Currently, new EP strategies are under development to extend its applicability to different histological hallmarks tumors. EP combined with injection of supraphysiological doses of calcium has been recently proposed as a simple and inexpensive tool for anti-cancer therapy. This emerging therapeutic approach supports the theory that noncomplex chemical drugs can be combined with EP to cure cancer. We thus proposed to use EP in combination with PALs with the aim to potentiate its cytotoxic effect and enhance their delivery within 3D models in vitro or tumor in vivo.

In the present study, we evaluated the response to single treatment with **plasma-activated phosphate buffered saline**(P-A PBS) compared to dual-mode treatments (P-A PBS combined with EP) using colorectal cancer cells MCTS. For this purpose, we checked for MCTS growth, viability, and global morphological changes by live cell video-microscopy. In addition, the induction of caspases activation, appearance of DNA damages, as well as the early modifications in the cellular ultrastructure, were investigated. Our results showed that P-A PBS could penetrate deeper in the MCTS when EP was performed, spreading the cytotoxic effects to the entire MCTS. The in-depth spheroid death was correlated with an earlier onset of DNA damages and caspases activation, leading to mitochondrial stress and nuclear damages, which completely abolished MCTS growth. This work evidenced that**electropermeabilization greatly potentiates the cytotoxic effect of P-A PBS** *in vitro* on a three-dimensional cancer cell model. This first *in vitro* proof-of-concept will be further study on tumors *in vivo* where a more complex microenvironment is present including the immune system.

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Photodynamic therapy activity of new porphyrin-xylan-coated silica nanoparticles in a human colorectal cancer in vivo model

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Photodynamic therapy (PDT) using porphyrins has been approved in treatment of several solid tumors thanks to generation of cytotoxic reactive oxygen species (ROS). However, low physiological solubility and lack of selectivity towards tumors sites are the main limitations of their clinical use. Indeed, targeted drug delivery is an important issue for tumor therapy. Nanoparticles are able to spontaneously accumulate in solid tumors through the enhanced permeability and retention (EPR) effect due to leaky vasculature, poor lymphatic drainage and increased vessel permeability. The purpose of our study was to demonstrate added value of nanoparticles vectorization strategy on anticancer efficacy and tumor-targeting of the 5-(4-hydroxyphenyl)-10,15,20-triphenylporphyrin (TPPOH). Using the 80 nm silica nanoparticles (SNPs) coated with xylan-TPPOH conjugate (TPPOH-X), we first showed very significant phototoxic effects of TPPOH-X SNPs in HT-29 human colorectal cancer cell line compared to TPPOH free. Then, on HT-29 tumor-bearing nude mice, we highlighted without toxicity, a high anticancer efficacy of TPPOH-X SNPs through an improvement of tumor-targeting compared to TPPOH free.

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Detection of lipid droplets by MCARS microspectroscopy in cells expressing TrkB

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Cancer is characterized by uncontrolled cell growth, and cells spread to other sites in the organism, to generate metastasis [1]. In fact, specific markers are associated to cancer processes [1,2]. Among them, TrkB receptor, a member of the neurotrophin family, seems to be of particular interest. Surprisingly, this receptor family has been discovered in central and peripheral nervous systems, thereby regulating the growth and differentiation of neurons [3].

Expressed in other cells and activated by its ligand (BDNF), it is associated to tumorigenesis and metastasis [4]. Mainly, the BDNF/TrkB complex is strongly associated to colorectal cancer (CRC) allowing a cell growth, metastasis formation leading to a poor prognosis [5]. Lipid accumulation has already been observed in several human cancers such as brain, colon, breast, prostate, and is associated to the aggressiveness of cancer cells [6].

The aim of our study is to establish a link between the activation of TrkB and the accumulation of lipids in cells. For this purpose, we evaluated lipid metabolism changes by multiplex coherent anti-Stokes Raman scattering (MCARS) microspectroscopy, which is a label-free and non-destructive vibrational imaging technology, allowing the visualisation of lipids in cells with high sensitivity [7,8]. Cells were mapped by means of high spectral resolution (< 1 cm^{-1}) MCARS microspectroscopy in the 2500-3200 cm^{-1} range and images were reconstructed for the CH_2 (2850 cm^{-1}) vibrational signature, mainly associated to lipids.

We analysed three CRC cell lines (HCT-116, HT-29 and SW-620), which represent three stages of CRC, and differently express TrkB. Cell images at 2850 cm^{-1} show the presence of lipid droplets, mainly for HT-29 cells, which have the highest TrkB expression level.

To correlate the expression of TrkB receptor with lipid metabolism, we used HEK cell line, which does not express TrkB receptor. Cells were stably transfected in order to obtain a cell clone with a high expression of this receptor. When analysing HEK-Clones by MCARS microspectroscopy, we observed a higher intensity of CH_2 signature in cytoplasm for cells treated with BDNF. Moreover, CH_2 signature increases for longer treatment time and appears punctiform. It corresponds mainly to endoplasmic reticulum (ER) [9] where neutral lipids are synthesized. This shows that lipid metabolism increase observed in HEK-Clones depends on the presence of activated TrkB receptor. More specifically, we highlight the two major steps of biogenesis of lipid droplets: accumulation of neutral lipids in ER bilayer (diffuse signal) and generation of lipid droplets (punctiform signal) in function of time [10].

As a conclusion, we show that a high level of TrkB receptor expression in cells and its activation by BDNF foster an increase of lipid metabolism leading to lipid droplet accumulation in cytoplasm. This variation of lipid content was easily monitored by MCARS microspectroscopy. Thus, MCARS imaging proves to be a helpful tool to detect cancer cells without preliminary staining, and to set up a treatment since the presence of lipid droplets is associated to chemotherapy resistance [11].

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Imaging of cancer cell death induced by magnetic hyperthermia

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Thermotherapies use heat as therapeutic tools. For cancer treatment, according to the thermal dose delivered to tissues, temperature increase may induce thermo-ablation, indirect cell death by potentiation of other therapeutic agents or thermo-induced phenomena like gene expression or drug release. Magnetic nanoparticles (MNPs) placed in an alternative magnetic field (AMF) induce local hyperthermia. The present project examines the potential of MNPs for tumor thermotherapies.

MNPs are multicore iron oxide particles (18nm), with a high heat power (Specific Absorption Rate: 230W/g). They were coated with a thin silica layer doped by red and near infrared dyes and chemically surface-modified so as to make them positively charged in physiological conditions (patent pending).

Human glioblastoma cells (U87) and mouse prostate cancer cells (RM1) are genetically modified for constitutive expression of Firefly luciferase (LucF) for both cells or nanoluciferase (Nluc) for RM1 cells. For *in vitro* studies, cells were plated in 16-wells Nunc™ LabTek® microscopy chambers. MNPs were added in the culture medium at different concentrations and for different incubation times. For *in vivo*studies, cells (MNP-loaded or not) were injected subcutaneously into mice. Three mice species were used: ID mice are immunodificient NOG mice for U87-CMV-LucF cells, IC mice are immunocompetent C57bl6 albinos mice for RM1-CMV-LucF cells and thermosensitive mice are immunocompetent C57bl6 albinos mice genetically modified for thermo-induced LucF gene expression (Hsp70 promoter) for RM1-CMV-Nluc.

AMF were generated using an *in vitro/in vivo* setup working at 4 different frequencies. During AMF application, temperature raise was monitored using optical probes and infrared camera. Cells viability was followed by bioluminescence imaging (BLI). MNPs internalization was quantified *in vivo* by reflectance fluorescence imaging (FRI) or *in vitro* by flow cytometry. Fluorescence and electronic microscopies were performed to determine the MNPs localization into cells.

For *in vitro* studies, cells were incubated with increasing MNPs amount and followed in time for loading and viability. Higher internalization level was reached at 24h of MNPs incubation for concentrations equal and more than 250µg Fe/mL (300pg Fe/cell). MNPs alone did not affect cell viability and were mainly found in cytosol. MNPs-loaded cells were submitted to AMF, *in vitro*, or subcutaneously injected before AMF applications and in both cases, cells viability was not affected.

Then, MNPs were injected into subcutaneous tumors (1.3 or 0.6mg Fe/tumor) and submitted to 4 AMF applications (473.5kHz; 15mT; 15min) which resulted in temperature raise in the tumor. The decrease of BLI signal were observed 24h after AMF in regions corresponding to the MNPs location and maximum heating. For small tumors, MNPs injection and AMF applications resulted in complete disappearance of the BLI signal, which correspond to a total tumor thermo-ablation.

Magnetic hyperthermia effects on the tumor microenvironment (µE) was studied by thermo-activation of Hsp70 promoter. MNPs were injected into subcutaneous tumors (0.6mg Fe/tumor) implanted in thermosensitive mice and submitted at AMF. MNPs and AMF induced raise of temperature in the tumor, leading to a decrease of Nluc BLI signal of the tumor and an increase of thermo-induced LucF BLI signal of the µE. All together, these results show combined thermo-ablation of the tumor and thermo-modulation of the µE.

To conclude, cell-loaded MNPs were unable to induce cell death even at maximum internalization concentration, *in vitro* and *in vivo*. However, MNPs injected into the tumor followed by AMF application induce both cell death in the tumor and Hsp70 promoter activation into the µE. These data establish the proof of concept of combined tumor thermo-ablation and µE thermo-modulation induced by magnetic hyperthermia for synergetic therapies.

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Development of remotely controllable polymersomes for image guided drug-delivery

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Medical applications in nanotechnology are rapidly growing, with significant impact on diagnosis and therapeutics for the treatment of human diseases in particular cancer. Nanoparticle (NP) based drug delivery is of particular interest as these materials may show prolonged circulation half-life, reduced non-specific uptake, and increased accumulation in specific tissues and organs through enhanced permeation and retention (EPR). Among a high number of NP-based therapeutic approaches, our technology focus on the delivery of an active compound either by an external trigger or by an intrinsic chemical or biochemical stimulus of tumor environment, leading to gated drug release. Nano-systems allowing "on demand" liberation are relying on stimuli responsive (also termed "smart") materials triggered by pH, temperature modifications, variation of magnetic fields, or, light irradiation. Although this strategy promises considerable advantages in term of reduced general toxicity and diminished resistance against the drug, the field is still in infancy: external activation of prodrugs with localized liberation of compounds stays a major challenge.

The flash talk will describe the chemical part of a larger program that aims at the design, synthesis and study of remotely controllable polymersomes for biomedical applications and wish to finalize the development of a novel class of multisite device applicable in term in therapy, deep within the body. Polymersomes have proven their utility to deliver therapeutic agents to specific tissues/organs with potential therapeutic and theranostic applications where the therapeutic delivery can be simultaneously combined with diagnostic capabilities. They are extremely stable and robust - often too stable - for efficient drug delivery. The present application suggests method for image-guided local activation. The use of double selecting criteria, such as biological uptake and site selective activation would result in considerable reduction of adverse effects of many chemotherapy treatments what is always of paramount importance. At the heart of this novel activation methodology, we use recently developed fragmentation reaction that is based on (local) electron-transfer reaction triggered by penetrating X-ray, or gamma ray light; the method was patented, and optimizations for biomedical applications are actively pursued. The method allows X-ray-gated delivery of virtually unrestricted variety of compounds having therapeutic interest in otherwise inaccessible (body) spaces, with the ability to follow the distribution and the liberation in real time by different bio-imaging modalities, with the potential for multimodality. The technology uses a series of new redox fragmenting elements with charge-neutral nanoparticles (NPs) as sensitizers, in particular iron oxide NPs that are considered among the few nanomaterials that are nontoxic, biocompatible, approved for therapeutic use and can be imaged by MRI. The proposed technology has the potential in theranostic applications combining thus both the ability to deliver a drug on a controlled manner and to monitor its bio-distribution.

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Numerical investigation of the role of mechanical constraints on the growth of 3D tumour cells aggregates

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Recent years have seen a growing interest in the modelling of cancer from a mathematical and physical point of view. In this emerging field, a relevant analogy allows modelling tumor cell agglomerates as viscoelastic fluids with interfacial tension [1]. These agglomerates coexist in tumor environment with other phases (death cells, living cells, healthy cells, interstitial fluids etc.) inside the extracellular matrix. The dynamic of the cancer is then governed by multiphase flow dynamics in porous media [2]. However, this approach usually lacks of accuracy for modelling the subscale behaviour of cells populations. Consequently, it is not suited for reproducing in vitro mechanobiological experiment on individual tumor aggregate, such as in Cellular Capsule Technology (CCT) essays.

To provide new insights on the microscale collective motion of tumor cells, a mathematical model has been developed directly at the scale of the tumor aggregate. It makes use of the viscoelastic fluid analogy to describe growth evolution and mass exchanges between tumor cells and their environment. This approach permits to provide original explanation on CCT experimental observations [3], showing the relevance of the multiphase flow framework for the tumor growth description and the predictive capacity of the model. Particularly, the effect of mechanically constrained environment is explored in details, and its effect on tumor growth evolution is simulated quantitatively. This new theoretical model is aimed at providing rigorous microscale predictive capabilities to physical oncologic model, in order to help at understanding further the multi-scale nature of cancer biophysic.

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Session 3A – Mechanical constraints in oncological processes

3A / 1

Mechanisms and consequences of large nuclear deformation: from microchannels to breast tumors

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In tissues, extracellular matrix fibers and cells limit space. Migrating and proliferating cells thus often face situations of crowding and confinement, which can result in strong cell deformations. We showed that, in the case of migrating immune and cancer cells, such strong deformation can result in transient events of nuclear envelope ruptures accompanied by DNA damage and repair. I will present new results from a study aiming at understanding the long-term consequences of these nuclear envelope rupture events for proliferating cells. Starting with non-transformed culture cells, I will show that they result in induction of senescence, due to TREX1 dependent DNA damage - TREX1 depleted cells showing no senescence upon strong confinement. I will then describe the case of MCF10DCIS.com cells - a model of cultured human cells capable of producing duct carcinoma in situ in xenograft mice. In these cells, externally imposed as well as self-induced nuclear envelope ruptures due to growth and migration inside closed compartments, leads to TREX1 dependent DNA damage, activation of ATM and MT1-MMP dependent collagen degradation. This led us to propose that transformed p53 defective cells growing in the confining space of the mammary ducts, because they remain motile, deform their nucleus and rupture their nuclear envelope. This leads to DNA damage, activation of the DNA repair pathway, inducing collagen degradation, opening of holes in the duct walls, allowing formation of micro-invasions. Because these cells are p53 defective and thus do not turn on senescence upon DNA damage, this eventually leads to growth of tumor cells outside of the ducts and could thus favor an invasive state of the tumor. I will show also preliminary results testing this hypothesis in mice xenograft tumors and on samples from human patients.

3A / 2

A new way to escape: How structural centrosome aberrations promote invasive behaviors of epithelial cells

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Centrosomes are the main microtubule-organizing centers of animal cells. Although centrosome aberrations are common in tumors, their consequences remain subject to debate. Notably, centrosome aberrations are generally present in only a fraction of all tumor cells and, moreover, expected to impair cell viability. Hence, the question persists of whether and how centrosome aberrations contribute to cancer in humans. Here, we studied the impact of structural centrosome aberrations, induced by deregulated expression of ninein-like protein (NLP), on epithelial spheroids grown in Matrigel matrices. We demonstrate that NLP-induced structural centrosome aberrations trigger the escape ("budding") of living cells from epithelia. Remarkably, all cells disseminating into the matrix were undergoing mitosis. This invasive behavior reflects a novel mechanism that depends on the acquisition of two distinct properties. First, NLP-induced centrosome aberrations trigger a re-organization of the cytoskeleton, which stabilizes microtubules and weakens E-cadherin junctions during mitosis. Second, atomic force microscopy reveals that cells harboring these centrosome aberrations display increased stiffness. As a consequence, mitotic cells are pushed out of mosaic epithelia, particularly if they lack centrosome aberrations. We conclude that centrosome aberrations can trigger cell dissemination through a novel, non-cell-autonomous mechanism, raising the prospect that centrosome aberrations contribute to the dissemination of metastatic cells harboring normal centrosomes.

3A / 3
Making, watching and stressing tumor organoids in 3D

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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 allows us understand the biomechanical regulation of tumor progression and cell escape. We also describe applications to tissue bioengineering that exploit self-assembly of cell mixtures or that rely on the production of stem cells-derived organoids for cell therapy.

3A / 4

MAGI1 suppresses luminal breast cancer through its interaction with AMOTs and the regulation of YAP signaling.

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Alterations to cell polarization or to intercellular junctions are often associated with cancer progression in epithelial tissues, including breast cancers. We show here that the loss of the Tight Junction localized and scaffold protein MAGI1 is associated with bad prognosis in luminal breast cancers, and promotes anchorage-independent cell growth, clonal mammosphere formation, and tumor growth in xenografted nude mice. Mechanistically, we show that depending on extracellular matrix rigidity, MAGI1 loss promotes canonical or non canonical Hippo pathway activation to promote the phosphorylation of YAP. On rigid matrices, the interaction between MAGI1 and the apical scaffold and Hippo pathway negative regulator AMOTs, prevents the binding between AMOT and YAP and stabilizes AMOT binding to F-Actin. Accordingly, the absence of MAGI1 promotes the cytoplasmic localization of YAP and down-regulation of canonical YAP targets. These effects after MAGI1 loss are suppressed in the absence of AMOTL2, the main AMOT member in luminal breast, leading us to propose a model in which low levels of MAGI1 promote anchorage-independent cancer cell growth through a non-canonical cytoplasmic AMOTL2/YAP axis.

Session 3B – Recherche interventionnelle (1)

3B / 1
La recherche interventionnelle : science des solutions

Louise POTVIN

Université de Montréal (Canada)

Résumé :
Depuis longtemps, la recherche dans le domaine de la santé publique s'intéresse en priorité à la découverte des causes de la maladie constituant ainsi une véritable science des problèmes, ce qui perpétue le mythe que la connaissance des facteurs de risque est suffisante pour une santé publique fondée sur des données probantes. En contrepoint, la recherche interventionnelle en santé des populations (RISP) propose une science des solutions qui pose en objet de recherche les interventions de santé publique visant à modifier la distribution des risques dans la population. Cette présentation explorera les éléments distinctifs de cette « nouvelle science » et les défis auxquels elle doit faire face.

Note biographique :
Louise Potvin est professeure titulaire au Département de Médecine sociale et préventive à l'École de Santé publique de l'Université de Montréal et titulaire de la Chaire de Recherche du Canada sur les Approches communautaires et les inégalités de santé. Ses principaux intérêts de recherche sont la recherche interventionnelle en santé des populations (RISP) et le rôle des environnements sociaux dans la production et la reproduction des inégalités sociales de santé. En plus d'avoir dirigé ou co-dirigé la publication de 8 anthologies et 11 numéros spéciaux de revues, elle a publié tout près de 300 articles, chapitres de livre, éditoriaux et commentaires. Elle est Rédactrice-en-Chef de la revue canadienne de santé publique. Elle est membre de l'Académie canadienne des sciences de la santé. Elle est récipiendaire du Prix Acfas Pierre-Dansereau 2017 et du prix Pionnier 2019 de l'Institut de santé publique et des populations des Instituts de recherche en santé du Canada.

Table Ronde

L'intervention de Louise Potvin sera suivie d'une table ronde impliquant différents chercheurs du Cancéropôle GSO impliquées dans la recherche interventionnelle :

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Session 4A – Chemical biology and cancer

4A / 1
Prevalent Roles of Iron in Cancer

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Mesenchymal cancer cells represent a small fraction of solid tumors at a given time point. Typically, these cells are refractory to conventional therapeutic agents. Furthermore, this cell state has been linked to the development of metastasis and cancer relapse. The complex natural product alinomycin has been shown to selectively kill this population of cells across lineages. It was previously proposed that salinomycin mediates its activity by increasing cellular concentrations of alkali metals such as sodium and potassium. To further illuminate mechanisms underlying the selective activity of salinomycin, we used a combination of synthetic organic chemistry, high-resolution microscopy and molecular biology techniques. In particular, we have shown that salinomycin and its synthetic derivatives accumulate in lysosomes and sequester iron in this organelle. As a result, accumulation of iron leads to the production of reactive oxygen species and lysosomal membrane permeabilization, which in turn promotes cell death by means of ferroptosis. These findings revealed the prevalence of iron homeostasis in mesenchymal cancer cells, paving the way towards the development of next-generation therapeutics. Importantly, this work has led to the discovery that iron operates as a master regulator of cellular plasticity in the context of cancer.

4A / 2

Alternative therapeutic technologies to target undruggable proteins

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For decades, drug discovery mainly focused on the activation and inhibition of protein functions through the development of small molecules fitting into enzyme and receptor pockets. Although successful, this strategy cannot be applied to all biological targets, including proteins without enzymatic activity or proteins that function via protein-protein interaction (PPIs). At the end of the 20th century, there has been an emergence of new classes of therapeutics including biologics (in particular antibodies) and siRNA. Despite undeniable advantages, such molecules can present some drawbacks, such as size, ability to cross the cell membrane for targeting intracellular proteins, stability, delivery and off-target issues. Here, we present some alternative strategies to these molecules to develop drug candidates able to modulate non-conventional proteins involved in cancer, and for which an antagonist/inhibitor has not been identified yet. The first strategy concerns the design of specific therapeutic tools based on the stapled peptide technology for inhibiting PPI interactions, which are essential to target protein functions.1 The second strategy is based on the use of the proteolysis-targeting chimeras (PROTAC) technology to trigger the target protein for degradation.

4A / 3
Programming molecules for cancer therapy

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In our research team, we are mainly interested by "molecular programming" with the aim to explore or manipulate complex biological systems such as living cells or organisms. In other words, we design molecules that have built into their structure a chemical program enabling them to perform specific tasks autonomously within biological environments.

Recently, we developed various molecular devices programmed for the selective delivery of anticancer drugs. These functional systems were designed to allow: (1) the transport in the body of potent anticancer agents in an innocuous manner toward safe tissues, (2) the efficient recognition of malignant specificities located either at the surface of cancer cells or in the tumor microenvironment and (3) the controlled release of the parent drug exclusively at the tumor site.

The therapeutic efficacies of these novel drug delivery systems have been evaluated for the treatment of various solid tumors in mice. Main results obtained in the course of this research program will be presented.

4A / 4
Targeting cancer stem cells with antibiotics

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Compelling evidence suggests that cancer stem cells (CSC) are the roots of current shortcomings in advanced and metastatic colorectal cancer treatment. CSC represent a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity, which can escape from both conventional and targeted therapies, disseminate and seed metastasis. For that reason, targeting CSC has become a major goal to design new therapeutic routes that may prevent tumor relapse and metastasis.

Most drugs possess off-target effects that might provide substantial benefit for cancer treatment. Drug repositioning now became a powerful alternative strategy to deliver cheaper and faster drug development. Amongst potential candidates, antibiotics are of particular interest. We focused our attention on aminoglycosides, and most particularly streptomycin (SM), a potent bactericidal antibiotic generally administered for the treatment of individuals with moderate to severe infections such as tuberculosis.

Our work on commercial and patient derived cancer cell lines clearly established that SM interferes with stem-like properties -such as self-renewal- inherent to CSC phenotype. Furthermore, SM affects colorectal, breast and lung cancer cell lines, suggesting a "pan-cancer" effect, independent of tissue origin and mutation profile. At the sub-cellular level, SM triggers an increased production of mitochondrial reactive oxygen species (ROS) in CSC, causing oxidative stress and leading to cell apoptosis. Remarkably, adjunction of divalent cations (Fe2+, Cu2+) may counteract the effect of SM and restore CSC properties. These ions are essential cofactors of the Superoxide Dismutase (SOD), a mitochondrial antioxidant defense system enzyme. Low ROS homeostasis and increased level of endogenous antioxidants capacity are critical to maintain CSC phenotype. We believe that SM disturbs this tenuous balance in cancer cells. A part of the mechanism may necessitate iron- and/or copper-catalyzed oxidation of the aldehyde group of SM towards carboxylic acids. Indeed, catalytic reduction of this moiety prevents ROS production and subsequent cancer cell death while maintaining bactericidal properties. In order to pinpoint SM target(s) and refine its molecular mechanism, we successfully designed and synthesized a tagged-SM while retaining anti-CSC properties. Based on in-cell click chemistry, this compound allows us to map SM distribution at the subcellular level, a significant challenge given its molecular complexity.

Our main objective is to evaluate whether SM could be exploited as a potential adjuvant chemotherapy agent in advanced and metastatic colorectal cancer. We plan to design SM derivatives with enhanced anti-CSC effect while restraining SM-driven toxicity/side effects.

4A / 5

Oligo-urea foldamers used as tools to induce apoptosis: Study case of the death receptor DR5/TRAIL-R2

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Ligand-oligomerization is known to be a key process for activating membrane receptors involved in signal transduction. Oligo-ureas designed to fold into a regular and stable helical structure can be used as scaffold for anchoring multiple ligands recognizing, oligomerizing and activating cell surface receptors. The use of olgo-urea scaffold for ligand anchoring not only allows to rationally control the degree of oligomerization, the spacing and the relative orientation between the peptides, but also drastically increase their half-life and duration of action. We present here the case of 16mer-peptides designed by phage display [1] which specifically recognize the pro-apoptotic Death Receptor 5 (DR5), a member of the Tumor Necrosis Factor receptor (TNF-R) family, and induce a high degree of apoptosis in BJAB lymphoma and tumorogenic BJELR cells [2,3]. Multivalent peptides, such as dimers and trimers, show an affinity comparable to the one measured for the natural ligand, the Tumor necrosis factor Apoptosis Inducing Ligand (TRAIL), and are able to induce apoptosis. In order to better decipher the ligand-induced activation process of DR5 receptors, we have used a multidisciplinary approach including spectroscopic studies, crystallographic analyses and binding studies. We over-expressed the ExtraCellular Domain of the receptor (DR5-ECD) in E. coli in 13C15N-labeled or unlabeled forms. Three-dimensional NMR experiments allowed us to achieve a full resonance assignment and to determine secondary structure elements: the protein adopts a β-sheet structure in solution [4], similar to the one determined by crystallography in the presence of TRAIL or monoclonal antibodies anti-DR5. NMR titration studies with monomeric synthetic ligands allowed us to determine a common binding site inside the first Cysteine-Rich Domain (CRD1). This domain has been reported to play a crucial role in the Pre-Ligand Assembly Domain (PLAD) of tumor necrosis factor receptors [5]. The HADDOCK model of peptide-protein complexes reveals a different binding mechanism compared to TRAIL and antibodies. Size-exclusion chromatography shows that multivalent peptides induce a dimerization of the receptor, explaining the extension of the binding site to the CRD2 observed by NMR spectroscopy. We are currently trying to crystallize the receptor in the presence of dimeric peptides in order to solve the three-dimensional structures of the multimeric complexes. Our results revealed a new and unexpected mode of interaction to DR5, allowing us to propose to use synthetic ligands in combination of TRAIL as a bi-therapy to treat cancer.

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Session 4B – Recherche interventionnelle (2)

4B / 1
Les enjeux du déploiement national d'interventions probantes

Antoine DEUTSCH

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4B / 2

Transformer l'essai de l'expertise en recherche partenariale et interventionnelle : le rôle des plateformes d'expertise universitaire en Santé Publique

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On constate aujourd'hui l'intérêt d'une recherche interventionnelle en Santé Publique qui soit portée conjointement par les acteurs de terrain et les chercheurs scientifiques. Cette recherche partenariale est prometteuse pour agir en Santé Publique et particulièrement pour impacter les inégalités sociales de santé persistantes en France, qui s'avèrent une situation multifactorielle et difficile à infléchir.

Les plateformes d'expertises universitaires comme la plateforme Aapriss - Apprendre et Agir pour Réduire les Inégalités Sociales de Santé, coordonnée depuis Toulouse par l'Institut Fédératif de Recherches et d'Études Interdisciplinaires Santé Société (IFERISS), sont des espaces importants d'émergence de recherches interventionnelles et partenariales en Santé Publique. Six ans après sa création, la plateforme se maintient dans son rôle d'interface et de coordination entre les espaces de la recherche, de l'action et de la décision publique. Elle propose de réunir en réponse aux sollicitations des acteurs de terrain et des institutions publiques, des expertises scientifiques aux compétences variées. L'objectif étant de varier les partenariats entre différents acteurs de terrain et chercheurs pour faire coïncider les problématiques des premiers avec les compétences et thématiques de recherche des seconds. En cela, l'emboîtement de la plateforme d'expertise au sein d'une fédération interdisciplinaire de recherche est particulièrement approprié. La pluridisciplinarité de la fédération favorise la constitution d'une équipe compétente et l'interdisciplinarité permet d'apporter un éclairage et une ouverture supplémentaire à la requête des professionnels de terrain. Cette approche est indispensable à une discussion multifactorielle sur les inégalités sociales de santé et les acteurs de terrain et de la décision publique doivent y être, autant que faire se peut, associés.

Il faut cependant distinguer les relations de recherche qui relèvent de l'expertise au sein de Aapriss, impliquant une temporalité relativement courte sous forme le plus souvent de contrat de prestation et dont la problématique a été principalement prédéfinie par les acteurs professionnels ; des relations de recherche impliquant des rapports réellement partenariaux tournée vers une recherche collaborative et interventionnelle, dont la problématique et la méthodologie sont co-construites par les différentes parties, impliquant parfois un consortium important d'acteurs et s'inscrivant dans la dynamique générale de recherche d'un organisme de recherche. En début de chaîne, Aapriss est idéalement positionnée pour être une interface et favoriser l'émergence de Recherche Interventionnelle en « transformant l'essai » de l'expertise. Mais cela implique de veiller au bon déroulement des interactions entre acteurs professionnels et chercheurs scientifiques et à la construction progressive d'une confiance réciproque.

Toutes les expertises portées par Aapriss n'aboutissent pas à unerecherche partenariale ou interventionnelle, mais lorsque cela s'est avéré propice, de nouveaux partenariats de recherche se sont développés pour plusieurs années autour de thématiques variées. En apportant ses expertises, Aapriss a contribué à l'émergence des partenariats avec l'Agence Régionale de Santé Occitanie pour la conception d'indicateurs de suivi des inégalités sociales de santé; avec l'Agence d'Urbanisme de Toulouse pour intervenir sur la distribution des facteurs de risque de cancer dans le champ de l'urbanisme; avec le centre de santé communautaire La Case de Santé pour évaluer une intervention prometteuse visant l'autonomie en santé ; et récemment avec les CPAM d'Occitanie pour améliorer l'activité des caisses en matière de prévention auprès des publics à risque. Ces recherches partenariales et parfois interventionnelles se révèlent aujourd'hui scientifiquement ambitieuses et prometteuses au regard de l'impact positif qu'ils pourraient avoir sur la réduction des inégalités sociales de santé.

4B / 3

Collaboration de recherche en ETP : retour d'expérience sur les freins et leviers

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Notre résumé s'inscrit dans le cadre du programme de recherche EXPERTISS, suite d'un projet d'amorçage (REFLEXISS) qui poursuit parmi d'autres un questionnement épistémologique de la recherche interventionnelle en santé des populations (Terral, 2013, Cambon, Alla 2014, Mentoura et al., 2007, Potvin et al., 2010). A ce titre, notre recherche s'établit en lien étroit entre des chercheurs issus de disciplines variées (psychosociologie, sociologie, ergonomie) et des acteurs de santé du Département Interdisciplinaire de Soins de Support pour le Patient en Onco-hématologie (DISSPO). Nos échangent se construisent autour de l'accompagnement et du développement du programme d'éducation thérapeutique « Cancer et traitement oral : Je gère ! » à destination des patients sous anticancéreux oraux.

Si notre collaboration s'affiche comme dynamique au regard de la durée de notre partenariat, des COPILS réalisés, des projets de productions qui semblent s'établir, elle est questionnée pour en saisir les contraintes et les leviers. Ainsi, ces moments d'échanges servent l'enjeux de la collaboration tout en représentant un matériau empirique qui en analyse les conditions et qui la qualifie. A ce titre, l'enjeu épistémologique est aussi celui de la réappropriation des savoirs scientifiques issus de la recherche (sociologie, ergonomie, psychosociologie) et de ses effets sociaux et politiques. Plus largement, comprendre la façon dont se construit, se maintient et évolue notre collaboration nécessite de s'interroger sur l'intercompréhension qui s'opère de façon variable sur différents registres (politique, conceptuel, organisationnel…) entre chacun des acteurs. En outre, la participation de patients se révèle être un indicateur qui caractérise la collaboration. Leur présence puis leur mise à distance interroge sur la confiance mutuelle des chercheurs et professionnels.

Le défi rencontré dans ce partenariat tient aux difficultés d'intercompréhension et au manque de visibilité des intérêts communs. Il réside aussi dans la méthode ethnographique utilisée et les temporalités différentes qu'elle induit entre porteurs et chercheurs. Néanmoins, les leviers participant au maintien de notre collaboration, tiendraient au regard que propose la sociologie ou la psychosociologie sur l'étude de l'ETP en pointant l'analyse des relations sociales et la prise en compte de contextes d'acquisition variés face aux sciences expérimentales. Ces prémices de résultats montrent la nécessaire construction d'une finalité partagée et visible. Il s'agit de se comprendre en hybridant des savoirs et d'animer, de faciliter les échanges. Différents niveaux de collaboration s'analysent selon l'appropriation des savoirs et de l'acculturation réciproque des formes de travail et du milieu professionnel de chacun des acteurs. Cette acculturation s'appuie notamment sur le rôle d'une médiation humaine qui crée des relations interpersonnelles plus constantes, qui traduit les savoirs, articule les enjeux interprofessionnels et contribue à donner du sens au travail commun.

4B / 4

Pour des interventions justes nécessaires : élaboration d'un outil d'aide au repérage et de prise en charge du retour et/ou maintien en emploi pour des femmes diagnostiquées d'un cancer du sein. Projet REWORK-BC (SIRIC ILIAD)

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Introduction : Le diagnostic de cancer du sein, les symptômes et les effets secondaires des traitements, entraînent de multiples déficits qui peuvent avoir des effets délétères sur la vie quotidienne et professionnelle des patientes (Duijts et al., 2014). Pendant et après les traitements, certaines patientes retrouvent progressivement leurs capacités à travailler, alors que d'autres n'arrivent plus à y prendre pleinement part pendant de nombreuses années (Flechtner & Bottomley, 2003). De fait, l'objectif 9.4 du Plan Cancer 2014 - 2019 vise à délivrer aux personnes atteintes de cancer, une information plus adaptée et individualisée quant à leurs droits et mesures qui peuvent être utilisés pour faciliter leur retour/maintien en emploi. Toutefois, la personnalisation de cette information requiert d'identifier, en amont, les individus à risque de présenter des difficultés de retour/maintien en emploi. Un des objectifs du projet REWORK-BC du SIRIC ILIAD consiste à développer un outil simple, à destination des professionnels de santé rencontrés lors du parcours de soin et/ou de la reprise du travail permettant d'identifier les patientes les plus à risque de présenter des difficultés de retour en emploi sur la base des facteurs de risque suggérés dans la littérature internationale.

Méthode : L'identification des facteurs de risque a été réalisée à partir des revues de la littérature existantes (Cocchiara et al., 2018; Gragnano et al., 2018; Wang et al., 2018). Une mise à jour a également été effectuée sur PsycInfo et Medline en utilisant les termes relatifs au cancer du sein et au maintien en emploi, définis en MESH. 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 du maintien en emploi des femmes ayant un cancer du sein.

Résultats : Les facteurs de risque associés au non-retour à l'emploi incluent l'âge, les revenus, le niveau d'étude, la chimiothérapie, la gravité de la maladie, le temps écoulé depuis le diagnostic, la présence de douleurs, le soutien organisationnel perçu, la pénibilité au travail, l'implication professionnelle, la capacité de travail, la santé globale perçue, le fonctionnement physique et cognitif ainsi que le sentiment d'auto-efficacité à retourner au travail. L'ensemble de ces facteurs, préalablement validés par un consensus formalisé, seront intégrés sous forme d'items dans un questionnaire permettant aux personnels de santé d'établir un score a priori de retour/maintien en emploi de leurs patientes lors de leurs consultations. Ce questionnaire pourra être délivré à différents temps d'évaluation, correspondant aux différents temps de la maladie : au diagnostic, pendant et après les traitements, et en rémission. La liste d'items devra être adaptée à ces temps de la maladie.

Discussion/Conclusion : Bien que de nombreux déterminants du maintien en emploi émergent au sein de la littérature scientifique et malgré l'importance des questions liées au travail et à l'emploi dans le cadre de l'étude de la qualité de vie des patients, il existe actuellement peu de tentatives pour étudier cette question dans une perspective pluridisciplinaire associant la médecine, l'épidémiologie et la psychologie. L'élaboration de dispositifs simples, informatisables, de détection et de prévision des difficultés probables de maintien en emploi après cancer permettra d'identifier les patientes les plus à risque de non-retour / maintien en emploi et de les inclure dans des programmes justes nécessaires de soutien au retour à l'emploi après cancer. Ces dispositifs contribueront également à enrichir les programmes éducatifs pour les patients, les professionnels de santé et les employeurs afin de mieux répondre aux enjeux de sécurisation et d'aménagement des parcours professionnels des personnes atteintes de cancer.

Session 5A – Genome dynamics and cancer

5A / 1
How BRCA-deficient tumors ensure DNA replication and repair

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Basal-like breast (BLBCs) and ovarian (OCs) carcinomas are aggressive tumors with few treatment options and high recurrence rates. BLBCs and OCs often demonstrate defects in homologous recombination (HR)-mediated DNA repair. Loss of HR, which occurs essentially through mutations in the BRCA1 and BRCA2 genes, causes genomic instability and dependence on alternative DNA repair mechanisms, setting the stage for synthetic lethality-based targeted therapy. This is exemplified by the recent approval of poly (ADP-ribose) polymerase inhibitors (PARPi) for the treatment of HR-deficient (HRD) tumors. However, the clinical efficacy of these molecules is hampered by the frequent development of drug resistance which limits the effectiveness in achieving cancer remission and severely reduces patients' survival. This stresses the absolute need to develop alternative curative options for the treatment of PARPi-resistant HRD tumors.

Gaining recognition in the last few years, the alternative end-joining (alt-EJ) DNA repair pathway was recently shown to be required for cancer cell viability in the absence of homologous recombination (HR)-mediated DNA repair. Unraveling the functions and composition of this pathway will facilitate the identification of new targets for the tailored treatment of cancer. In this seminar, I will talk about the mechanisms of alt-EJ repair as well as its potential oncogenic roles in cancer cells.

5A / 2

New synthetic lethality approaches targeting DNA safeguard pathways and the mitochondrial step of nucleotide (pyrimidine) neosynthesis in breast cancer

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Our previous work showed that upon knockout of E4F1 transcription factor transformed cells elicited major mitochondrial dysfunctions including a drastic reduction in levels of orotic acid which is the limiting precursor of pyrimidine synthesis. Dihydroorotate dehydrogenase (DHODH) which converts dihydroorotic acid into orotic acid has emerged as a new therapeutic target in a wide spectrum of pathologies as *de novo* pyrimidine synthesis is extensively used in rapidly proliferating human or parasitic cells. Reduction in nucleotide pools through DHODH inhibition has been demonstrated to effectively reduce cancer cell proliferation and tumour growth. Furthermore limiting precursors of DNA synthesis have been reported as a source of genetic instability. As we also showed that E4F1 controls the transcription of Chk1 kinase we sought to generate DNA damage upon DHODH inhibition in a p53-compromised background and jeopardize genome stability or induce cell death through the abrogation of checkpoints that are controlled by Chk1. We therefore evaluated the association of DHODH and Chk1 inhibitions as a new option to reduce proliferation of p53-deficient cancer cells.

A preliminary study showed that the pharmacological activity of DHODH inhibitors teriflunomide and IPP-A017-A04 was more prominent in transformed mouse embryonic fibroblasts than their primary or immortalized counterparts. This effect was enhanced when cells were also exposed to PF477736 Chk1 inhibitor. The choice of very low effect (IC10) PF477736 concentration we used for these combinations was motivated to minimise off-target effects reported with checkpoint kinase inhibitors. Phospho-Ser296 Chk1 levels were reduced in a concentration-dependent manner, with the lowest level observed using IC10 PF477736, which confirmed optimal kinase inhibition at that concentration.

Flow cytometry analyses revealed significant cell cycle perturbations such as the accumulation in S and G2/M phases followed with the appearance of a hyperploid population and a sub-G1 fraction of transformed cells upon exposure to the combination. Annexin V / 7-AAD assays and detection of cleaved caspase-3 by immunoblotting confirmed the eventual conversion of two cytostatic effects into cytotoxicity. A similar significant increase in cell death was observed upon dual siRNA-mediated depletion of Chk1 and DHODH in both murine and human cancer cell models. Combining these inhibitors also sensitised human triple negative breast cancer cell lines SUM159, HCC1937 and MDA-MB-231 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.

This study shows that targeting DHODH is effective in p53-deficient cells provided that Chk1 function is inhibited and suggests that TNBC patients may be eligible for future therapeutic strategies aiming at inhibiting both DHODH and Chk1. The anti-tumour activity of combined DHODH and Chk1 inhibitions was assessed in SUM159 xenografts however the current *in vivo* protocol requires further optimising before this strategy can be considered as a suitable alternative to conventional chemotherapies. The combination of safer and more selective DHODH and Chk1 inhibitors is currently under investigation in a panel of TNBC cell lines and PDX models.

5A / 3

Generation of cells resistant to tyrosine kinase inhibitors in chronic myeloid leukemia by a genome editing technique

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Efficient genetic screening, now even more possible with the convergence of CRISPR-Cas9 gene editing technology, next-generation sequencing and bioinformatics, is an important tool for deciphering novel cellular processes, such as resistance to treatment in cancer. Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterised by the t(9;22) genetic abnormality, which encodes the driver of CML, the BCR ABL1 fusion protein. Imatinib mesylate, a tyrosine kinase inhibitor, specifically eliminates CML cells by targeting and blocking the kinase activity this protein, yet, as for all targeted therapies in cancer, resistance to treatment exists. In order to discover alternative BCR-ABL1 independent mechanisms of imatinib resistance, we utilized a genome-scale CRISPR knock-out library to screen for imatinib sensitising genes in vitro on K562 cells. We revealed genes that seem essential for imatinib induced cell death, such as proapoptotic genes (BIM, BAX) or MAP-kinase inhibitor SPRED2. Specifically inducing apoptosis in BIM KO cells with BH3-mimetics, and inhibiting MAP-kinase signalling in SPRED2 KO cells with MEK inhibitors restores sensitivity to imatinib, overcoming resistance phenotypes. However, in our study, BAX is essential for the induction of apoptosis in response to BH3-mimetic treatment. We further discuss alternative potential mechanisms of imatinib resistance, which we did not specifically analyse in our work, such as the implication of the Mediator complex, mRNA processing and protein ubiquitinylation. Gene editing and high throughput genetic screening allows for the discovery and study of many pathological processes implicated in cancer progression. In this work, we discovered previously identified and novel pathways that modulate response to imatinib in CML cell lines. Targeting these specific genetic lesions with combinational therapy can overcome resistance phenotypes and paves the road for the use of precision oncology.

5A / 4

Spatial distribution of FTO adjusts colorectal cancer stem-like properties through RNA modification

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Cancer stem cell (CSC) represents a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity, which can escape from chemotherapies, disseminate and seed metastasis. Understanding the molecular mechanisms that underlie CSC abilities is a major goal to design new therapeutic strategies that may prevent both tumor relapse and metastasis formation. Despite accruing evidence establishing a link between deregulation of epitranscriptome-related players and tumorigenic process, the role of messenger RNA (mRNA) modifications dynamic in the regulation of CSC properties remains poorly understood. Here, we show that the fat mass and obesity-associated protein (FTO) impedes CSC abilities in colorectal cancer through its m^6A_m (N6,2'-O-dimethyladenosine) demethylase activity. While m6Am is strategically located next to the m^7G-mRNA cap, its biological function is not well understood and has not been addressed in cancer. Here we show that low FTO expression in patient-derived cell lines elevates m^6A_m level in mRNA which results in enhanced *in vivo*tumorigenicity and chemoresistance. In the contrary, inhibition of the recently identified m6Am methyltransferase, PCIF1/CAPAM, partially reverses this phenotype. We demonstrate that the FTO/ m^6A_m axis constitutes a novel, reversible pathway controlling CSC abilities that does not involve transcriptome remodeling, but rather modulates translation efficiency of selected m^6A_m marked transcripts. Finally, tumor microarrays analysis suggests a compartment-specific role of FTO in colorectal cancer (CRC) initiation and progression. While its expression is strictly nuclear in benign lesions (stage 0), FTO is found in both the nucleus and cytoplasm following malignant transformation (stage 1, 2, 3 and 4). Recent reports suggest that spatial distribution of FTO may modulate its accessibility toward relevant substrate. Our latest data echoes this hypothesis and demonstrate that cytoplasmic FTO hampers CSC properties through cap-m^6A_m demethylation. Altogether, our findings bring to light the first biological function of the m6Am modification and its potential adverse consequences for CRC management.

Session 5B – Translational Research, From Biology to Clinics

5B / 1

Resistance of Melanoma to Immune Checkpoint Inhibitors is Overcome by Targeting the Sphingosine Kinase 1

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Immune checkpoint inhibitors (ICI) have dramatically modified the prognosis of several advanced cancers, however many patients still do not respond to treatment. Optimal results might be obtained by targeting cancer cell metabolism to modulate the immunosuppressive tumor microenvironment. Here, we identify sphingosine kinase-1 (SK1) as a key regulator of anti-tumor immunity. We observed that high expression of SK1 in tumor cells is associated with shorter survival in melanoma patients treated with anti-PD-1. Interestingly, silencing of SK1 in preclinical models led to attenuated tumor growth and Treg recruitment, and enhanced the CD8/Treg ratio in tumors. Moreover, using epigenetic and pharmacological approaches to target SK1, we show that SK1 expression impairs the responses to ICI in murine models of melanoma, breast and colon cancer. Mechanistically, SK1 silencing decreased the expression of various immunosuppressive factors in the tumor microenvironment to limit regulatory T cell (Treg) infiltration. Accordingly, a SK1-dependent immunosuppressive signature was also observed in human melanoma biopsies. Altogether, this study identifies SK1 as a new checkpoint lipid kinase that could be targeted to enhance immunotherapy.

5B / 2
Definition of new biomarkers of aggressiveness in glioma

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Gliomas are primary brain tumors whose cellular heterogeneity and lack of valid diagnostic criteria make diagnosis and management particularly difficult. The main objective of this work was research markers of aggressiveness of glioma.
We performed differential transcriptomic analysis of 80 tumors of different types of glioma. We have identified molecular markers with promising diagnostic and/or prognostic value depending on the grade (grade II, III, IV). The analysis of patients from a cohort of the Limoges and Montpellier centers and 671 patients (from the international TCGA cohort) revealed two genes of interest CHI3L1 and NTRK2 (TrkB) that have emerged as biomarkers.

Molecular studies use tissue from resection and/or surgical biopsy; these methods can present a major disadvantage, due to tumor heterogeneity. One alternative is the use of liquid biopsies such as exosomes, circulating micro vesicles issued from tumors. After demonstrating that, on human glioblastoma cell lines, exosomes allow the transfer of neurotrophin receptors (TrkB and p75NTR) to neighboring cells in the microenvironment, we analyzed the expression of TrkB and p75NTR, in the circulating exosomes of 21 glioma and brain metastases. We observed that TrkB and p75NTR were expressed in exosomes of healthy controls with, in the case of p75NTR, a protein ratio close to non-aggressive grade II tumors. But the relative quantification of TrkB and p75NTR proteins increased mainly with tumor grade. These observations suggest that the secretion of exosomes by tumor cells and the expression of TrkB and p75NTR markers depend directly on the expression level of both biomarkers inside the tumoral tissues.

Unexpectedly, we have identified the expression of a new biomarker (PD-L1) whose expression level was correlated to that of p75 NTR and could also improve glioma stratification. Considering the immunohistochemical co-expression of PD-L1, p75NTR and TrkB in glioblastoma, we investigated the presence of PD-L1 and p75NTR in glioblastoma cell lines and primary glioblastoma cultures (WCL). We also analyzed their expression in extracellular vesicles from these primary cultures. p75 NTR and PD-L1 were co-expressed in primary cultures of glioblastoma patients with very low p75NTR expression levels. On the contrary, in exosomes from these same primary cultures, significantly, higher levels of p75NTR were found and this expression was associated with PD-L1.

Using sortilin knockdown cell lines in which p75NTR was increased, we demonstrated an increased regulation of p75NTR/PD-L1 expression in all glioblastoma cells and their derived exosomes. This increase in expression might have a direct effect on the tumor microenvironment, particularly on the activation and proliferation of T cells.

Altogether, our results suggest the interest of using TrkB and/or p75NTR in gliomas to stratify these tumors before surgery or possibly to monitor tumor progression. This work could also benefit treatment monitoring and new therapeutic approaches by using p75NTR and TrkB content in exosomes as circulating biomarkers. In addition, the co-expression of PD-L1 and p75NTR could be used as a specific biomarker to monitor and optimize the efficacy of immunotherapy in glioblastoma and reduce recurrences. The p75NTR and TrkB content of exosomes might afford new circulating biomarkers that could provide new insights to improve the monitoring and treatment of glioblastoma.

5B / 3

Mutations of the B-cell receptor pathway confer chemoresistance in primary cutaneous diffuse large B-cell lymphoma leg-type

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Background

Primary cutaneous diffuse large B-cell lymphoma leg-type (PCLBCL-LT) is the most aggressive cutaneous B-cell lymphoma requiring
a combination of poly-chemotherapy with Rituximab as first line therapy. About 50% of patients will experience progression or relapse without so far any predictive biologic marker. We previously characterized the specific mutational profile of PLCBCL-LT of activated B-cells leading to constitutive activation of the NF-κB and B-cell receptor (BCR) signaling pathways, as reported for central nervous system or testicular lymphoma (Mareschal et al., 2017).

Aims

Here, we tried to determine if the genomic profile may predict therapeutic response and help to design personalized second-line therapy. Using lymphopanel next generation sequencing, we analyzed 14 PCLBCL-LT cases with complete response and 18 with relapsing/refractory disease. Among the latter, 14 tumor pairs at diagnosis and relapse/progression were analyzed to assess genetic changes.

Results

PCLBCL-LT patients harboring one mutation that targets one of the following BCR signaling genes (CD79A/B or CARD11) displayed a reduced progression-free survival and specific survival (median 18 months, P=0.002 and 51 months, P=0.03 respectively, whereas median duration in the wild type group was not reached) and were associated with therapeutic resistance (P=0.0006). Longitudinal analyses showed that both MYD88 and CD79B were the earliest and among the most conserved mutated genes. Evaluating the genomic profile of cutaneous large B-cell lymphoma has not only a descriptive/diagnostic interest but may also help to predict therapeutic resistance in patients with BCR mutations who may benefit from adjuvant or second-line selected therapy (Ducharme et al., 2019).

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5B / 4

The endoplasmic reticulum resident-AGR2 protein: a novel secreted biomarker with pro-oncogenic properties

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Cancer cells multiply abnormally fast and therefore produce protein molecules faster than normal cells. To avoid becoming stressed by this overproduction, cancer cells make use of proteins that fold new proteins inside the cell. One of these protein folders is called Anterior Gradient-2 (AGR2) and has been shown to be highly overexpressed in diverse human cancers and involved in cell transformation, drug resistance and metastatic growth. Previous research has shown that Endoplasmic Reticulum (ER)-resident AGR2 can also be found outside cells, such as in the blood or urine of cancer patients. Therefore, it has been suggested that measuring the levels of AGR2 in body fluids may be a useful marker for detecting cancers.

Thus, we hypothesized that - apart from becoming a promising diagnostic tool - the AGR2 protein itself, specifically when found outside cells, might make cancer cells more aggressive. To test this hypothesis, healthy lung cells were grown into lung organoids, and in a key experiment, the addition of extracellular AGR2 (eAGR2) in the microenvironment was enough to convert healthy organoids into tumoroids. Further experiments then revealed that AGR2 plays a dual role in cancer development, first by exerting its expected protein quality control functions in the ER and second through gain-of-function extracellular. We have elucidated this gain-of-function as a novel extracellular regulator of epithelial morphogenesis, tumorigenicity and pro-inflammatory phenotypes. Therefore, understanding the intra- and extracellular AGR2 (i- and eAGR2) molecular and cellular mechanisms points towards the identification of novel potential therapeutic target. Indeed, in preclinical studies and ongoing clinical trials, targeting tumor micro-environmental signals has shown promises in halting tumor progression in various human cancers.

5B / 5

Tumor antigen-specific CD8 T cells identified by TIM-3 expression predict response to PD-1 blockade in head and neck cancer

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While our understanding of T cell exhaustion is widely based on mouse models, in depth analysis of T cell exhaustion in cancer patients will provide cues of tumors sensitivity to immune checkpoint blockade (ICB). Here, in ovarian, cervical and head and neck cancers, 3 epithelial malignancies exhibiting resistance to ICB, we combined phenotypic, single-cell RNA sequencing (scRNA-seq) and functional approaches to characterize exhaustion of tumor antigen-specific CD8 T cells at the tumor site.

We show that along chronic stimulation of tumor-specific T cells, but not bystander cells, immune checkpoints (IC) expression is sequentially acquired leading to a population expressing the 4 IC under investigation, i.e. PD-1, TIGIT, CTLA-4 and TIM-3, that we named quadruple positive (QP) cells. Checkpoints incremental acquisition was accompanied by a sequential increase in the expression of tissue-resident memory T cell (Trm) markers, of the ectonucleotidase CD39, and of the transcription factor TOX associated to a T-cell exhaustion program in chronic infection models. Remarkably, QP cells exhibited significant loss of CD28, which could be reproduced by T-cell stimulation in the presence of transforming growth factor-beta (TGF-β), a central cytokine of immune evasion.

Despite their exhausted phenotype, QP cells were endowed with high cytotoxic potential and expressed the C-X-C motif chemokine receptor 6 (CXCR6), which could contribute, together with Trm markers, to their tumor residency and co-localization with tumor cells. *Ex vivo* phenotyping of circulating and tumor-infiltrating cancer antigen-specific T cells argued in favor of the *in situ* acquisition of the exhausted Trm-like phenotype by memory tumor-specific CD8 T cells once they infiltrate tumors.

In addition, we show that circulating specific PD-1^{int}CD28^{+} T cells respond to anti-PD-1 mAb by enhancing their proliferation in response to antigen stimulation. Instead, the same cells within tumor-infiltrating lymphocytes (TIL), which were PD-1^{hi}CD$28^{+/-}$, exhibited a reversal of their functional exhaustion.

Finally, and in agreement with their tumor specificity and responsiveness to PD-1 inhibition, QP cells, quantified by multiplex immunohistochemistry, were predictive of response to therapy and of overall survival in a cohort of 30 head and neck cancer patients treated by PD-1/ PD-L1 blockade therapy. Predictors of response to ICB will be instrumental for an optimized clinical output of current and future immunotherapies.

5B / 6

Epithelial to mesenchymal transition (EMT) is associated with attenuation of succinate dehydrogenase (SDH) in breast cancer, through reduced expression of SDHC

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Introduction: Epithelial to mesenchymal transition (EMT) is a well characterized process of cell plasticity that may involve metabolic rewiring. In cancer, EMT is associated with malignant progression, tumor heterogeneity and therapy resistance. In this study we investigated the role of succinate dehydrogenase (SDH) as a potential key regulator of EMT in breast cancer.

Methods: Associations between SDH subunits and EMT were explored in gene expression data from breast cancer patient cohorts, followed by in depth studies of reduced SDH function as a potential mediator of EMT in cultured cells and 3D sphere structures.

Results: We found an overall inverse association between EMT and the SDH subunit C (SDHC) in breast cancer patient cohorts. This was particularly evident in carcinomas of basal-like molecular subtype compared to non-basal like tumors, and a low SDHC expression level tended to have a prognostic impact in those patients. Studies in cultured cells revealed that EMT was induced by SDH inhibition through SDHC CRISPR/Cas9 knockdown, or by the SDH enzymatic inhibitor malonate. Conversely, overexpression of EMT-promoting transcription factors TWIST and SNAI2 caused decreased levels of SDHB and C and reduced rates of SDH-linked mitochondrial respiration. Cells overexpressing TWIST had reduced mitochondrial mass, and the organelles were thinner and more fragmented compared to controls.

Discussion: Based on previous reports suggesting that mitochondrial dysfunctions and SDHB mutations promote EMT, we hypothesized that altered SDH enzyme function may be a determining factor and an integral part of EMT in cancer development. Our findings suggesting reduced SDHC expression and overall lower SDH activity in cells associated with a mesenchymal phenotype, suggest SDH to be involved in cellular plasticity.

Conclusions: Our findings suggest that SDH inhibition is a driver of the EMT program, and that this is accompanied by structural remodeling of the mitochondrial organelles. This may confer survival benefits upon exposure to hostile microenvironment including oxidative stress and hypoxia during cancer progression.

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Towards Precision Medicine using Tumor-adapted H-1PV oncolytic virus in Preclinical Models of PDAC

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The rat parvovirus H-1 (H-1PV) is nonpathogenic in humans and has a natural oncolytic activity, as it kills a wide spectrum of cancer cells by activating several cell death pathways. The safety and tolerability of H-1PV treatment was recently demonstrated during early clinical studies in glioma and pancreatic adenocarcinoma (PDAC) patients. However, H-1PV is often unable to completely eradicate cancer cells cultured in vitro, and tumors in vivo, including in patients. The aim of this project was to better characterize the oncolytic activity of H-1PV in primary models of PDAC, a cancer with no cure. During this work, we first found that H-1PV is poorly oncolytic in PDAC-derived cellular models, as compared to the highly permissive NB324K control cells. H-1PV could hardly induce apoptosis of PDAC cancer cell lines in vitro, even at very high multiplicities of infection, as monitored non-invasively using the Incucyte Zoom technology; moreover, we found using qPCR analysis that H-1PV amplification is very limited in PDAC cells. To address this concern, wild-type (wt) H-1PV was tumor-adapted in a semi-permissive PDAC cell line as well as a patient-derived primary PDAC cell (PDPC), using a serial passaging protocol. In vitro, we managed to produce clonal, tumor-adapted (TA) H-1PVs at similar titers than wt H-1PV. Remarkably, TA-H1PVs induced rapid lysis of their target cells in vitro, when wt H-1PV had only very limited effect. The PDPC-adapted virus showed a much wider oncolytism than the wt during a screening of various PDPCs and PDAC cells lines, while infection of normal pancreatic cells remained similar to the one of the wt H-1PV. In vivo, the PDPC-adapted H1PV demonstrated greater anti-tumor effect than wt H-1PV, following intraveneous administration in an experimental model of orthotopic pancreatic tumors engrafted in immunodeficient mice. Taken together, these results demonstrate for the first time that H-1PV can be adapted to primary cultures of patients with pancreatic cancer, and that TA-H1PV replicates and kills cancer cells with a high efficacy both in vitro and vivo, while sparing normal cells. This study represents the first step for precision medicine strategies based on patient-tailored oncolytic viruses.

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Targeting proteolytic notch activation inhibits PD-1 expression and improves cytotoxic T lymphocytes (CTL) cytotoxicity against MSI and MSS tumor cells and enhances tumor-infiltrated CTLs and tumor regression

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Notch is synthesized as a proprotein (ProNotch-1) that requires proteolytic maturation by the proprotein convertases (PCs) to generate a transmembrane form (NTM). The latter is then cleaved by ADAM17 at a second site to generate the Notch extracellular truncation (NEXT) domain and finally by γ-secretase to generate the Notch intracellular cytoplasmic domain (NICD). We found that inhibition of PCs represses PD-1 expression in cytotoxic T lymphocytes (CTL), and their exhausted phenotype by preventing their proliferation impairment and progression to apoptosis and improves their efficacy against microsatellite instable (MSI) and stable (MSS) colon cancer cells. In vivo PCs inhibition enhances CTL infiltration in tumors induced in mice and mediates more tumor clearance in syngeneic mice while compared to immunodeficient mice. Immunoblotting analysis revealed that while NTM form and ProNotch-1 form are observed in control T cells, ProNotch-1 was the major form observed in cells with repressed PCs activity. PD-1 expression in activated T cells was repressed by DAPT. While the presence of PCs inhibitor repressed PD-1 expression, the lentiviral-mediated expression of NICD induced PD-1 expression. The intracellular calcium concentration in activated T cells was inhibited by DAPT. Similarly, nuclear accumulation of NFAT in activated T cells was reduced following DAPT treatment as assessed by western blotting analysis and following cells transfection with the EGFP-based reporter plasmid that contained an NFAT promoter. Further analysis revealed that cells treatment with DAPT had no effect on NF-κB and ERK phosphorylation in activated T cells. These findings indicate that Notch cleavage is required for calcium mobilization and NFAT activation, pathways involved in PD-1 and other immune checkpoint molecules expression. Altogether, we propose a mechanism of action in which PCs inhibition disrupts PD-1 and other immune checkpoint molecules expression in T cells through Notch processing (probably other precursors), calcium/NFAT and NFκB pathway blockade. In consequence, the reduced expression of these molecules, particularly PD-1 receptor at the cellular membrane of T cells, allows these cells to bypass the PD-L1/PD-1 mechanism developed by cancer cells to avoid the immune response.

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Preclinical xenograft and culture models of Sézary syndrome reveal cell of origin diversity and subclonal heterogeneity

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Sézary Syndrome (SS) is a rare but an aggressive epidermotropic cutaneous T-cell lymphoma (CTCL) defined by erythroderma, pruritis and a circulating atypical CD4+ T-cell clonal population. The diversity of Sézary cells (SC) phenotype and genotype possibly reflects either plasticity or heterogeneity that is difficult to assess, as SC are difficult to expand with very few cell lines available. Therefore, we developed six new defined culture conditions allowing the amplification of SC defined by their phenotype and monoclonality in 4 of 7 patients. The SC expansion in response to different culture conditions by addition of several cytokines and stromal cells is heterogeneous between patients. This shows the importance of microenvironment for tumor SC cell growth. Engraftment of SC into immunodeficient NOD.Cg-Prkdc(scid)Il2rg(tm1Wjll)/SzJ (NSG) mice was achieved in 2 of 14 cases. Secondary xenograft by subcutaneous injection mimicked several clinical features of SS with dermal infiltration, epidermotropism and blood spreading. Such models permitted to assess the intra-individual heterogeneity of patient SC. Such subclones sharing the same TCR gene rearrangement evolved independently according to culture condition and/or after xenografting. This clonal selection was associated with phenotypic differences and limited genomic evolution both *in vitro* and *in vivo*. The long-term amplification of SC allowed the development of eight new SC lines derived from four different patients. They represent the cell of origin diversity of SC cells and new tools to evaluate their functional properties. Indeed, SC lines demonstrate differential responses to therapies according to the cells of origin of SC. The new *in vivo* model we developed mimicking both skin and blood involvement of SS represents a new preclinical model to test therapeutic agents as well as the mechanisms regulating the balance between blood and skin compartments of SC cells.

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Expression by immunohistochemistry of Anaplastic Lymphoma Kinase (ALK) in Glioblastoma Multiforme: Foreshadow of clinical implications (GLIMAL1 study)

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Introduction: ALK gene rearrangement has implications in a variety of cancers and show clinical and therapeutic advantages in lung cancer with ALK expression. Fundamental research on glioblastoma (GBM) models pinpoint pleiotrophin (PTN) signaling via ALK in the development of GBM. Furthermore, ALK inhibitors show tumor control in xenograft models prefiguring their use as targeted therapy of GBM.

Methods: Fifty seven consecutive biopsy or surgery samples of human GBM were tested for ALK expression by immunohistochemistry (IHC) treated at our university hospital between november 2018 and june 2019.

Results: ALK expression was detected in 16 samples of 57 consecutive patients (28.07%). The 95% exact confidence limits being 16.97% and 41.54%. This confidence interval is wide accounting for the small number of tissue samples, though the minimum frequency of ALK expression (16.97%) remains an important indicator foreshadowing clinical implications of therapies targetting ALK in GBM.

Conclusions: ALK expression in GBM seems to be a promissing finding for clinical and therapeutic implications. Consequently, more GBM samples are being included in order to correlate the prevalence of ALK to clinical features, prognostic significance and outcomes after standard primary treatment. Future perspectives include a multicenter clinical trial of ALK inhibition in recurrent cases after standard primary treatment in cases with ALK expression.

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Targeting Apelin cleavage sites for colorectal cancer treatment

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Colon cancer is a leading cause of death worldwide. Liver metastasis is the fatal hallmark of advanced stages of colon cancer and treatments are ineffective due to resistance to current therapies. We report the preclinical development of apelin double mutant (APLN-DM), obtained following alteration of the two furin cleavage sites of APLN precursor (ProAPLN), a bioactive chemokine with diverse biological activities, including growth-promoting and survival actions which has a central role in angiogenesis, tumor progression and metastasis. Expression of APLN-DM in colon cancer cells or treatment with APLN-DM peptide caused colon tumor growth, liver metastasis and angiogenesis inhibition and increased tumor apoptosis. APLN-DM impaired the growth and migration of colon cancer cells, endothelial cells and smooth muscle cells and selectively affected APLNr affinity, internalization and signaling. ADME-Tox study revealed that APLN-DM peptide is specific, safe, and stable in human plasma and in vivo in mice and easily metabolized by the liver. These findings suggest that APLN-DM may be a promising therapeutic strategy against colorectal cancer and derived metastasis.

Session 5C – Ethique et prévention : aspects individuels et collectifs

Présentation de la session

Pourquoi une session sur éthique et prévention ? Tout simplement, parce que c'est un sujet toujours oublié et même considéré comme non pertinent. « Faire de la prévention ne peut pas faire de mal ! ». C'est pour faire réaliser à quel point ce présupposé est faux que nous avons décidé de consacrer une séance à cette question.

Les principes fondateurs de l'éthique : bienfaisance, non malfaisance, autonomie et justice sont depuis Hippocrate toujours les mêmes. La traduction de ces principes en lois et règlements s'est peu à peu imposée dans le contexte clinique, en particulier avec l'enregistrement et la surveillance des essais thérapeutiques. Par contre, l'éthique a été totalement ignorée pendant des décennies en épidémiologie de population. Maintenant que les financeurs de larges projets, y compris d'études épidémiologiques au niveau européen ou international, demandent une conformation à des règles éthiques, réfléchir à cette question s'est imposé. Néanmoins, la situation semble se restreindre à des listes d'injonctions érigées en chartes mais dont parfois le souffle parait absent. Dans le domaine de la recherche étiologique en épidémiologie des cancers et encore plus dans les programmes de prévention qui, logiquement, devraient leur succéder, deux types de cancérogènes doivent être clairement distingués et traités de façon radicalement différentes : d'une part les cancérogènes liés aux modes de vie (tabac, alcool, alimentation, exposition au soleil, etc.) et d'autre part les cancérogènes liés à l'environnement, qu'ils soient chimiques, physiques ou biologiques.

Parce que ces cancérogènes impliquent des relations très différentes, mais toujours complexes, entre les dimensions collectives et individuelles du risque de cancer, ils doivent nous amener à nous interroger sur nos pratiques de prévention.

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Cette session viendra clore une journée de l'axe 4 « Enjeux individuels et collectifs » consacrée à la recherche interventionnelle et à la prévention. Elle sera ouverte par Emmanuelle Rial-Sebbag et prendra la forme d'un ensemble d'échanges autour de différentes communications et d'une table ronde avec l'ensemble des participants

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Penser l'éthique au-delà de l'individu : pour une éthique collective

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L'éthique s'inscrit dans une tradition de la protection individuelle que ce soit pour les participants à la recherche ou pour les patients. Ces principes bien connus de tous, que sont la bienfaisance, la non-malfaisance, la justice et l'autonomie, vont bien au-delà de leur dimension conceptuelle puisqu'ils sont aujourd'hui largement inscrits dans notre droit. Cependant, la santé publique et la mise en œuvre de ses politiques nous invitent à les repenser dans une dimension plus collective de la protection des groupes ouvrant un large éventail de nouveaux défis.

5C / 2

Effect of PSA-based screening on prostate cancer mortality: results from two departements with cancer registry (French section of ERSPC)

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Objectives: Prostate cancer (PCa) remains a major public health problem and represents the most common cancer in men worldwide. Two large trials (ERSPC and PLCO) evaluated the effect of screening with PSA on PCa mortality, but their results were discordents.

Main objective: to assess the PCa-specific mortality based on two departments (Tarn and Hérault) of southern France which have a cancer registry necessary to carry out such as trial.

Material and methods: This randomised controled trial started in 2001, it involved 80 696 aged 50-69 yr (including 38 474 in screening group). Screening group was invited to a PSA testing after their written and informed consent. Positive tests were defined as a PSA >= 3.0ng/mL. Biopsy was recommended for subjects having positive PSA. Participants were followed until diagnosis of PCa, death or end date (December 31, 2013). Primary outcome was mortality from Prostate cancer. Poisson regression analysis was used to estimate Rate Ratio (RR) in the screening vs. the control group.

Results: In the screening group, compliance rate of PSA was 31.3%. After a median follow-up of 9 years, incidence of PCa increased by 10% in the screening arm compared to the control (RR=1.10; IC95%=[1.04-1.16], p=0.0014).PCa Mortality was 0.222 and 0.215 deaths per 1000 person-year, respectively in the screening and control group, showing a non-statistically difference between the two group (RR=1.03 [0.75-1.41], p=0.88) even after stratification on PSA compliance (RR=0.76 [0.44-1.24], p=0.29).

Discussion and conclusions: Results didn't confirm the significant reduction of PCa mortality in screening group when compared to the control group. This can partly explained by the fact that the beginning of this trial was concomitant with the national screening recommendation which promote a PSA screening for men 50-75 years which probably lead to high contamination in control group. Further follow up was needed to evaluate the potential long-term effects of screening.

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Etat des lieux de l'information relative à l'oncofertilité pour les femmes jeunes atteintes d'un cancer du sein en ex-région Midi-Pyrénées : approches épidémiologique et éthique.

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Introduction/Objectifs

L'INCa estime le taux de survie à 5 ans des femmes de 18 à 44 ans atteintes d'un cancer du sein à 90%. Ces femmes jeunes doivent souvent avoir recours à des chimiothérapies. Etant considérées par l'ASCO depuis 2004 comme « à risque intermédiaire d'aménorrhée post-traitement », ces chimiothérapies justifient la mise en place d'une préservation de la fertilité dont la proposition est devenue une obligation médico-légale depuis 2004. Néanmoins, peu d'études ont été menées pour savoir comment cette proposition est en pratique faite ou non.

L'objectif principal de notre étude est de connaître la proportion de femmes n'ayant pas reçu l'information sur les risques d'infertilité liés à la mise en place d'une telle chimiothérapie. L'objectif secondaire est d'étudier les facteurs médicaux et socio-économiques pouvant influencer la transmission de l'information par l'oncologue.

Matériel/méthodes

Nous avons inclus les patientes âgées de 18 à 40 ans au moment du diagnostic du cancer, traitées pour un cancer du sein invasif et ayant initié une chimiothérapie néoadjuvante ou adjuvante sur le territoire de l'ex-région Midi-Pyrénées entre Janvier 2012 et Décembre 2017. La liste des patientes a été obtenue via un croisement des données entre le Dossier Communicant en Cancérologie du réseau Onco-Occitanie et les données des deux centres agréés pour la préservation de la fertilité dans la région. Après tirage au sort, notre étude comportait 367 patientes.

Après une description des informations recueillies à la consultation d'annonce et d'oncofertilité, nous avons mené des régressions logistiques ajustées sur l'âge en guise d'analyses bivariées puis un modèle multiniveau centré sur le fait d'aborder la fertilité en consultation d'annonce par le médecin.

Résultats

La fertilité n'a pas été abordée par l'oncologue au moment de la consultation d'annonce chez 61% des femmes. La consultation d'oncofertilté a été réalisée pour 27% d'entre elles et la préservation a été effectuée pour 11% des femmes.

Notre modèle multiniveau montre que le fait d'aborder la fertilité est significativement influencé par le type de structure de la prise en charge : la prise en charge dans l'établissement public toulousain augmente les chances de transmission de l'information de la part du praticien (OR = 12, IC=[2.18 ; 61]). La transmission de l'information varie en fonction de l'âge : plus une femme est âgée moins elle sera informée (OR = 0.8, IC=[0.75 ; 0.89]). Aussi, plus le nombre d'enfant de la femme au moment du diagnostic est important, moins l'information est transmise (pour 0 enfant : OR=1, pour 1 enfant : OR=0.43, IC=[0.19 ; 0.99], pour 2 enfants : OR=0.20, IC=[0.09 ; 0.46], pour 3 enfants : OR=0.13, IC=[0.04 ; 0.40]). Egalement, le fait d'avoir un cancer d'emblée métastatique diminue la transmission de l'information (OR=0.06, IC=[0.02 ; 0.20]). Enfin l'abord de la fertilité varie en fonction de l'année de diagnostic : l'information est plus transmise depuis 2012 avec néanmoins une légère diminution en 2017.

Conclusion/Discussion

Nos premiers résultats montrent que des données concernant la patiente (son âge et sa parité), le type de structure de la prise en charge, l'année de diagnostic et l'urgence de la situation (cancer d'emblée métastatique) influencent le fait d'aborder la fertilité en consultation d'annonce.

Dès lors, des actions de terrain sont envisagées par le groupe de travail Oncofertilité du réseau OncoOccitanie avec notamment la mise en place de guides d'informations à destination des patient(e)s et praticiens pour améliorer cette situation.

Une réflexion éthique sur ces résultats est menée en parallèle, questionnant la notion d'information (claire, loyale, appropriée et surtout équitable) en santé, ainsi que ses fondements philosophiques kantien ; la place et l'importance de l'éthique de la sollicitude dans ce contexte de vulnérabilité dans lequel les patientes peuvent être plongées.

Session 6 – Translational research: from biology to surgery

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Planification - Simulation- Navigation: Toward a precise surgery

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Minimally invasive surgery represents one of the main evolutions of surgical techniques. However, minimally invasive surgery adds difficulty that can be reduced through computer technology.

From a patient's medical image [US, computed tomography (CT) or MRI], we have developed an Augmented Reality (AR) system that increases the surgeon's intraoperative vision by providing a virtual transparency of the patient. AR is based on two major processes: 3D modeling and visualization of anatomical or pathological structures appearing in the medical image, and the registration of this visualization onto the real patient. We have thus developed a new online service, named Visible Patient, providing efficient 3D modeling of patients. We have then developed several 3D visualization and surgical planning software tools to combine direct volume rendering and surface rendering. Finally, we have developed two registration techniques, one interactive and one automatic providing intraoperative augmented reality view.

Virtual patient modeling should be mandatory for certain interventions that have now to be defined, such as liver surgery. Augmented reality is clearly the next step of the new surgical instrumentation but remains currently limited due to the complexity of organ deformations during surgery. Intraoperative medical imaging used in new generation of automated augmented reality should solve this issue thanks to the development of Hybrid OR.

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Digital Innovations in Liver Surgery : Toward the Digital Tween

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Surgery is the best treatments for malignant liver tumor but 3-month mortality reaches 8% after major hepatectomy. It is a maladaptive regeneration of the liver, responsible for post-operative liver failure (POLF), which causes death.
To decrease POLF, we developed tools to improved planification of liver surgery using digital simulation. We observed high portal pressure at the end of surgery in patients that developed POLF. (Allard…Vibert et al. Ann Surg 2013). A mismatch between mesenteric hemodynamics and the remaining liver to explain tissue lesions of the remaining liver was validated on models of hepatectomies in pigs. (Bekheit, J Surg Res 2017). An adjustable perivascular ring (AVR) was placed around the portal vein to protect the remaining liver from hemodynamic barotrauma showed its effectiveness. (Bucur, Ann Surg 2017). In order to optimize the mechanical modulation of portal vein diameter after hepatectomy, a collaboration was developed between INRIA Paris and INSERM U1193 to mathematically modelized physiological hypotheses after major hepatectomy. (Audebert, J Biomech 2017). The results obtained with these models were compared with experimental measurements in pigs then in humans.
From 2018, we develop new 3D models that integrating vascular flow into hepatic vein according to their spatial orientation. This work concerning the hemodynamic modeling of the liver is currently complemented with a team from INRIA Strasbourg (Stéphane Cotin) aiming at the realization of 3D digital models of deformable livers. The manual deformations imposed on the real liver by the surgeon are automatically reproduced on the 3D digital model.
Our aim is to couple hemodynamic simulation mathematical models to 3D anatomical models in order to achieve optimal preoperative planning tools before the real surgery.

Current and Future research

1. To set up methods that will validate that the deformations of the internal structures of the liver (vessels and tumors) are as accurate as the surface deformations that are easily validated by the simultaneous vision of the real and the virtual
2. To use these 3D anatomical models of high-fidelity deformable livers usually used in preoperative planning as teaching simulation tools for the learning of liver surgery. This work will involve integrating these models into immersive reality systems with virtual reality headsets and haptic devices. This type of project will be based on collaborations with engineering schools of Paris Saclay University, Institut Mines Telecom and INRIA already set up through the annual organization of a specific workshop dedicated to the use of digital in surgery: The Week End of Surgical Innovation (WIC - https://hopscotch.key4events.com/?e=130)
3. To couple hemodynamic simulation mathematical models to 3D anatomical models in order to achieve optimal preoperative planning tools capable of predicting the hemodynamic and therefore functional consequences of the planned hepatectomies performed virtually before the real surgery

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From the bench to the bedside : development of SGM-101, a CEA-targeting agent for intraoperative fluorescence imaging of colorectal carcinoma

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Tumour-targeted fluorescence imaging has the potential to advance current practice of oncological surgery by selectively highlighting malignant tissue during surgery. However, the development of tumor-targeted imaging agents for fluorescence-guided surgery has been much slower than that of drug therapies, although surgery represents one of the few curative treatments for many solid tumors. SGM-101 is a recently described, innovative fluorescent conjugate in which the near-infrared fluorochrome BM-104 is covalently linked to a chimeric monoclonal antibody against carcinoembryonic antigen (CEA). SGM-101 was developed to provide oncology surgeons with an intraoperative imaging tool that allows the visualization of CEA- overexpressing tumors. This antigen is overexpressed in more than 90% of colorectal cancers and in a wide range of human carcinomas, such as gastric, pancreatic, non-small cell lung and breast carcinomas.

Since the first description of a fluorescent anti-CEA-antibody for the detection of colorectal cancer by the team of André Pèlegrin in the early 1990s, a lot of work has been done to develop both tumor-specific fluorescent compounds and Near-InfraRed (NIR) cameras that are needed in the operating room for the visualization of fluorescence. Following several years of academic research, we created SurgiMab in 2011 with the aim to bring SGM-101 to the clinic.

We then characterized SGM-101 safety prior to its clinical testing for real-time cancer mapping by oncology surgeons. Safety pharmacology and toxicology studies were performed after intravenous injection of SGM-101 in Wistar rats and in Beagle dogs. SGM-101 metabolism and pharmacokinetics were analyzed in rats and mice. Finally, the potential toxicity of the BM-104 dye and SGM-101 cross-reactivity were assessed in a panel of 42 human tissues. Our pre-clinical toxicology, pharmacology and pharmacokinetic results demonstrated the absence of significant adverse effects of both SGM-101 and BM-104 at doses well above the anticipated maximal human exposure. Taken together, the results of these studies supported the development of SGM-101 as a potentially useful and safe tumor-specific imaging tool that might improve the complete tumor resection rate.

We then launched a first-in-human study in 18 patients presenting peritoneal carcinomatosis of colorectal origin at Montpellier Cancer Institute. We thus demonstrated the absence of toxicity at doses that were compatible with intraoperative imaging.

An open-label, ascending dose (5 - 15 mg), exploratory study was then performed in patients with primary or recurrent colorectal cancer to confirm the safety data and assess the performance of SGM-101 for the intraoperative detection of colorectal neoplastic lesions.

Fluorescence imaging was performed with the Quest Spectrum Platform (e.g. at 700nm). Before fluorescence imaging was employed, initial visual and/or palpation assessment was performed to identify or explore the lesion(s) of interest.

The performance of SGM-101 was determined by calculating the tumor-to-background ratio (TBR) of each lesion during surgery and defining the concordance of the fluorescent signal with the histopathologic tumor status. We could thus show that the use of SGM-101 for the detection of primary and locally recurrent colorectal cancer is safe and feasible, showing additional lesions and changing the surgical plan in an important number of patients (24%). The optimal dose of 10 mg with a dosing-surgery interval of 4 days, is among others, based on a tumor-to-background ratio of 1.9. Moreover this dose showed a negative predictive value of 94% and a sensitivity of 96%. In patients with a recurrent cancer or peritoneal metastases, the proportion of patients who had a change in their surgical plan was even higher (35%).

These results show a promising base for the multinational phase III study that enrolled the first patients in June 2019.

Session 7 – Ethics in cancer research

7 / 1
Current challenging ethical issues in oncology research

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In the field of oncology research as in all fields of medicine, as soon as we deal with clinical research, we will have to address some of the most common ethical issues affecting participants in clinical trials. In particular, we must take into account the vulnerability of cancer patients at different stages of their disease and also the specificity related to their age: specific challenges araise for children or elderly. New questions are emerging around access to clinical trials, understanding the purpose of clinical research, the conditions for collection and understanding informed consent. It is also important to consider the perception of research by the patient and the public. This involves understanding the fundamental questions that are asked, which differ according to the phases of clinical trials. Potential conflicts of interest remain a major issue. The importance of genomics and genetics in oncology research also has ethical issues. In a recent Note from the Inserm ethics committee, we studied the ethical challenges raised by all genome sequencing technics.

In another recent Note from the Inserm ethics committee, we studied the challenging aspects of information obtained on the Internet and new ways of recruiting patients for clinical trials. How do these new ways of doing things challenge our traditional rules? Research physicians and their potential research participants must address concerns about the availability of and access to appropriate clinical trials. The Internet can bring unexpected greater opportunities through better knowledge mapping. The Internet can also bias some aspects of patient inclusion. The understanding of the research objectives, the implications of participation (implications for physician and patient), the roles and responsibilities of the physician/researcher and participant, informed consent processes, and the patient/participant's understanding of the trial objectives must be clearly thought out and the Internet can help or blur.

Perceptions of research for patients and physician researchers may differ. Both can expect good results from participation in the trial, but the meaning of what a good result is can differ greatly for the patient and the investigator. The patient, as a participant, can expect a "cure" or "relief of suffering" or "relief of disease". However, the results are often negative or incremental.

Emerging issues also include big data, biobanks, clinical and research tissue, and informed consent related to tissue-based research. They also include for cancer, like many chronic diseases, a heavy cost on the health-care system. Ethical issue concern redistributive justice since new treatment have sky-rocketting prices, but the most salient toll may be also in terms of the vulnerability of disease, caregiver burdens, loss of personhood, death. Finally some question the real results of new treatments whereas prevention, earlier detection, more prompt treatment of localised disease are the important yet underfinanced priorities. Responsible research and innovation is also among the ethical challenges in cancer research.

Session 8A – Microenvironment & Invasion

8A / 1

Mechanisms of extracellular rigidity sensing via the adhesion nexus

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In pancreatic ductal adenocarcinoma (PDAC), an extensive stromal reaction drives tumour progression and contributes to the lethality of the disease. An understanding of the causes of this desmoplastic response, and the consequent effects of a highly rigid stromal extracellular matrix on tumour cell phenotype, would therefore be a pivotal step in the quest to improve patient outcomes.

To profile rigidity-induced cellular signalling networks, we have investigated the sensing of stromal rigidity at the adhesion nexus, the junctional structure that links cells to the extracellular matrix via integrin receptors. Since stromal fibroblasts are the source of much of the desmoplastic response in PDAC, our initial approach has been to define tumour-specific alterations in force-sensitive components of the adhesion nexus and rigidity-dependent changes in signalling networks in these cells.

For this purpose, we have used the proximity-dependent labelling method BioID to assemble an in situ adhesome network. Through the use of 16 different BioID baits, most known adhesome components have been identified, together with many potential new candidates. The quantitative changes in this network (a) in response to actomyosin inhibition with blebbistatin and (b) when adhesive substrates of varying rigidity are employed have been determined. These studies suggest mechanosensitive pathways that are operative in stromal fibroblasts.

8A / 2

Glioblastoma metabolism and microenvironment: putting tumor back in context

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Glioblastomas are among the most malignant primary brain tumors. GBMs are highly angiogenic, exhibit invasive growth, and elevated glycolysis. Under glycolytic conditions, glucose from the blood is metabolized in astrocytes into lactate by LDHA, and exported by MCT4 into the extracellular compartment, inducing a concomitant acidification of the microenvironment. LDHB, generally expressed in oligodendrocytes or neurons, metabolizes lactate into pyruvate for generating ATP in mitochondria. LDH expression was reported to be linked to phenotypic modifications in vitro in GBMs but the mechanisms and the precise role in vivo have not yet been investigated.

We designed LDHA and LDHB Crispr-Cas9 constructs for infecting glioblastoma stem-like cells. In vitro tumor cell invasion was not significantly impaired in sgLDHA glioblastoma cells, even under extreme hypoxic conditions. Tumor development was moderately impacted in terms of invasion or vascular density. We then explored the role of LDHB in these processes. LDHB knock-out cells had decreased invasive properties in vitro but surprisingly tumors were highly hemorrhagic and angiogenic, supporting a role of tumor-derived LDHB in blood vessel development. We furthermore evaluated the consequences of a double LDHA and LDHB knock-out in the glioma cells. Under hypoxic conditions, sgLDHA/B cell invasion was dramatically decreased in comparison to control cells, and apoptosis was also increased. Tumor development was dramatically impaired for LDHA/LDHB knockout tumors. Metabolomics study reveals that double KO cells use original metabolic pathway for compensating apoptotic effects, due to hypoxic environment.

These results indicate the complex role of LDH enzymes in glioblastoma development. It constitutes the basis for further mechanistical studies linking lactate metabolism to brain tumor development and perturbation of the neuro-vascular microenvironment.

8A / 3

Mechanosensitive TRP channels push cancer cells invasion and metastasis formation

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Calcium ion (Ca2+) is the simplest and most versatile second messenger in biology. Ca2+ signaling relies on specialized plasma membrane proteins called Ca2+ channels. Chemical, physical or mechanical clues trigger the opening of these ion-conducting proteins allowing Ca2+ to flux inside the cell. The spatiotemporal patterns of the resulting increase in intracellular Ca2+ are decoded by multiple Ca2+-sensitive effectors in order to selectively trigger adapted cellular responses. Thereby, finely tuned Ca2+ signaling controls numerous physiological cell responses, such as normal cell adhesion and migration, and any dysregulation leads to pathologies. During cancer progression, Ca2+-dependent signaling pathways are hijacked by tumour cells to gain proliferative or invasive potentials. Over the last decade, accumulating evidences have demonstrated in particular that the altered activity and/or expression of some TRP or ORAI channels fuels cancer cells exacerbated migration and invasion capacities, promoting metastasis formation.

Cutaneous malignant melanoma is an aggressive and highly metastatic cancer. Once it has metastasized to distant sites, treatment options become more complicated and the issue is often fatal. Our work has identified two mechanosensitive TRP channels that are overexpressed in advanced melanoma tumours and promote melanoma cells invasive properties. Mechanistically, these channels control melanoma cells adhesion dynamics and actin cytoskeleton architecture. During spreading, cancer cells have to respond to variable mechanical constraints. Hence, these plasma membrane mechanosensitive ion channels likely regulate cell invasion by translating mechanical cues into intracellular biochemical signal, for a fast adaptive response. Due to their display at the cell surface and their accessibility to a pharmacological modulation, they hold great promises as potential therapeutic targets for Metastatic Melanoma.

8A / 4

Role of Leukaemia Inhibitory Factor (LIF) on the tumorigenic properties of Cancer Stem Cells in gastric adenocarcinoma

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Introduction

Cancer stem cells (CSCs), a small cell subpopulation having intrinsic chemo-resistance mechanisms and expressing CD44 cell surface glycoprotein, have been characterised in gastric adenocarcinoma. The link between the Hippo/YAP/TEAD pathway, key regulator of organ size and tissue homeostasis, and CSCs properties has recently been suggested in gastric adenocarcinoma. Recent studies have defined Leukaemia Inhibitory Factor Receptor (LIFR) and its ligand Leukaemia inhibitory Factor (LIF) as being upstream regulators of the Hippo pathway and LIF/LIFR signalling as having an anti-metastatic role in breast cancer cells. Interestingly, the impact of LIF on gastric CSC properties has never been investigated.

Aims & Methods

Consequently, this study aimed to determine the effect of LIF supplementation on the YAP/TEAD pathway and its impact on CSC phenotype and properties in gastric adenocarcinoma. AGS and MKN45 gastric cancer cell lines as well as patients-derived gastric adenocarcinoma cells were used. The expression of Hippo/YAP/TEAD pathway-related genes and of CSC markers was assessed by RTqPCR, western blot and immunofluorescence analysis. YAP/TEAD transcriptional activity was evaluated by TEAD-luciferase reporter assay and proliferation as well as tumorsphere assays were carried out in vitro to evaluate CSC functional properties.

Results

Results demonstrate that LIF supplementation represses the YAP/TEAD pathway through a decreased YAP translocation to the nucleus and decreased expression of YAP/TEAD target genes. In addition, LIF decreases proliferation, tumorsphere initiation capacity and expression of gastric CSC markers in gastric adenocarcinoma cells.

Conclusion

Our results indicate that LIF represses the YAP/TEAD pathway and presents anti-tumorigenic effects on gastric adenocarcinoma cells. Whether the effect of LIF on CSC properties passes through the Hippo/YAP/TEAD pathway activation needs to be further investigated. This could in fine lead to the development of targeted strategies against CSCs to help decrease the number of relapse cases and bad prognosis in gastric cancer.

8A / 5

Regulation of tumor-derived DNA potential to activate anti-tumor immune responses by extracellular DNases

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The current wave of immunotherapy has demonstrated potent therapeutic impact for cancer patients. The major modalities gaining broad clinical applicability aim at blocking regulatory pathways silencing the immune system within tumors. However, a minority of patients (~30-40%) respond to such treatment arguing that understanding mechanisms regulating anti-tumor immune responses is critical for improving their efficacy. The sensing of tumor-derived DNA by tumor infiltrating dendritic cells and macrophages was recently shown to play a critical role in type I interferon (IFN-I) production which is essential for the activation of cytotoxic lymphocytes that ultimately eliminate tumors. However, while the majority of tumor cells release DNA, not all patients show an IFN-I signature and a spontaneous T cell mediated anti-tumor immunity, suggesting that tumor-derived DNA immunogenicity is tightly regulated. We have recently characterized a nuclease called DNase1L3 with a unique capacity to degrade DNA associated with microparticles released by apoptotic cells. This property of DNase1L3 prevents the accumulation of self-DNA, its ability to stimulate immune cells and consequently the development of systemic autoimmune disorders. Given the regulatory properties of the Dnase1L3 and its high expression in tumor infiltrating dendritic cells and macrophages, we hypothesized that the Dnase1L3 within the tumor microenvironment may regulates tumor-derived DNA immunogenicity and consequently anti-tumor responses. We have observed that DNase1L3 deficiency in spontaneous and transplantable mammary tumor models did not affect neither tumor growth nor spontaneous anti-tumor immune responses. However, DNase1L3 deficiency prevented the therapeutic impact of a common immunogenic chemotherapy doxorubicin, compared to wild-type mice. These results suggest that the DNase1L3 may promote tumor DNA-sensing by the innate immune cells, following tumor DNA release caused by chemotherapy. Next, we have shown that doxorubicin caused tumor cells necrosis and the release of compact and unfragmented DNA compared to staurosporin which induced tumor cells apoptosis and release of fragmented tumor DNA. Exogenous treatment by DNase1L3 of doxorubicin or staurosporin treated cells potently increased the fragmentation of their DNA. Thus, DNase1L3 may process tumor DNA to promote its sensing by innate immune cells. We also have observed that the supernatants of tumor cells treated with doxorubicin or staurosporin increase the expression of the DNase1L3 within dendritic cells, supporting the hypothesis that this enzyme is involved in the regulation of anti-tumor immune responses. While DNase1L3 may regulate the immunogenicity of chemotherapies, we need to further decipher its mechanisms of action in the regulation of dendritic cells and macrophages activation by tumor DNA. Furthermore, we plan to extend the study of DNase1L3 in the development of anti-tumor immune responses following multiple therapeutic context targeting tumor cells death such as immunotherapy and radiotherapy. Ultimately our study will shed light on novel mechanisms regulating immune responses induced by tumor-derived DNA and therefore may contribute to the development of therapeutic strategies to increase anti-tumor immunity.

Session 8B – Mathematical modeling for therapy response prediction

8B / 1

Multi-omics contextualisation of signalling pathways to identify drug targets and essential genes in cancer

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Individualized treatments benefit greatly from the expansion of big data. From the same sample/patient, we can know all its molecular features, such as the genomic and the expression profiles. At the same time, the extensive investigation of the interactions between biological molecules has drawn a better picture of how cells behave as a system. Molecules interact creating a complex interconnected network that regulates biological processes. The connexions of the network can change to adapt or deal with internal and external requirements. Thus, misregulation of components within the network can lead to arise disruptive phenotypes such as cancer. We work on systems-level approaches to integrate molecular information into networks. By doing this, we aim to identify misregulation within the networks to link them to potential essential or druggable targets.

We have developed CARNIVAL, a tool that uses expression profiles to reconstruct networks. It connects initial signalling receptors to final effectors, the ones that sift biological processes. Along with the expression profile, CARNIVAL requires a network to navigate. We use Omnipath, a comprehensive collection of literature curated human signaling pathways, to extract the network. We further refine this network by incorporating both genomic and transcriptomic profiles. The gene expression identifies the non-expressed genes. The genomic information is translated into functional impact, identifying disrupted interactions or even non-functional proteins. The integration of the molecular information into the general network provides us with sample-specific networks.

For each sample, the inferred CARNIVAL network is combined with drug responses and essentiality scores. Through different well-established methodologies, we explore the associations between the activation status of the reconstructed networks and these biological insights. We analyse the network's topology and the activation status of around 730 genes derived from CARNIVAL for more than 330 anti-cancer drugs, tested on 983 cancer cell lines from the Genomics of Drug Sensitivity in Cancer (GDSC). 306 cell lines are also characterised through essentiality analysis. We focus on paediatric cancer and its application to guide individualized treatments. As children are particularly sensitive to the aggressive treatments against cancer, precision medicine is the best strategy to identify the most effective treatment with minimized side-effects.

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8B / 2

Early evaluation of cancer treatments using modeling and AI

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The main goal of this talk is to present examples of how mathematical modeling and AI may help clinicians following the evolution of cancer.

The first example uses machine learning to evaluate the efficacy of neoadjuvant chemotherapy of soft-tissue sarcoma. Standard of care for advanced stages (grade 3) is the following: neoadjuvant chemotherapy (6 cycles), curative surgery and then adjuvant radiotherapy. Unfortunately, for some patients, chemotherapy does not improve the situation. In clinical routine, two MR exams are performed on patients: one before the chemotherapy and one after two cycles. Using a retrospective study of more than 60 patients from Institut Bergonié, we investigate whether the differences between these two exams may be correlated with response to chemotherapy. For this matter a radiomics approach is used with novel handcrafted features specific to the disease. On the cohort, the results we obtain are better than state of the art.

In the second example, we try to evaluate the efficacy of tyrosine kinase inhibitors (TKI) for patients with EGFR mutated Non-Small Cell Lung Carcinoma. Patients almost always end up relapsing. Our goal is to analyze if an insight on this relapse may be obtained from the early response to treatment. We built a mathematical model - based on a set of PDE - of the response to TKI. This model is personalized for each patient of a retrospective cohort from Institut Bergonié. For the patient-specific model, we compute a novel marker that we show to be correlated with risk of relapse.

Finally, a new data assimilation technique will be presented that is able to recover patient-specific parameters of a PDE model of growth of brain metastases. It may be used to predict the evolution of these metastases.

8B / 3

Tumor microenvironment cellular network inference and analysis from bulk and single cell transcriptomes

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The microenvironment of tumors plays a fundamental role in their progression and resistance to therapy. We have developed a database of ligand-receptor interactions together with algorithms for both bulk RNA-seq or single cell transcriptomic data that allow us to infer (part of) the complex network of cellular interactions taking place in the tumor. We will use its potential on the two types of data with examples from salivary duct carcinoma for bulk transcriptomics and melanoma and normal mouse skin for single cell transcriptomics. Our methods could also be applied to the nascent field of single cell proteomics.

8B / 4

Radio-genomics approach for therapy response prediction

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Medical imaging techniques play a central role in the evaluation of progression of cancer and proper images analysis is essential for determining the location and stage of tumors, for diagnosis and prognosis assessment, guiding therapeutic decisions and for monitoring tumor response during and after treatment. It also supports interventional radiology acts (i.e. biopsies, thermo-ablations or embolization). Yet, this source of information, which is critical for the decision-making process, is not being used to its full potential. Besides, NGS technics allow the precise characterization of the genomic profile of a tumor by detecting mutations, evaluating the TMB and providing additional information such as the PD-L1 status. We have used an AI-based strategy to improve the stratification of cohorts of patients suffering from lung cancer and brain tumors. Using an advanced segmentation technology, we were able to quickly and precisely extract 3D Radiomic characteristics from the images. We then combined extracted heterogeneity and texture indicators with the biology information thanks to a machine learning based methodology. We have applied this strategy to stage 4 NSCLC with EGFR mutation treated with TKI and have shown that stratification of the cohort with respect to the OS can be delivered using the base-line CT-scan and the first two exams used for the evaluation of the early response to the treatment. A second example concerns low grade gliomas and the stratification of patients with respect to the PFS. We will also give some applications for the follow-up of meningiomas.

Session 9 – Research in thoracic oncology

9 / 1
Targeting K-RAS mutant lung tumors: an unmet medical need

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K*RAS* oncogenes are responsible for the development of one fourth of all human tumors including some of the worse tumor types such as lung and pancreatic adenocarcinomas. Development of suitable therapies to treat these tumors has remained elusive and patients are still treated with old chemotherapy drugs. To address this important health issue, we decided to use genetically engineered mouse tumor models that closely recapitulate the natural history of these tumor types in order to deconstruct, by genetic means, oncogenic K*Ras* signaling with the ultimate goal to identify molecular targets whose inhibition will result in significant therapeutic activity. To this end, we have designed a new generation of mouse tumor models in which we can separate, both temporally and spatially, tumor induction from target inhibition. These new tumor models make use of the yeast frt-FLp(o) recombinase system to induce cancer-driving mutations in K*Ras* and Trp53 in either lung neumocytes or in pancreatic acinar cells. In addition, these strains carry conditional Cre-lox knock-out or knock-in alleles of those molecular targets whose therapeutic potential we want to validate. Finally, these mice also carry a transgene that encodes the inducible CreERT2 recombinase driven by the human Ubiquitin promoter that allows its expression in most, if not all, adult cells and tissues. Exposure of these compound mice to a tamoxifen-containing diet once they have developed advanced tumors is allowing us not only to evaluate the therapeutic consequences of ablating/inactivating selected targets, but to determine the potentially toxic effects derived from its systemic elimination or inactivation.

We have used this sophisticated experimental strategy to interrogate the therapeutic and toxic consequences of ablating/inactivating each of the members of the MAP Kinase cascade, including the Raf, Mek and Erk kinases and the PI3KCA. pathway including PI3K p110alpha and mTOR. We have also evaluated the Cyclin-dependent cell cycle kinases (Cdks) and the EGF Receptor. This systematic approach has revealed that most of the KRas signaling effectors are not suitable therapeutic targets due to either lack of therapeutic activity, such as Cdk2, Cdk6 A-Raf or B-Raf, or to the induction of unacceptable toxicities such as the Mek1/2 and Erk1/2 kinases, PI3k p110alpha and Cdk1. Therefore, only c-Raf, EGFR and Cdk4 turned to be suitable therapeutic targets, based not only on their anti-tumor properties, but also on the well tolerated toxicities observed upon their systemic ablation/inactivation. Ablation of c-Raf expression in advanced lung tumors driven to significant tumor regressions. Importantly, systemic abrogation of c-Raf expression did not inhibit canonical MAPK signaling, hence, preventing unacceptable toxicities (Sanclemente et al.. Cancer Cell, 33: 217-228, 2018). In pancreatic tumors, combined ablation of EGFR and c-RAF expression results in complete regression of a significant percentage of tumors while inducing limited toxicities that are well-tolerated. Finally, inhibition of EGFR and c-RAF expression effectively blocked tumor progression in nine independent patient-derived xenografts (PDX) carrying *KRAS* and *TP53* mutations (Blasco et al.. Cancer Cell, 35:573-587, 2019). These results should the door to the development of targeted therapies for patients carrying KRAS mutant lung and pancreatic tumors.

9 / 2

Understanding and overcoming resistance to targeted therapy in lung cancer

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

9 / 3

Targeting acquired vulnerabilities in drug resistant BRAFV600E lung adenocarcinoma patients

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Lung adenocarcinoma (LUAD) is the leading cause of cancer death worldwide. Mutations of the MAP kinase (MAPK) pathway are the most frequent oncogenic drivers of LUAD. BRAF kinase activating mutations represent 5% of LUAD cases, among which BRAFV600E mutation is the most frequent. In LUAD, metastatic patients bearing BRAFV600E mutation receive a combination of BRAF (Dabrafenib) and MEK (Trametinib) inhibitors as a third line therapy after classical chemotherapy and/or anti-PDL1 immunotherapy. This treatment has been shown both to induce tumor regression and to improve patient outcome/survival. Unfortunately, the initial clinical response to targeted kinase inhibitors is almost always temporary, as acquired resistance to these drugs invariably develops. Afterwards, patients are treated again with standard chemotherapy with very low response rate and median survival time. Therefore, the acquisition of resistance to BRAF and MEK inhibitors represents a major problem in clinic.

The achievement of resistance can lead to the acquisition of vulnerabilities also called "collateral sensitivity". Therefore, our hypothesis is that targeting acquired vulnerabilities could represent a new line of anti-cancer therapy for BRAFV600E mutated LUAD patients resistant to BRAF and MEK inhibitors.
We have obtained DFCI471 cells derived from a BRAFV600E mutated LUAD patient that acquired resistance to Dabrafenib and Trametinib from the Dana-Farber Cancer Institute (Boston, USA). As observed previously in melanoma cells harboring BRAFV600E mutation and resistant to BRAF/MEK inhibitors, our results showed that DFCI471 cells are sensitive to Vorinostat (HDAC inhibitor) associated with a toxic increase of oxidative stress. We have generated a second resistant cell lines by treating BRAFV600E mutated LUAD HCC364 cells with increasing concentration of Dabrafenib/Trametinib during several months until we obtained a resistant cell lines (HCC364R). In contrast with DFCI471 cells, HCC364R cells did not display an increased ROS level compared to sensitive HCC364 cells and are not sensitive to Vorinostat. These results suggest that DFCI471 and HCC364R cells did not acquire the same vulnerabilities after the development of resistance to BRAF and MEK inhibitors. Indeed, while DFCI471 cells have shown an acquired mutation of NRAS (NRASQ61K) as resistance mechanism, we did not detect any mutation on H-, K- and N-RAS gene in HCC364R cells. In order to evaluate the resistance mechanism(s) in HCC364R cells, we performed a screening of alternative signaling pathways. Remarkably, we observed a high phosphorylation level on AKT on both ser473 and thr308 in HCC364R compared to control cells. This high activity of AKT is associated with a higher activation of one of its downstream targets, mTORC1. We then tested the sensitivity of HCC364R cells to different inhibitors of this pathway: mTORC1, mTORC1/2, and dual PI3K-mTORC1/2 inhibitors. Our first results demonstrated that HCC364R are more sensitive to these inhibitors compared to parental cells with mTORC1 inhibitors (Everolimus and Temsirolimus) showing the highest difference. Strikingly, HCC364R cells were more than 5000-fold more sensitive to mTORC1 inhibitor than parental cells.
Based on our preliminary results, we hypothesized that the acquired vulnerabilities could be different depending on the mechanism of acquired resistance to BRAF and MEK inhibitors. When resistant cells display a reactivation of the MAPK pathway, they could be sensitive to an increase of oxidative stress with HDAC inhibitors. When resistant cells activate AKT-mTORC1 pathway, they could be sensitive to mTORC1 inhibitors. In vivo experiments as well as validation on patient samples are ongoing to confirm our in vitro results. After, we expect that this new treatment will be set up in clinic as a fourth-line therapy to achieve durable clinical responses in BRAFV600E mutated resistant LUAD patients.

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Notch Inhibition Overcomes Resistance to Tyrosine Kinase Inhibitors Promoted by Gate-Keeper Mutations in EGFR-Driven Lung Adenocarcinoma

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EGFR mutated lung adenocarcinoma patients treated with gefitinib and osimertinib showed a therapeutic benefit limited by the appearance of secondary mutations, such as EGFRT790M and EGFRC797S. It has been generally assumed that these secondary mutations render EGFR completely unresponsive to the inhibitors, indicating that the use of single drug to treat efficiently EGFR-driven lung adenocarcinoma might have limited value while a strategy based on combinational drug therapy could be more effective at mitigating the effects of gatekeeper mutations.

We uncover here that gefitinib and osimertinib increase STAT3 phosphorylation (pSTAT3) in EGFRT790M and EGFRC797S tumoral cells. Interestingly, we also found that concomitant Notch inhibition with gefitinib or osimertinib treatment induces a pSTAT3-dependent strong reduction in the levels of the transcriptional repressor HES1. Importantly, we show that tyrosine kinase inhibitor resistant tumors, with EGFRT790M and EGFRC797S mutations, are highly responsive to the combined treatment of Notch inhibitors with gefitinib and osimertinib respectively. Finally, in patients with EGFR mutations treated with tyrosine kinase inhibitors, HES1 protein levels increase during relapse and correlate with shorter progression-free survival.

Our results show that the Notch pathway plays a major role in the relapse of lung adenocarcinoma patients treated with EGFR TKIs, providing a rationale to treat patients that become resistant to EGFR TKI with a combination of the same TKI and Notch inhibitors.

Posters – Axis 1 “Cell signaling and Therapeutic Targets”

P101

ER-resident oxidoreductase surfaces to promote liver tumor invasiveness

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Metastasis is a major driver of cancer morbidity; it requires metalloproteases (MMPs) cleaving peptidic bonds in collagen fibers. Whether other enzymatic collagen processing is required is unknown. Metastasis of liver tumors is strongly dependent on the GALA pathway, which induces protein O-glycosylation in the ER (Nguyen et al., 2017). Here, we show that GALA also leads to O-linked glycosylation of ER resident protein calnexin (cnx), which along with oxidoreductase ERp57, traffics to the cell surface and accumulates at sites of ECM degradation called invadosomes. We show that cnx/ERp57 complex in the presence of secreted glutathione reduces abundant disulfide bonds in the ECM, a process that is essential for collagen degradation. These findings uncover a moonlighting function or cnx/ERp57 essential for disulfide bond reduction during collagen degradation by metastasizing cancer cells.

P102
Targeting cancer stem cells with antibiotics

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Compelling evidence suggests that cancer stem cells (CSC) are the roots of current shortcomings in advanced and metastatic colorectal cancer treatment. CSC represent a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity, which can escape from both conventional and targeted therapies, disseminate and seed metastasis. For that reason, targeting CSC has become a major goal to design new therapeutic routes that may prevent tumor relapse and metastasis.

Most drugs possess off-target effects that might provide substantial benefit for cancer treatment. Drug repositioning now became a powerful alternative strategy to deliver cheaper and faster drug development. Amongst potential candidates, antibiotics are of particular interest. We focused our attention on aminoglycosides, and most particularly streptomycin (SM), a potent bactericidal antibiotic generally administered for the treatment of individuals with moderate to severe infections such as tuberculosis.

Our work on commercial and patient derived cancer cell lines clearly established that SM interferes with stem-like properties -such as self-renewal- inherent to CSC phenotype. Furthermore, SM affects colorectal, breast and lung cancer cell lines, suggesting a "pan-cancer" effect, independent of tissue origin and mutation profile. At the sub-cellular level, SM triggers an increased production of mitochondrial reactive oxygen species (ROS) in CSC, causing oxidative stress and leading to cell apoptosis. Remarkably, adjunction of divalent cations (Fe2+, Cu2+) may counteract the effect of SM and restore CSC properties. These ions are essential cofactors of the Superoxide Dismutase (SOD), a mitochondrial antioxidant defense system enzyme. Low ROS homeostasis and increased level of endogenous antioxidants capacity are critical to maintain CSC phenotype. We believe that SM disturbs this tenuous balance in cancer cells. A part of the mechanism may necessitate iron- and/or copper-catalyzed oxidation of the aldehyde group of SM towards carboxylic acids. Indeed, catalytic reduction of this moiety prevents ROS production and subsequent cancer cell death while maintaining bactericidal properties. In order to pinpoint SM target(s) and refine its molecular mechanism, we successfully designed and synthesized a tagged-SM while retaining anti-CSC properties. Based on in-cell click chemistry, this compound allow us to map SM distribution at the subcellular level, a significant challenge given its molecular complexity.

Our main objective is to evaluate whether SM could be exploited as a potential adjuvant chemotherapy agent in advanced and metastatic colorectal cancer. We plan to design SM derivatives with enhanced anti-CSC effect while restraining SM-driven toxicity/side effects.

P103

Contribution of autophagy, EVs secretion in glioma aggressiveness

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Background: Glioblastoma is the most aggressive brain tumor leading to relapses and very short survival. In this context, Cancer Stem Cells (CSC) seemed to be a key element of tumor aggressiveness using autophagy process and large cell communication by extracellular vesicles to resist to therapies. We explore RAB27a rule in these processes and the potential impact on CSC behavior. We focuse on the potential implication of the Arf6 protein, part of the small G proteins family.

Material & Methods: Using shRNA approach in glioblastoma cell line U87, we quantify nanovesicles using Nanosight and explore the impact on Cancer Stem Cell population, by flow cytometry and clonogenic assay. Autophagic process is classically monitored by LC3II and Beclin1 expression.

Results: It appears that decrease of RAB27a expression, in normoxia and hypoxia, seems to alter Cancer Stem Cells development, decreases cell growth, increases rate of cell death, slows down autophagic process and in fine decreases extracellular vesicles secretion in our cellular model. Furthermore, inhibition of the autophagic process, seems to lead to a decrease of the Arf6 protein expression in cell lines lacking Atg5 or Beclin1 expressions. Similar analysis are in progress on shRAB27a cell line.

Conclusion: Even if these are preliminary results, it's the first time RAB27a could be considered as a protein linker between autophagy and extracellular vesicles secretion process in glioma that could lead to the tumor aggressiveness. Besides, to our knowledge, the link between Atg5 and Arf6 has never been demonstrated before.

P104

DHODH inhibition for chemoprevention and combination therapy of UVB-induced skin cancers

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Cutaneous squamous cell carcinomas (cSCCs) are mainly causes by ultraviolet radiation. Unlike other cancers where the incidence is stabilized or decreased, the rate of cSCCs increases constantly due to sun exposure and elderly population. cSCCs typically manifest as a spectrum of progressively advanced malignancies, ranging for precursor actinic keratosis (AK) to a squamous cell carcinoma, initially in situ then invasive and metastatic. Recently, multiple studies have highlighted the role of energy metabolism in cancer progression.
We tried to identify the specific alterations at an early stage of carcinogenesis. Using a multistage model of UVB radiation-induced skin cancer and by applying a quantitative proteomic and targeted metabolomics approaches, we have found that specific metabolic modifications occur at the very early stage of photocarcinogenesis.

Investigating the mechanism underlying those early metabolic changes, we showed that a specific mode of electrons fueling to the electron transport chain (ETC) occurs following chronic irradiation. We showed that glycolysis, TCA cycle and fatty acid b-oxidation were decreased at a very early stage of photocarcinogenesis, while mitochondrial ATP synthesis and the distal part of electron transport chain (ETC) were up-regulated. Furthermore, we showed that increased ETC activity was related to the activity of dihydroorotate dehydrogenase (DHODH), the enzyme that catalyzes the fourth step of pyrimidine synthesis. To evaluate the impact of DHODH upregulation and ETC activation on UVB-induced skin carcinogenesis we created a mouse model of inducible Tfam knockout targeted to keratino- cytes (K14-Cre-ERT2/Tfamflox/flox), -Tfam is the main regulator of mtDNA transcription and consequently of the mitochondrial genes encoding ETC subunits. Tfam ablated mice had impaired ETC and failed to develop pre-malignant and malignant lesions under UVB irradiation, owing to decreased DNA repair capacity and subsequently increased apoptosis. We then evaluate the impact of DHODH inhibition using Leflunomide (LFN), a potent but non-specific inhibitor of DHODH, FDA-approved in rheumatoid arthritis. Chronic inhibition of DHODH by LFN blocks UVB-induced tumor initiation, owing to decreased DNA repair capacity and subsequently increased apoptosis. When then performed human tumor xenograft and revealed that LFN treatment reduces growth of established tumors when used in combination with a genotoxic agent, 5-fluorouracil (5-FU).

To establish what accounts for DHODH gene overexpression following irradiation, we revealed that UVB-transcriptional upregulation of DHODH was driven by STAT3. Therefore targeting the downstream effectors of STAT3 more narrow activitiesmight increase the likehood of developing promising target in effective anti-target therapy.

Our findings indicate that specific metabolic modifications precede primary skin tumor formation, highlighting the dynamic role of mitochondria in skin carcinogenesis, and suggest that modifications in energy metabolism can be exploited. DHODH is a promising target for both skin tumor prevention and curative combination therapy.

P105

Phos2net: a novel tool for network reconstruction and pathway extraction based on phosphoproteomic data

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Protein phosphorylation acts as an efficient switch controlling deregulated key signaling pathways in cancer. Computational biology aims to address the complexity of reconstructed networks but overrepresents well-known proteins and lacks information on less-studied proteins. We developed a bioinformatic tool to reconstruct and select relatively small networks that connect signaling proteins to their targets in specific contexts.

Based on existing proteomic data, we report here the generation of an interaction-based network of signaling pathways. We then combined shortest path computation with random walk processes to estimate the importance of individual interactions and selected biologically relevant pathways in the network.

To validate the potency of our tool, we applied it to two phosphoproteomic studies on oncogenic mutants of the well-known PIK3CA kinase and the unfamiliar SRMS kinase.
Our computational pipeline is publicly available and contains a user-friendly graphical interface (http://doi.org/10.5281/zenodo.3333687).

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P106

A drug-tolerant senescent-like state promotes EGFR-TKI resistance and can be targeted with Rho/AKT inhibitors in lung cancer.

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EGFR-mutated NSCLC (Non-Small-Cell Lung Cancer) patients benefit from EGFR-Tyrosine Kinase Inhibitors (TKI) but most of them relapse due to resistances. These resistances may arise from a small population of Drug-Tolerant Cells (DTC) that initially resist the treatment by entering a slow-to-non cycling state. DTCs have been described essentially in the EGFR-mutated PC9 lung cell line, which reproduces in vitro the main stages displayed in patients: a strong initial response during the first days of treatment with EGFR-TKI; a period of latency, which corresponds to the presence of remaining DTC, low proliferative cells that express cancer stem cell markers and that have undergone an epigenetic reprogramming without genotype alteration; after several weeks of treatment, some of these cells can acquire de novo genetic modifications such as the T790M mutation on EGFR gene allowing them to recover proliferative capacities despite the presence of the TKI.
This particular state remains very poorly characterized, and we still don't know by which mechanism(s) tumor cells evolve towards a DTC state, how these DTC generate resistance mutations without replicating, and at which extend how these cells can promote resistance in patients.

We recently reported the GTPase RHOB role in EGFR-TKI resistance in EGFR-mutated lung cancer patients, suggesting that RHOB pathway could be determinant in DTC state acquisition.
Our objective is to understand how the adaptive response of EGFR-mutated NSCLC cells to EGFR-TKI leads to secondary resistance by extensively characterize phenotypic and molecular changes associated with EGFR-TKI-induced DTC formation, and to determine the role of the RHOB/AKT pathway in this process.

We characterized phenotypic changes associated with EGFR-TKI-induced DTC formation in EGFR-mutated cell lines and investigated RHOB implication in DTC state acquisition. Time-lapse microscopy experiments showed that DTC state appeared to be more complex than previously reported; we observed a high inter-cell lines variability in cell division rate/cell arrest, cell shape rearrangement and kinetics of resistant clones' onset.

Several DTC showed enlarged shape and senescence-associated features such as Senescence-Associated-β-Galactosidase (SA-βGal) activity and Senescence-Associated Secretory Phenotype (SASP). This senescent-like phenotype seems to be reversible and regulated by p27/retinoblasma protein pRb/E2F pathway. Furthermore DTC harbored stress actin fibers associated with variations in EMT markers expression consistent with a pre-EMT phenotype.

Consistent with a role of RHOB in DTC survival, RHOB expression and activity were increased in DTC. Moreover, RHOB inhibition, as observed in RHOB-KO cells and in cells transfected with siRNA targeting RHOB or in cells treated with RHO/AKT pharmacological inhibitors, in combination with EGFR-TKI treatment lead to a DTC population decrease.
Characterization of these resistance processes will help to better understand the adaptive resistance to EGFR-TKI in NSCLC to bring new therapeutic approaches to eliminate reservoir of drug-tolerant cells and to prevent emergence of resistance mutations occurring during the slow-to-non cycling state of tumor cells.

P107

Validation of EZH2 as therapeutic target for diffuse midline glioma: pharmacological and genetic approaches

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Diffuse Intrinsic Pontine Glioma (DIPG) is a rare and highly aggressive pediatric tumor affecting children's brainstem and one of the deadliest cancers. The average survival time after diagnosis is less than one year. The only available treatment options are chemotherapy and radiotherapy with minimal survival benefits. Therefore, it is urgent to find novel effective treatment modalities.

DIPG is characterized by a mutation in histone H3 leading to a substitution of Lysine 27 to Methionine (H3K27M) which deregulates Polycomb Repressive Complex 2 (PRC2), including enzymatic activity of EZH2. Previous studies have shown that inhibition of EZH2 by chemical agents decreases DIPG cell proliferation and inhibits tumor growth in vivo. Our project aims to further validate EZH2 as therapeutic target using chemical EZH2 inhibitors, small interfering RNAs and a CRISPR/Cas9 approach in a series of DIPG tumor cell lines and to determine underlying molecular mechanisms of action.

Efficacy of EZH2 inhibitors and protein down-regulation were evaluated in DIPG cell lines by Western blot, proliferation and cell death assay. Knockout (KO) of the EZH2 gene was also realized using the CRISPR/Cas9 system and validated by Western Blot. A proteomic analysis is underway to determine molecular changes occurring in tumor cells under EZH2 inhibition. In vivo tumor growth inhibition is further evaluated using an experimental DIPG glioma model on the chick embryo chorioallantoic membrane (CAM).

GSK126 is an efficient inhibitor with consistent anti-proliferative and pro-apoptotic effects in DIPG cell lines. GSK126 treatment of experimental glioma demonstrates inhibitory effects on tumor formation. Inhibitory effects will be further confirmed using a murine DIPG tumor model. To minimize the toxic effects of pharmaceutical treatments, we also envision vectorization of EZH2 inhibitors using a novel prodrug delivery system.

P108

Splice switching oligonucleotides targeting the monoclonal immunoglobulin component as new therapeutic weapons to induce selective killing of myeloma cells

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The production of a monoclonal immunoglobulin (Ig) or its heavy or light chain components is a common feature of plasma cell (PC) tumors, including multiple myeloma (MM). Despite high genomic instability and subclonal diversification, CDR3 sequences that define the predominant malignant PC clone remain unchanged during the course of MM. Recent advances in exon skipping therapy using splice switching oligonucleotides (SSO) prompted us to examine a new antisense strategy targeting the variable (V) exon in myeloma cells. Indeed, we previously observed that the production of truncated Ig light chains, encoded by alternatively spliced mRNAs lacking V exons, heightened endoplasmic reticulum (ER) stress and provoke rapid apoptosis of antibody-secreting PCs. We designed SSO targeting the V exon, at either the 5' or 3' splice site (ss), in Igλ- (RPMI8226) and Igκ-expressing (SK-MM-2) myeloma cells. In each cell line, the passive administration of vivo-morpholino SSOs induced alternative splicing and the production of truncated Ig chains. Interestingly, myeloma cells were highly sensitive to specific SSO treatment in vitro and in tumor xenografts, compared to irrelevant control-SSO. RNA-seq experiments further confirmed that the SSO-mediated production of truncated Ig provoked a massive myeloma cell death through an exacerbated ER stress-associated apoptosis. In addition, high throughput sequencing of Ig repertoire demonstrated that treatment of LPS-stimulated mouse B cells with SSOs targeting the 5'ss of a given JH or Jκ segment on pre-mRNAs induced a drastic and selective elimination of given V(D)J-rearranged PC clones. Collectively, these data provide evidence that SSO targeting the V exon of monoclonal Ig can emerge as new weapons to induce selective killing of myeloma cells.

P109

Molecular profiling of leukemic cells in resistance to Midosaurin: CRISPR-Cas9 screening approach

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Acute myeloblastic leukaemias (AML) are particularly aggressive malignant hematological diseases. The recognition of cytogenetic and molecular alterations as prognostic and predictive markers in AML patients has marked a turning point in their management. The most common mutations observed in these patients are insertions called "ITDs" which affect the FLT3 tyrosine kinase receptor. This mutation is correlated to a pejorative prognosis with a dramatically higher rate of relapse after conventional treatment cessation (Aracytine + Anthracycline).

Over the past 20 years, the implementation of targeted therapy protocols using tyrosine kinase inhibitors (ITK) such as Midostaurin has improved patient survival. Nevertheless, despite these therapeutic advances and an increase of overall survival benefit, the treatment of AML remains a real challenge, primarily due to persistent relapses.

Our aim is to identify the molecular profile of resistant/sensitive FLT3-ITD AML cells to Midostaurin within the bone marrow microenvironment to find a potential therapeutic target.

To this end, we performed a functional genetic screen by genomic inactivation (using CRISPR-Cas9) in the AML cell line FLT3-ITD MV4;11 after a treatment with Midostaurin alone or in combination with conventional treatment, Aracytine. As the importance of the bone marrow microenvironment in the initiation and development of the AML neoplastic process has been highlighted over the last decade we performed our screen in conditions that partially mimic the bone marrow microenvironment. MV4;11 cells resistant to Midostaurin-only or in combination with non-targeted chemotherapy (Aracytine) were analyzed by NGS sequencing, followed by bioinformatics analysis.

Our screen was validated by the identification of severally genes already described in the literature for their key role in resistance to these treatments, linked in particular to drug metabolism or apoptotic pathways. This analysis also highlighted metabolic pathways involved in the development of resistance (mitochondrial dysfunction pathway, oxidative phosphorylation, Krebs cycle, glycolysis, etc.).

Currently, the most relevant candidate genes are being individually validated by conventional approaches (overexpression or inactivation).
Their role in resistance/sensitivity to new targeted therapies will thus be evaluated in vitro in different AML lines but also in patient blasts. The most promising genes will be evaluated in vivo in immunodeficient mouse models.

This work could pave the way for the discovery of new therapeutic targets or prognostic markers specific to the resistance of FLT3-ITD AML cells for promising treatments.

P110

Identification of new inhibitors of the androgen signaling axis to counteract prostate cancer resistance to castration.

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Resistance to castration is one of the major causes of death in prostate cancer patients. It is often linked to mechanisms that are dependent on the androgen receptor (AR) such as amplification or mutations of the receptor, expression of AR splice variants, in particular AR-V7, that are constitutively active because of a lack of the ligand binding domain, or overexpression of coactivators that stimulate AR transcriptional activity. Strategies to counteract resistance to castration have primarily focused on the identification of more specific and more potent AR antagonists leading to the approval of enzalutamide or darolutamide. However, fewer studies investigated other mechanisms that regulate AR transcriptional activity including the targeting of AR coactivators, probably because they were considered as undruggable targets and also because of their extensive number.

Our project aims at the identification of new molecules that can impair the transcriptional activity of full-length AR or AR-V7 by screening chemical libraries of diverse origins. They include the Prestwick Chemical and Natural Compounds) libraries and a library from the National Museum of Natural History that is composed of extracts from 80 different strains of endophitic fungi of brown algae with a unprecedented chemical diversity. For these purposes, we have generated dedicated cell lines stably expressing AR or AR-V7 and a luciferase reporter system allowing the quantification of AR transcriptional activity. We also implemented several models allowing us to measure the effect of specific coactivators on AR activity in order to identify specific inhibitors of these coactivators using dedicated two-hybrid screening models.

We will present the preliminary results of our screening and on the identification of FHL2, a coactivator of both AR and AR-V7 receptors, as a potential target. Identification of new inhibitors of the androgen axis and/or AR coactivators may be useful to potentiate the effect of AR antagonists currently used in the clinic to overcome resistance to castration.

P111

Impact of extracellular matrix stiffness alteration on the intestinal crypt cells phenotype, role in colon cancer initiation.

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Colorectal cancer is the third cause of death in the world. The colorectal crypt, in which stem cells are in charge of the renewal of the colonic epithelium, is established as one of the cancer initiation site. The phenotype of those cells and their outcome are strikingly controlled by the microenvironment surrounding them, including the extracellular matrix.

The aim of the project is to decipher whether the increase of matrix stiffness during chronic inflammation may induce phenotypic alterations in colonic stem cells/progenitors, leading to the acquirement of a pre-cancerous phenotype.

To address this hypothesis, intestinal cells (Caco-2) and human primary colonic cells are grown on polyacrylamide gels with an accurately controlled densities corresponding to the physiologic (3 kPa) or the inflammatory (16 kPa) stiffness of the colon mucosa, and coated with extracellular matrix (ECM) proteins allowing cell culture. Using imaging approach and gene expression analysis, we then characterize the phenotype of the colonic cells. Preliminary results show a differential expression of RNA encoding for proteins and factors implicated in the stem cell/progenitor phenotype of the cells, in function of the gel density and ECM coating. Polarity, differentiation and shape of the cells are also impacted.

P112

Role of Leukaemia Inhibitory Factor (LIF) on the tumorigenic properties of Cancer Stem Cells in gastric adenocarcinoma

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Introduction

Cancer stem cells (CSCs), a small cell subpopulation having intrinsic chemo-resistance mechanisms and expressing CD44 cell surface glycoprotein, have been characterised in gastric adenocarcinoma. The link between the Hippo/YAP/TEAD pathway, key regulator of organ size and tissue homeostasis, and CSCs properties has recently been suggested in gastric adenocarcinoma. Recent studies have defined Leukaemia Inhibitory Factor Receptor (LIFR) and its ligand Leukaemia inhibitory Factor (LIF) as being upstream regulators of the Hippo pathway and LIF/LIFR signalling as having an anti-metastatic role in breast cancer cells. Interestingly, the impact of LIF on gastric CSC properties has never been investigated.

Aims & Methods

Consequently, this study aimed to determine the effect of LIF supplementation on the YAP/TEAD pathway and its impact on CSC phenotype and properties in gastric adenocarcinoma. AGS and MKN45 gastric cancer cell lines as well as patients-derived gastric adenocarcinoma cells were used. The expression of Hippo/YAP/TEAD pathway-related genes and of CSC markers was assessed by RTqPCR, western blot and immunofluorescence analysis. YAP/TEAD transcriptional activity was evaluated by TEAD-luciferase reporter assay and proliferation as well as tumorsphere assays were carried out in vitro to evaluate CSC functional properties.

Results

Results demonstrate that LIF supplementation represses the YAP/TEAD pathway through a decreased YAP translocation to the nucleus and decreased expression of YAP/TEAD target genes. In addition, LIF decreases proliferation, tumorsphere initiation capacity and expression of gastric CSC markers in gastric adenocarcinoma cells.

Conclusion

Our results indicate that LIF represses the YAP/TEAD pathway and presents anti-tumorigenic effects on gastric adenocarcinoma cells. Whether the effect of LIF on CSC properties passes through the Hippo/YAP/TEAD pathway activation needs to be further investigated. This could in fine lead to the development of targeted strategies against CSCs to help decrease the number of relapse cases and bad prognosis in gastric cancer.

P113

New insights into p190RhoGAP regulation from the study of cancer-associated mutations

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A tight spatio-temporal regulation of RhoGTPases is required to achieve proper cell migration. The GTPase-activating protein, p190RhoGAP (p190A), the main negative regulator of RhoA, localizes to membrane protrusions such as lamellipodia and invadopodia. ARHGAP35, the gene encoding p190A, is mutated in 15% of endometrial tumors and 2% of global cancers. Our project aims to characterize the molecular and the functional aspects of p190A cancer-associated mutations. Previously, using a structure/function analysis of p190A, we identified the region of p190A sufficient to ensure its proper targeting to lamellipodia. Within PLS, we pointed out cancer-associated mutations (S866F and Δ865-870) that alter p190A lamellipodium localization. We further identified these mutations as gain-of-function mutations, increasing RhoGAP activity of the protein and favoring tumor cell migration. The present work focuses on the impact of p190A mutations on the protein regulation and on its role at invadosomes.

Our previous data suggest an intramolecular folding of the molecule, involving the PLS and masking the GAP domain. Using 2-hybrid screen, co-immunoprecipitation experiments and BRET assay, we identified the domains of the protein that do interact. We demonstrated that this interaction is lost upon introduction of S866F and Δ865-870 mutations, given a molecular explanation to the gain of function mutations. Moreover, we found that S866F mutant protein better interact with another S866F mutant protein than with the WT protein.

In parallel, we confirmed that p190A localizes to various invadosome organizations such as dots, rosettes and linear invadosomes. We found that alteration of the PLS (p190AΔPLS construct or S866F and Δ865-870 mutations) in p190A alters this localization. Moreover, PLS expression has a dominant negative effect on invadosomes, leading to a destabilization of these structures.

Altogether, our data unveil a new mechanism of regulation of p190A.

P114

Elabela, a new peptidic hormone involved in kidney cancer

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Cancer in the kidney constitutes about 3% of all solid tumors. About 85% of renal tumors are renal cell carcinoma (RCC) but to date, there is no reliable kidney cancer marker. Furthermore in 50 % of the case, kidney cancer is discovered fortuitously by echography and for 30 % its already metastatic. Additionally, survival after 5 years is about 60% and depends on the cancer stage. Elabela (Ela) also known as Toddler or Apela is a peptidic hormone recently identified as the second ligand of APJ, the apelin receptor. Produced as a precursor of 32 amino-acids (aa), is restrictedly expressed in human pluripotent stem cells and adult kidney. To date, there is no study about its role in kidney cancer. Ela is mostly expressed in kidney, and we demonstrate that its expression is reduced in human kidney cancer. In a xenograft animal model (subcutaneous, or sub-capsular injection) Ela inhibits tumor progression. These finding identify Ela as a new tumor suppressor gene in kidney and we proposed that decreased expression of Ela in kidney could be a marker of kidney tumor progression. We also emphasis our study on the effect of Ela on the angiogenesis, a central process in tumor growth, using the zebrafish fin regeneration assay. Preliminary results show that Ela is induced by regeneration meaning this hormone has a key role during angiogenesis and regeneration. The effect of Sunitinib (RCC gold standard treatment) on this model affects Ela expression. Collectively, the patient tissue analyses, and in vivo experiments, are consistent with the tumor suppressor function of Ela in kidney that could be used in synergy with Sunitinb.

P115

Infantile Hemangioma angiogenesis and sensitivity to propranolol rely on a cross talk between vascular and perivascular stromal cells

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Betaadrenegic antagonist propranolol is currently the first-line treatment for severe infantile hemangiomas (IH). Neither the molecular mechanism of action of propranolol nor the cell type target of the drug have been identified with a strong proof of concept. We have developed an IH in vitro model using patient derived endothelial cells (EC), pericytes (PER) and CD34+/PDGFR-α+ stromal cells named telocytes (TC). The aim of this study is to investigate the role of these perivascular cells in the antitumor effect of propranolol on IH angiogenesis. Developing a tube formation assay with 3 IH cell types, we revealed an antiangiogenic effect of low doses of propranolol that is cancelled when control foreskin-TC are used instead of IH-TC. None of the single cell-type assays could explain this effect. This study suggests that angiogenesis in IH as well as exquisite sensitivity of IH to propranolol rely on a cross talk between vascular and tumor associated telocytes

P116

LATS2 controls gastric epithelial integrity by restricting epithelial-mesenchymal transition and intestinal metaplasia induced by Helicobacter pylori infection

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Background & Aims. Gastric carcinoma is mostly related to infection with *Helicobacter pylori*, which disrupts the gastric mucosa turnover and elicits an epithelial-mesenchymal transition (EMT) and preneoplastic trans-differentiation. The Hippo pathway controls stem cell homeostasis; its core is constituted by the tumor suppressor kinase, LATS2, which negatively regulates the oncogenic co-transcription factors YAP1. This pathway was investigated in this context of infection.

Methods. Gastric epithelial cell lines (AGS and MKN74) and non-gastric non-cancerous epithelial cell lines (HMLE and RPE1) were challenged by *H. pylori* to investigate the regulation of the Hippo pathway after the infection. LATS2 was silenced using small interfering RNAs. The expression of Hippo pathway related genes, EMT and intestinal metaplasia markers expression was assessed by RTqPCR, western blot and immunostaining. EMT functional properties were evaluated by invasion assays *in vitro*.

Results. *H. pylori* stimulated YAP1 and LATS2 in a coordinated biphasic pattern characterized by an early and transient YAP1 nuclear accumulation and activation. This activation was followed by LATS2 up-regulation leading to YAP1 phosphorylation and inactivation. Loss-of-function experiments showed that LATS2 restricts *H. pylori*-induced EMT markers expression, invasion, and expression of intestinal metaplasia markers. These results support a role for LATS2 in maintaining the epithelial phenotype of gastric epithelial cells by constraining *H. pylori*-induced preneoplastic changes**.**

Conclusion. *H. pylori* infection engages numbers of signaling cascades that alienate mucosa homeostasis, including the Hippo LATS2/YAP1 pathway. The Hippo signaling appears as a protective pathway limiting the loss of gastric epithelial cell identity that precedes gastric carcinoma development.

P117

A better understanding of the E3 ubiquitin ligase Trip12 heterogeneity to better treat pancreatic cancer

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Context: An absence of effective treatments and early diagnostics explain a poor prognosis of pancreatic cancer but also the lack of understanding in the molecular mechanisms. We found that the E3 ubiquitin ligase TRIP12 (Thyroid hormone Receptor Interacting Protein 12) is involved in PTF1a (Pancreas Transcription Factor 1a) degradation, a factor essential in maintaining the acinar phenotype. TRIP12 is heterogeneously overexpressed in many pre-neoplastic lesions of pancreatic cancer. We hypothesize that TRIP12 contributes to the transdifferentiation of acinar cells into ductal cells and therefore to the initiation of pancreatic cancer. Our objective is to determine the cause of TRIP12 altered expression in pancreatic cancer as well as the influence of its expression on the initiation and progression stages of the disease.

Methods: Human pancreatic cancer cell lines (BxPC-3, Capan-1, Capan-2, Mia-PACA-2, and PANC-1) as well as patient derived cell lines were used to determine the intracellular localisation (by immunofluorescence) and expression level (by RT-qPCR and Western Blot) throughout the cell cycle. We also generated a TRIP12fl/fl murine model which is a conditional knockout of TRIP12 (deletion of exon 8 within the TRIP12 genome) that we bred with a KPE (Kras; P53; ElasCreER) murine model.

Results: Our work demonstrates that TRIP12 expression varies within pancreatic cancer and patient derived cell lines. We showed that this heterogeneous expression is partly due to varying levels of TRIP12 mRNA within these cell lines but is also caused by a modification of protein expression regulation throughout the cell cycle with the implication of the deubiquitinase USP7 (Ubiquitin Specific Protease). Furthermore, our primary results show TRIP12 contribution to the development and functionality of the pancreas. Indeed, a homozygote knockout of TRIP12 in the pancreas during embryogenesis is not lethal. However, the mice are glucose intolerant and present an atrophied pancreas. In the consensus KPE model, the homozygote knockout of TRIP12 inhibits acinar ductal metaplasia, the first step of pancreatic carcinogenesis.

Conclusion: Our work elucidates the heterogeneous expression of TRIP12 in pancreatic cancer cell lines as well as its implication in the development and function of the pancreas. This would imply that the heterogeneous expression of TRIP12 in the pancreas participates in the heterogeneity of the acinar population. TRIP12 would contribute to tumour heterogeneity through the degradation of PTF1a which in turn instigates varying levels of acinar transdifferentiation.

P118

Effects of oncostatin M on oropharyngeal squamous cell carcinoma development

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Oropharyngeal squamous cell carcinoma (OpSCC) is one of the most common head and neck cancer worldwide and its incidence is rising due to HPV infections. We previously shown that Oncostatin M (OSM), a cytokine belonging to the IL-6 family, exerts a pro-tumoral effect on skin squamous cell carcinoma (Oncotarget. 2018 Nov 23;9(92):36457-36473). The present study investigate the role of OSM in opSCC development, associated or not to HPV infection.

We collected tumoral and normal tissue from patients during medical care in Poitiers University Hospital, under a protocol approved by the Ethics Committee. Using q-RT-PCR analyses we shown that OSM and its receptor OSMRII were overexpressed in tumor samples (n=14) compared to the contralateral normal mucosa, with a similar expression between HPV+ and HPV- samples.

In order to understand the consequence of OSM overexpression in cancer development, we further study *in vitro* if OSM could targets the oropharyngeal cancer cell lines Cal-33 (HPV-) and SCC-90 (HPV+). Indeed, OSM induced STAT-3 and ERK signalization and increased the proliferation of both cell lines. Using a wound healing assay, we also demonstrated that OSM promotes the migration of Cal-33 and SCC-90 by 150% and 100% respectively after 48 hours treatment. Finally, Affymetrix analysis showed an overexpression of Epithelial to Mesenchymal Transition (EMT) specific genes as Transglutaminase 2 (TGM2) or SERPINB3 in response to OSM compared to untreated cells, and a downregulation of Cytokeratin 13 (CK13) and 7 (CK7) expression which may be interpreted as a loss of epithelial features in both cell lines.

We hypothesize that the pro-aggressive effect of OSM on oropharyngeal cancer cells may go through the activation of the EMT program. We will further study the role played by EMT on OSM induced cancer development using SERPINB3 sh-RNA. We will also develop a mouse OpSCC model in wild type and OSM KO animals in order to evaluate OSM involvement *in vivo*.

In conclusion, these results support a pro-tumoral role of OSM in OpSCC development and suggest that a new therapeutic approach targeting this cytokine should be considered.

P119

Oligo-urea foldamers used as tools to induce apoptosis: Study case of the death receptor DR5/TRAIL-R2

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Ligand-oligomerization is known to be a key process for activating membrane receptors involved in signal transduction. Oligo-ureas designed to fold into a regular and stable helical structure can be used as scaffold for anchoring multiple ligands recognizing, oligomerizing and activating cell surface receptors. The use of olgo-urea scaffold for ligand anchoring not only allows to rationally control the degree of oligomerization, the spacing and the relative orientation between the peptides, but also drastically increase their half-life and duration of action. We present here the case of 16mer-peptides designed by phage display [1] which specifically recognize the pro-apoptotic Death Receptor 5 (DR5), a member of the Tumor Necrosis Factor receptor (TNF-R) family, and induce a high degree of apoptosis in BJAB lymphoma and tumorogenic BJELR cells [2,3]. Multivalent peptides, such as dimers and trimers, show an affinity comparable to the one measured for the natural ligand, the Tumor necrosis factor Apoptosis Inducing Ligand (TRAIL), and are able to induce apoptosis. In order to better decipher the ligand-induced activation process of DR5 receptors, we have used a multidisciplinary approach including spectroscopic studies, crystallographic analyses and binding studies. We over-expressed the ExtraCellular Domain of the receptor (DR5-ECD) in E. coli in 13C15N-labeled or unlabeled forms. Three-dimensional NMR experiments allowed us to achieve a full resonance assignment and to determine secondary structure elements: the protein adopts a β-sheet structure in solution [4], similar to the one determined by crystallography in the presence of TRAIL or monoclonal antibodies anti-DR5. NMR titration studies with monomeric synthetic ligands allowed us to determine a common binding site inside the first Cysteine-Rich Domain (CRD1). This domain has been reported to play a crucial role in the Pre-Ligand Assembly Domain (PLAD) of tumor necrosis factor receptors [5]. The HADDOCK model of peptide-protein complexes reveals a different binding mechanism compared to TRAIL and antibodies. Size-exclusion chromatography shows that multivalent peptides induce a dimerization of the receptor, explaining the extension of the binding site to the CRD2 observed by NMR spectroscopy. We are currently trying to crystallize the receptor in the presence of dimeric peptides in order to solve the three-dimensional structures of the multimeric complexes. Our results revealed a new and unexpected mode of interaction to DR5, allowing us to propose to use synthetic ligands in combination of TRAIL as a bi-therapy to treat cancer.

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Posters – Axis 2 “Genome Dynamics and Cancer”

P201

Responses to mechanical cues: a model for cell fate decisions and epigenetic programs

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In pluricellular organisms, cells respond to environmental changes and external stimuli such as growth factors or mechanical cues: stretch, compression and extracellular matrix (ECM) stiffness. In the case of breast cancer, ECM is remodelled leading to tissue stiffening and this promotes cell motion, proliferation and invasive behaviour of cancer cells. Moreover, ECM stiffness promotes priming of Mesenchymal Stem Cells (MSCs) for specific differentiation programs: at low tension cells go toward adipogenesis, at medium tension toward myogenesis and at high tension toward osteogenesis. How are these signals integrated and how do they influence transcriptional programs remain largely elusive. Mechanical signals are sensed by the cell through « mecano-sensors», integrated to the nucleus and induce modifications of cytoskeleton contents and gene expression. Here, we analysed and identified transcriptional programs in response to ECM stiffness in two different breast cancer cell lines: MDA-MB-231 and MCF-7 cells and in bone marrow derived MSC using RNA-seq and hydrogel based culture with tuneable elasticity. Interestingly, transcriptional responses in MDA-MB-231 is closer to those found in MSC rather than in MCF-7. In MDA-MB-231 and MSC, our results revealed regulatory circuits involving the Hippo/YAP/TAZ and Rho/actin/MRTF pathways as expected, as well as novel mechano-responsive transcriptional networks regulating cell metabolism, cell cycle and lipid biosynthesis. However, target genes of Hippo/YAP/TAZ and Rho/actin/MRTF are not activated in MCF-7. Nevertheless, despite their differences, some common pathways and putative transcription factors have been identified.
As nuclear lamina is directly connected to cytoskeleton through the LINC complex and involved in transcription regulation and mechanotransduction, we looked at the protein expression of lamina components. We found a drastic reorganisation of the nuclear lamina in response to stiffness. We are now developing ChIP-seq approaches at low cell density to identify regulatory elements such as enhancers and promoters that are responding to mechanical cues. We will further investigate how transcriptional regulation occurs using siRNA, chemical compounds for functional studies and to determine how these networks influence the epigenetic landscape, invasiveness and cell fate decisions.

P202
Investigation of genetic factors increasing cutaneous radiosusceptibility in Hodgkin disease

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Radiosusceptibility is an individual's risk of radiation-induced cancer. Secondary cancers following Hodgkin disease are frequent, but some patients show a high radiosusceptibily. Genetic analysis of patients who were treated with radiotherapy for a medulloblastoma and then developed a peculiar basal cell carcinoma radiosusceptiblity led to the discovery of Gorlin syndrome with PTCH1 gene inactivation

Six patients with Hodgkin disease developed early multiple basal cell carcinoma within their irradiation field. Their germline DNA was analyzed by whole exome sequencing to try and find a common monogenic explanation for their phenotype, with similar reasoning than for Gorlin syndrome.

50 rare, truncating variants were identified. None of these variants were found in the same gene so we cannot apply a recurrent criterion for validation. Variants were then analyzed by function. Four potentially pathogenic variants were identified: two were located in the citric cycle succinate ligase (SUCLA2 and SUCLG1) and two are implicated in the DNA repair (POLQ and RAD1)

In conclusion, no common variants were found between the 6 patients. However, four independent variants may explain the radiosusceptibility in our study. Screening for variants in these genes in patients with a similar phenotype and look for radiosusceptibilty in cell cultures derived from the 3 patients in our study could argue in favor of their implication in the phenotype observed.

P203
Telomerase beyond immortalization in cutaneous T-cell lymphomas

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As a major cancer hallmark, there is a sustained interest in understand telomerase contribution to cancer cells' abilities in order to therapeutically target this enzyme. This is particularly relevant in primary cutaneous T-cell lymphomas (CTCL), a malignancy known to have telomerase dysregulation. We investigated mechanisms involved in telomerase transcriptional activation and activity regulation in a Franco-Portuguese cohort of 94 CTCL patients, as well as 8 cell lines, and compare them with 101 healthy controls. We showed that, not only polymorphisms located at hTERT (human telomerase reverse transcriptase) promoter (rs2735940 and rs2853672) but also at gene coding region (rs2853676) could influence CTCL risk, and that hTERT promoter mutations even if rarely, occur at -146 position from the ATG start site. Our results sustained that post-transcriptional regulation of hTERT plays a crucial role in CTCL. Sézary patients present a specific pattern of hTERT splicing variants, different from healthy controls, which not only correlate with the characteristic shorter telomere length of Sézary cells, but may also explain the delayed apoptosis and the low proliferation index observed in this disease. Indeed, we manipulated with shRNAs, hTERT splicing transciptome in aggressive CTCL cell lines, which allowed us to observe that each pattern of hTERT variants had a specific biological consequence. As so, α+β- transcripts seems to protect cells from cell death, while α-β+ in a specific context seems to induce it. Moreover, we hypothesize that α-β- transcripts has an indirect role in telomerase activity regulation.

P204

The histone variant macroH2A1.1 inhibits cellular migration by activating paused gene transcription in triple negative breast cancer cells.

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The histone variant mH2A1 is involved in cellular growth, differentiation and cancer progression. Seemingly contradictory functions of mH2A1 have been reported likely due to variations in expression and localization of its two splicing isoforms, mH2A1.1 and mH2A1.2. To date, chromatin distribution of endogenous mH2A1.1 alone has in fact never been unveiled. Here, we determine the genome-wide localization and associated chromatin environment of endogenous mH2A1.1 in breast cancer cells. We show that mH2A1.1, like mH2A1.2, localizes at facultative heterochromatin and super-enhancers. However, mH2A1.1 can be recruited to chromatin independently of mH2A1.2. In particular, mH2A1.1 binds to the TSS of highly transcribed genes. When recruitment of mH2A1.1 is confined to the TSS, mH2A1.1 is required for regulating transcription of active genes. Strikingly, RNA Polymerase II was in pause at mH2A1.1-activated genes. Conversely, when the recruitment of macroH2A1.1 stretches over the promoter region and the gene body, presumably often in the presence of mH2A1.2, macroH2A1.1 inhibits transcription. Functionally, we propose that mH2A1.1-dependent regulation of a subset of paused genes impedes cellular migration. Interestingly, in contrast to mH2A1.1, the second isoform (mH2A1.2) is required to stimulated cellular migration. Thus, our study brings novel insight into the molecular mechanism underlying the synergistic and antagonistic functions of the histone mH2A1 isoforms in the context of cellular migration of cancerous cells.

P205

The IgH 3' regulatory region enhancer recruits HDAC1 in response to B-cell activation

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Histone deacetylase inhibitors (HDACi) (such as Vorinostat also known as SAHA) are used in the treatment of various mature B-cell lymphomas. HDACi affect B-cell proliferation and Ig synthesis (Waibel and al., 2015). Nevertheless, the mechanism allowing HDACi to disturb B-cell functions is still unknown. B-cell fate, Ig synthesis and class switch recombination (CSR) are under the control of the IgH 3' regulatory region (3'RR) transcriptional enhancer (Saintamand and al., 2017). In this study, we investigated the ability of SAHA to affect 3'RR activation and function.

SAHA was found to affect the LPS-induced proliferation of mouse B-cell splenocytes in a dose-dependent manner. The dose of 2 µM of SAHA was reported to reduce CSR toward IgG3 (LPS stimulation) and IgG3 synthesis without affecting B-cell proliferation. The same dose of SAHA also reduced natural IgM synthesis. In order to understand how HDACi could affect these different processes in B-cells, we studied if 3'RR activation required HDAC recruitment. ChIP experiments indicated the recruitment of HDAC1 (but not HDAC2 or HDAC3) on the 3'RR enhancer in response to two-day LPS treatment of B-cell splenocytes. Specifically, HDAC1 was recruited on the hs1,2 enhancer element of the 3'RR (four enhancer elements encompassing the 30kB structure of this region). Partial deletion of the palindromic structure of the 3'RR is detrimental for CSR and Ig synthesis (ΔIRIS mice, Saintamand et coll., 2016). Of interest, HDAC1 was not recruited on the hs1,2 enhancer in ΔIRIS mice showing the key role of the 3'RR palindromic structure for its efficient activation and HDAC1 recruitment.

The 3'RR is well known to be an oncogene deregulator in various models of transgenic mice including mice with a knock-In of c-myc into the IgH locus. IgH-c-myc mice developed mature B-cell lymphomas due to the long range transcriptional 3'RR effect on the translocated c-myc. Our results indicated that 2 µM of SAHA efficiently reduced the growth of freshly isolated LPS-stimulated B-cell lymphomas from IgH-c-myc mice. We currently work on the ability of SAHA to modulate the *in vivo* development of B-cell lymphomas in IgH-c-myc mice.

The specific inhibition of the 3'RR activity by HDACi make it an interesting therapeutic target in the treatment of B-cell lymphomas characterized by an oncogenic translocation to IgH locus and upregulated by this enhancer. We are currently working on the ability of HADACi to modulate *in vivo* the development of B-cell tumors.

P206

Spatial distribution of FTO adjusts colorectal cancer stem-like properties through RNA modification

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Cancer stem cell (CSC) represents a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity, which can escape from chemotherapies, disseminate and seed metastasis. Understanding the molecular mechanisms that underlie CSC abilities is a major goal to design new therapeutic strategies that may prevent both tumor relapse and metastasis formation. Despite accruing evidence establishing a link between deregulation of epitranscriptome-related players and tumorigenic process, the role of messenger RNA (mRNA) modifications dynamic in the regulation of CSC properties remains poorly understood. Here, we show that the fat mass and obesity-associated protein (FTO) impedes CSC abilities in colorectal cancer through its m^6A_m (N6,2'-O-dimethyladenosine) demethylase activity. While m6Am is strategically located next to the m^7G-mRNA cap, its biological function is not well understood and has not been addressed in cancer. Here we show that low FTO expression in patient-derived cell lines elevates m^6A_m level in mRNA which results in enhanced *in vivo*tumorigenicity and chemoresistance. In the contrary, inhibition of the recently identified m6Am methyltransferase, PCIF1/CAPAM, partially reverses this phenotype. We demonstrate that the FTO/ m^6A_m axis constitutes a novel, reversible pathway controlling CSC abilities that does not involve transcriptome remodeling, but rather modulates translation efficiency of selected m^6A_m marked transcripts. Finally, tumor microarrays analysis suggests a compartment-specific role of FTO in colorectal cancer (CRC) initiation and progression. While its expression is strictly nuclear in benign lesions (stage 0), FTO is found in both the nucleus and cytoplasm following malignant transformation (stage 1, 2, 3 and 4). Recent reports suggest that spatial distribution of FTO may modulate its accessibility toward relevant substrate. Our latest data echoes this hypothesis and demonstrate that cytoplasmic FTO hampers CSC properties through cap-m^6A_m demethylation. Altogether, our findings bring to light the first biological function of the m6Am modification and its potential adverse consequences for CRC management.

P207

A new role for cytidine deaminase in the control of DNA replication and genome stability in pancreatic cancer cells

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Context and Rationale. Cytidine deaminase (CDA) is involved in the pyrimidine salvage pathway, by converting cytidine and deoxycytidine into uridine and deoxyuridine, for DNA and RNA synthesis. Loss of CDA is associated with genomic instability in Bloom Syndrome, and its overexpression with tumor chemoresistance. However, the precise role of CDA per se in cancer cells has been totally underexplored so far.

Results. Preliminary results demonstrated that CDA is overexpressed in pancreatic tumors (PDAC), associated with a worse prognosis and essential to experimental tumor growth. We found that PDAC cells depleted for CDA show altered production of nucleotides, high level of DNA replicative stress (exemplified by DNA single and double-strand breaks during S-phase) and genomic instability (formation of ultrafine bridges and micronuclei during and after mitosis, respectively). Interestingly, overexpressing CDA in pancreatic cancer cells strongly decreases the aforementioned hallmarks, increases the proportion of cells in late S-phase and reduces DNA-damage transmission to daughter cells. This role is totally dependent on CDA catalytic activity. In these cells, CDA is recruited to chromatin and DNA replication forks in response to replicative stress as monitored by iPOND, to increase DNA replication efficiency, as monitored by DNA spreading, and also that CDA promotes late DNA synthesis during mitosis to resolve ultrafine bridges. Last, we found that CDA protects PDAC cells from drugs targeting DNA replication such as camptothecin.

Conclusion. Taken together, our results reveal for the first time that CDA controls DNA replication and genome stability in cancer cells, by increasing DNA replication efficiency, and DNA repair synthesis in mitosis. Thus, our work advocates for a new role of CDA in controlling DNA replication and genome stability. This program may help define novel synthetic lethal therapeutic approaches based on CDA targeting to help manage patients with this incurable disease.

P208

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

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Ribosomal DNA (rDNA) is the most transcribed genomic region and contains hundreds of tandem repeats. Maintaining these rDNA repeats as well as the level of rDNA transcription is essential for cellular homeostasis. DNA damages generated in rDNA need to be efficiently and accurately repaired. Here, we describe that the histone demethylase JMJD6 is rapidly recruited at nucleolar DNA damage and is crucial for the relocalisation of rDNA in nucleolar caps. Yet, JMJD6 is dispensable for rDNA transcription inhibition. JMJD6 interacts with the nucleolar protein Treacle and modulates its interaction with NBS1. Moreover, cells deficient for JMJD6 show increased sensitivity to nucleolar DNA damage as well as loss and rearrangements of rDNA repeats upon irradiation. Altogether our data reveals that rDNA transcription inhibition is uncoupled from rDNA relocalisation into nucleolar caps and that JMJD6 is required for rDNA stability upon the rDNA damage response through its role in nucleolar caps formation.

P209

LSM2-8 and XRN-2 contribute to the silencing of H3K27me3-marked genes through targeted RNA decay

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In fission yeast and plants, RNA-processing pathways contribute to constitutive and facultative heterochromatin silencing, complementing well-characterized pathways of transcriptional repression. However, it was unclear whether this additional level of regulation occurs in metazoans. Here we describe a pathway of silencing in C. elegans somatic cells, in which the highly conserved, RNA binding complex LSM2-8 selectively silences heterochromatic reporters and endogenous genes bearing the Polycomb mark H3K27me3. Importantly, the LSM2-8 complex works cooperatively with XRN-2, a 5'-3' exoribonuclease, and disruption of the pathway leads to mRNA stabilization. This selective LSM2-8-mediated RNA degradation does not target nor depend on H3K9me2/me3, unlike previously described pathways of heterochromatic RNA degradation. Intriguingly, the loss of LSM2-8 coincides with a localized drop in H3K27me3 levels on lsm-8-sensitive loci only.

Together this reveals that in higher eukaryotes facultative heterochromatin enriched with the Polycomb mark can be silenced by specific degradation of transcripts arising from H3K27me3-regions, and not only by transcriptional repression, as it was believed. H3K27me3 modifications and associated genes reponsible for the deposition of this mark have major roles in cell fate decisions and the maintenance of cellular identity, and their misregulation contributes to many types of cancer. Therefore, it is crucial to understand now whether this specific LSM8-mediated silencing mechanism is conserved in mammals and to understand in C. elegans the details of this mechanism which crosstalk between epigenetics state and RNA fate.

P210

High throughput sequencing reveals that class switch recombination junctions are not affected by the absence of the Eμ and 3'RR cis-transcriptional enhancers

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The immunoglobulin heavy chain (IgH) locus undergoes numerous changes during B-cell differentiation, affecting transcription, V(D)J accessibility to recombination, class switch recombination (CSR) and somatic hypermutation (SHM). Ongoing recombinations and mutations throughout B-cell development, via Rag1/Rag2 and AID targeting, make the IgH locus a hotspot for oncogenic translocations. Numerous human mature B-cell lymphomas are marked by oncogenic translocations into the IgH locus. Cyclin D1/D3, c-myc or c-maf translocations found in myeloma are thus clearly related to an abnormal CSR. Transcription of the IgH locus is under the control of *cis*-regulatory elements. These transcriptional enhancers (5'Eμ and 3'RR) obviously intervene in oncogene deregulation during B-cell lymphomagenesis. In the present study we have investigated if these two IgH enhancers might also be implicated in the faulty end-joining process for the resolution of DNA double strand breaks generated during CSR.

We recently reported a new computational tool (CSReport) for automatic analysis of CSR junctions sequenced by high-throughput sequencing (Boyer et al. J Immunol 2017). We thus used CSReport and high-throughput sequencing to analyze the molecular signature of Sμ-Sγ3 (IgG3), Sμ-Sγ1 (IgG1) and Sμ-Sα (IgA) junctions in 5'Eμ- and 3'RR-deficient mice. The computational tool developed for experiments performs junction assembly, identifies not only breakpoints in Sμ,Sγ1,Sγ3,Sα but also junction structures (blunt, micro-homology, large homology or junction with insertions) and outputs a statistical summarization of identified junctions. NGS analysis of several thousand junctions (when conventional Sanger sequencing allows detection of few dozen junctions) demonstrated that the balance between the non-homologous end joining (N-HEJ) and alternative end joining (A-EJ) pathways was not affected in 5'Eμ- and 3'RR-deficient conditions. Our results thus do not argue in favor of a 5'Eμ and/or 3'RR role in the recruitment of specific DNA repair factors during CSR and thus of their role in the aberrant recombination leading to the oncogene insertion into the IgH locus.

The contribution of 5'Eμ and 3'RR during B-cell lymphomas seems only related to their long range transcriptional effect on the translocated oncogene.

P211

Control of intestinal homeostasis and cell lineage by the histone variant H2A.Z

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Incorporation and post-translational modifications of histone variants are important regulatory mechanisms which have been involved in cell proliferation, gene expression as well as in the determination of cell fate. Thus, the Tip60/p400 chromatin-modifying complex, which have H2A.Z histone variant as effector, regulates important signaling pathways, such as Wnt. We recently showed the involvement of H2A.Z in intestinal epithelial homeostasis, which is dependent on the finely-tuned equilibrium between stem cells renewal and differentiation, under the control of such pathway. Using human established intestinal cell models (Caco-2 cells), as well as materials from inducible knock-out mice for H2A.Z (tissue sections and ex vivo organoids), we are currently investigating the role of H2A.Z isoforms on intestinal homeostasis. We specifically study the differential effects of the specific depletion of each H2A.Z paralog on the proliferation abilities and the differentiation features of intestinal cells, and we analyze the involved mechanisms. This study should reveal the importance of the isoforms of H2A.Z histone variant in the determination of lineages, cell fate and the maintenance of tissue homeostasis.

P212
CELIGO imaging to address DNA-damage signaling with multiplex labeling

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Current methods for measuring DNA damage are relatively labor intensive and are usually based on Western blotting and/or flow cytometry analyses. They require numerous cells and are often limited to a single protein assessment. Here, we propose a Celigo-based multiplexed assay that can evaluate cell response to various DNA-damaging agents (chemotherapy for instance) based on a panel of biomarkers associated with specific repair pathways.

We used this technology to address the effects of new drug combinations that are currently tested in the clinic and performed the quantification of replicative stress markers such as RPA, a protein covering persisting ssDNA, together with gH2AX that is used as a gold-standard for the measurement of DNA breaks. For instance, we could readily assess the respective labelling of both markers in cell cultures and perform kinetics and dose-response analyses. We showed that our drug combination was first inducing replicative stress that was further converted into DNA double-strand breaks.

We are currently implementing the level of multiplexing using a combination of 3 or 4 different antibodies that are already validated for Immunofluorescence assays and that respectively target H2AX, 53BP1, RPA, pATR, pCHK1, pATM, pCHK2, MRE11, RAD51, RAD50 and pP53.

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

P301

Comparative study of cancer stem cells from primary tumors versus metastases of colorectal cancer: regulatory pathways and chemosensitivity/chemoresistance

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Introduction:
Colorectal cancer (CRC) is a leading cause of cancer-related death worldwide. Early-stage CRC is curable with surgical treatment, whereas advanced or metastatic disease may only be treated to prolong survival without curative intent such as chemotherapy. After well-directed curative treatment, the persistence of cancer stem cells (CSCs), with self-renewal and multi-lineage differentiation capacities, would be responsible for the microscopic residual disease and promotes metastases development. CSCs represent less than 5% of the tumor mass and their isolation is a challenge. In our lab, the sedimentation field-flow fractionation (SdFFF) technique has been adapted to sort homogeneous populations of cells according to their differentiation degrees, especially undifferentiated/stem cells.
The objective of this research project is to use SdFFF to isolate CSCs (1) from cell lines representative of tumor stages*in vitro*, (2) from CRC patient samples, and (3) from PDX (Patient-derived-xenograft) models using mice *in vivo*, in order to analyze the chemosensitivity of tumor cells according to their degrees of differentiation and tumor stages. Finally, this project aims to develop a tool to characterize the sensitivity of each patient to personalized therapy.
Materials and methods:
Four cell lines representative of different CRC stages were used and sorted by SdFFF to isolate four fractions; one of them enriched with CSCs. The expression of stem cell markers was analyzed by flow cytometry, RT-qPCR and western blot, and the capacity to form colonies by soft agar assay. To study chemotherapies response, chemosensitivity tests were performed and cell proliferation were analyzed. Chemotherapies used in CRC treatment are: 5-fluorouracil generally associated with folinic acid, oxaliplatin and irinotecan, and are commonly administered in combination such as FOLFOX, FOLFIRI or FOLFIRINOX. Therefore, chemosensitivity tests were done with chemotherapies alone and in combination.
Results:
We have characterized our cell lines at the phenotypic and functional level *in vitro*. We have shown that the four cell lines express at the protein and transcriptomic level stem cell markers such as Oct4, Nanog, Sox2 and more specific CRC markers such as Lgr5, Bmi1, CD44 and EpCAM. Soft agar assay has demonstrated that these cell lines are able to form colonies. With regard to chemosensitivity tests, the four cell lines are sensitive to the four chemotherapies tested, but to varying degrees. The IC50s obtained for the chemotherapies alone and the combinations FOLFOX, FOLFIRI and FOLFIRINOX have highlighted that the most aggressive cell line used, derived from lung metastases of CRC, is the most resistant of the four cell lines. Using SdFFF, we have sorted each cell line and isolated a fraction enriched with CSCs. We have pointed out an increase in stem cell markers expression by flow cytometry, western blot and RT-qPCR in these fractions compared to the unsorted cell line. At the functional level, we have observed the ability of these enriched fractions to form a higher number of colonies and bigger colonies than unsorted cell line.
Conclusions:
Phenotypic and functional characterization confirms the interest of SdFFF to isolate cell populations enriched with CSCs. We shown an increase in stem cell markers expression and in clonogenic capacities of the CSCs enriched fractions compared to the unsorted cell line. We highlighted a difference in sensitivity to chemotherapies between cell lines from primary tumors and metastases of CRC. My short-term prospects are to continue the phenotypic and functional characterization of these fractions enriched with CSCs, to carry out chemosensitivity tests (alone and in combination) on these fractions and finally to analyze regulatory pathways that can be associated with chemotherapy resistance. In the medium term, all these analysis will be carried out on CRC patient samples and *in vivo* on PDX models using mice.

P302

The endoplasmic reticulum resident-AGR2 protein: a novel secreted biomarker with pro-oncogenic properties

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Cancer cells multiply abnormally fast and therefore produce protein molecules faster than normal cells. To avoid becoming stressed by this overproduction, cancer cells make use of proteins that fold new proteins inside the cell. One of these protein folders is called Anterior Gradient-2 (AGR2) and has been shown to be highly overexpressed in diverse human cancers and involved in cell transformation, drug resistance and metastatic growth. Previous research has shown that Endoplasmic Reticulum (ER)-resident AGR2 can also be found outside cells, such as in the blood or urine of cancer patients. Therefore, it has been suggested that measuring the levels of AGR2 in body fluids may be a useful marker for detecting cancers.

Thus, we hypothesized that - apart from becoming a promising diagnostic tool - the AGR2 protein itself, specifically when found outside cells, might make cancer cells more aggressive. To test this hypothesis, healthy lung cells were grown into lung organoids, and in a key experiment, the addition of extracellular AGR2 (eAGR2) in the microenvironment was enough to convert healthy organoids into tumoroids. Further experiments then revealed that AGR2 plays a dual role in cancer development, first by exerting its expected protein quality control functions in the ER and second through gain-of-function extracellular. We have elucidated this gain-of-function as a novel extracellular regulator of epithelial morphogenesis, tumorigenicity and pro-inflammatory phenotypes. Therefore, understanding the intra- and extracellular AGR2 (i- and eAGR2) molecular and cellular mechanisms points towards the identification of novel potential therapeutic target. Indeed, in preclinical studies and ongoing clinical trials, targeting tumor micro-environmental signals has shown promises in halting tumor progression in various human cancers.

P303

Effective therapeutic of sortilin derived peptides in anti-EGFR strategies in lung adenocarcinoma

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Lung adenocarcinoma remains the most incurable cancer where aberrant activation of tyrosine kinase receptors occurs in a majority of cases. Indeed, the Epidermal Growth Factor Receptor (EGFR) activated mutations drive tumor initiation and progression irrespective of disease stages. Clinical trials using tyrosine kinase inhibitors (TKI) showed a decrease in EGFR signaling intensity and patient's disease course; however used alone their clinical benefits decline inevitably even when the last TKI generation is used. Hence, to imbalance the relapsing program of EGFR in acquired resistance mechanisms, we used peptides derived from sortilin, a sorting protein belonging to the VPS10 family, which acts as a key regulator of EGFR trafficking. Indeed, because sortilin expression remains strongly correlated with survival, especially in patients with EGFR amplification, we engineered these peptides to support TKI benefits. We reported anticancer properties of these peptides by limiting both EGFR proliferative signaling and transcriptional program. In this context, cancer cells viability decreased, encouraging its clinical orientation. Altogether, we purpose a model where engineered peptides may provide innovative approaches to guide anti-EGFR strategies.

P304

Development of a screening test to detect high-grade serous carcinomas in at-risk women (mutated to a predisposition gene: BRCA1, BRCA2, RAD51C or RAD51D). Analysis of aneuploidies in plasma cell free DNA by NGS capture.

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Introduction

Despite their low incidence (7.5/100,000 in 2018 in France[1]), ovarian cancers have a high mortality rate (3.8/100,000 in 2018 in France) and a five-year survival rate of less than 50% for all ages combined[2]. Since ovarian cancers are diagnosed at a disseminated stage in 60% of cases, improving screening is one of the challenges for improving care.

In the context of the hereditary predisposition linked to mutations in the *BRCA1, BRCA2, RAD51C, RAD51D* genes, women can develop high-grade serous carcinomas (HGSC) (with penetrations at age 80 of 44% and 17% for *BRCA1* and *BRCA2*[3]). A bilateral salpingo-oophorectomy is proposed to women with a deleterious mutation, in order to reduce the residual cancer risk (4-5%)[4].

It has recently been shown in patients with HGSC that plasma cell free DNA (pcfDNA) is detectable not only in the advanced stage but also in the early stage (non-disseminated)5. The genomic profile of HGSCs is characterized by numerous aneuploidies (gains, amplifications, loss of genetic material) and few deleterious point mutations except on the TP53 gene, mutated in 98% of cases[6].

Materials and methods

The project consists of developing a screening test to detect tumor-induced aneuploidies in the pcfDNA of followed patients before and after bilateral salpingo-oophorectomy.

The method chosen is a next generation sequencing technique (NGS) using an "Oneseq" capture bank (Agilent company) that makes it possible to capture targeted gene regions frequently changed in HGSC on the one hand and the entire genome with low coverage on the other hand in order to detect large aneuploidies.

We are currently conducting a preliminary feasibility study by analyzing by NGS oneseq the pcfDNA of 16 patients with active-phase HGSC (recent diagnosis or relapse) and a series of 16 controls.

Objectives

Detect aneuploidy profiles in pcfDNA for patients with HGSC, and normal profiles for healthy controls. The objective is to validate the feasibility of aneuploidy analysis in pcfDNA by NGS oneseq to detect HGSC. This will make it possible to consider testing this technique under screening conditions through a prospective study.

Confirm the tumour origin of the aneuploidies observed in pcfDNA by analysing DNA samples from fixed and paraffin-included tumours from the 16 affected patients using NGS oneseq.

Compare the aneuploidies observed by NGS oneseq with a SNP array technique (Oncoscan-CNV) performed on the 16 fixed tumor DNA and 4 pcfDNA samples from patients).

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P305

Epithelial to mesenchymal transition (EMT) is associated with attenuation of succinate dehydrogenase (SDH) in breast cancer, through reduced expression of SDHC

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Introduction: Epithelial to mesenchymal transition (EMT) is a well characterized process of cell plasticity that may involve metabolic rewiring. In cancer, EMT is associated with malignant progression, tumor heterogeneity and therapy resistance. In this study we investigated the role of succinate dehydrogenase (SDH) as a potential key regulator of EMT in breast cancer.

Methods: Associations between SDH subunits and EMT were explored in gene expression data from breast cancer patient cohorts, followed by in depth studies of reduced SDH function as a potential mediator of EMT in cultured cells and 3D sphere structures.

Results: We found an overall inverse association between EMT and the SDH subunit C (SDHC) in breast cancer patient cohorts. This was particularly evident in carcinomas of basal-like molecular subtype compared to non-basal like tumors, and a low SDHC expression level tended to have a prognostic impact in those patients. Studies in cultured cells revealed that EMT was induced by SDH inhibition through SDHC CRISPR/Cas9 knockdown, or by the SDH enzymatic inhibitor malonate. Conversely, overexpression of EMT-promoting transcription factors TWIST and SNAI2 caused decreased levels of SDHB and C and reduced rates of SDH-linked mitochondrial respiration. Cells overexpressing TWIST had reduced mitochondrial mass, and the organelles were thinner and more fragmented compared to controls.

Discussion: Based on previous reports suggesting that mitochondrial dysfunctions and SDHB mutations promote EMT, we hypothesized that altered SDH enzyme function may be a determining factor and an integral part of EMT in cancer development. Our findings suggesting reduced SDHC expression and overall lower SDH activity in cells associated with a mesenchymal phenotype, suggest SDH to be involved in cellular plasticity.

Conclusions: Our findings suggest that SDH inhibition is a driver of the EMT program, and that this is accompanied by structural remodeling of the mitochondrial organelles. This may confer survival benefits upon exposure to hostile microenvironment including oxidative stress and hypoxia during cancer progression.

P306

2-phenylethynesulfonamide (PES), a HSP70 inhibitor, enhances nuclear accumulation and anti-tumoral activity of doxorubicin in neuroendocrine pancreatic cancer cells

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Lysosomes were showed to play an important role in Multi-Drug Resistance (MDR) by sequestrating protonated hydrophobic weak base chemotherapeutics drugs like Doxorubicin (DOX) and preventing them to act on target sites. Moreover, Heat shock protein 70 (HSP70), which is highly expressed in human tumors and especially on the lysosomes, maintains the lysosomal membrane integrity and therefore acts in MDR. In this study, we investigated the effect of pharmacological HSP70 inhibition, by PES, in combination with DOX on neuroendocrine pancreatic cancer cells. Our results demonstrate that INR1-G9 and BON cells treatment with PES synergistically promotes the anti-tumoral activity of DOX by inhibiting cell viability and incrising cell death. Further, this study reveals, that PES promotes the lysosomal membrane permeabilization leading to the release of sequestrates DOX from the lysosome and increasing DOX accumulation in the nucleus. Besides, PES enhaces ROS production, promotes the reduction of mitochondrial membrane potential induced by DOX and caspase-1 and 3 activity, leading to the cell death. Our findings suggest that PES potentiates the anticancer effect of doxorubicin in neuroendocrine pancreatic cancer cells and that combination of conventional chemotherapy with HSP70 inhibition may provide a more efficient anticancer therapy.

P307

Tumor antigen-specific CD8 T cells identified by TIM-3 expression predict response to PD-1 blockade in head and neck cancer

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While our understanding of T cell exhaustion is widely based on mouse models, in depth analysis of T cell exhaustion in cancer patients will provide cues of tumors sensitivity to immune checkpoint blockade (ICB). Here, in ovarian, cervical and head and neck cancers, 3 epithelial malignancies exhibiting resistance to ICB, we combined phenotypic, single-cell RNA sequencing (scRNA-seq) and functional approaches to characterize exhaustion of tumor antigen-specific CD8 T cells at the tumor site.

We show that along chronic stimulation of tumor-specific T cells, but not bystander cells, immune checkpoints (IC) expression is sequentially acquired leading to a population expressing the 4 IC under investigation, i.e. PD-1, TIGIT, CTLA-4 and TIM-3, that we named quadruple positive (QP) cells. Checkpoints incremental acquisition was accompanied by a sequential increase in the expression of tissue-resident memory T cell (Trm) markers, of the ectonucleotidase CD39, and of the transcription factor TOX associated to a T-cell exhaustion program in chronic infection models. Remarkably, QP cells exhibited significant loss of CD28, which could be reproduced by T-cell stimulation in the presence of transforming growth factor-beta (TGF-β), a central cytokine of immune evasion.

Despite their exhausted phenotype, QP cells were endowed with high cytotoxic potential and expressed the C-X-C motif chemokine receptor 6 (CXCR6), which could contribute, together with Trm markers, to their tumor residency and co-localization with tumor cells. *Ex vivo* phenotyping of circulating and tumor-infiltrating cancer antigen-specific T cells argued in favor of the *in situ* acquisition of the exhausted Trm-like phenotype by memory tumor-specific CD8 T cells once they infiltrate tumors.

In addition, we show that circulating specific PD-1^{int}CD28^{+} T cells respond to anti-PD-1 mAb by enhancing their proliferation in response to antigen stimulation. Instead, the same cells within tumor-infiltrating lymphocytes (TIL), which were PD-1^{hi}CD$28^{+/-}$, exhibited a reversal of their functional exhaustion.

Finally, and in agreement with their tumor specificity and responsiveness to PD-1 inhibition, QP cells, quantified by multiplex immunohistochemistry, were predictive of response to therapy and of overall survival in a cohort of 30 head and neck cancer patients treated by PD-1/ PD-L1 blockade therapy. Predictors of response to ICB will be instrumental for an optimized clinical output of current and future immunotherapies.

P308

Modeling the differentiation dynamics of monocytes in contact with CLL B cells

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Monocytes are immune cells which can differentiate into macrophages to help defend the body against pathogens. Macrophages are polarized along a spectrum with two extreme phenotypic states: the M1 phenotype, pro-inflammatory and stimulating the immune system, and the M2 phenotype, anti-inflammatory and stimulating tissue repair **[1]**. In a tumour setting, some macrophages can become strongly linked to cancer cells. These are called tumour-associated macrophages and are mostly polarized towards the M2 phenotype **[2]**. In the case of chronic lymphocytic leukemia (CLL), tumour-associated macrophages are called nurse-like cells (NLCs). They reside mainly in the lymph nodes, where they protect leukemic B cells (BCLL) from spontaneous apoptosis and contribute to their chemoresistance **[3,4]**. NLC are differentiated from monocytes through contact with BCLL and soluble factors **[5]**, however, the precise mechanisms by which BCLL influence this differentiation are still unknown.

Here we propose an agent-based model (ABM) of monocyte differentiation in a BCLL culture. The goal is to study the dynamics of monocytes differentiation by reproducing mathematically an experimental in vitro setting, and characterizing it based on initial conditions and various characteristics of the cancer cells.

Three kinds of agents are represented in the ABM: BCLL (i.e. cancer cells), myeloid cells (monocytes and macrophages), and dead cells. Upon initialisation, only BCLL and monocytes are present, but during the course of the simulation, monocytes will differentiate into NLCs. This differentiation process is gradual, the monocytes start to emit a small apoptosis-blocking signal that is gradually increasing during the differentiation and that reaches its full strength when the differentiation is complete and monocytes have become NLCs. BCLL are attracted towards this signal, depending on its strength. If they cannot locate and get close to any NLC in time they will die, so the parameters governing the differentiation are paramount here. The in vitro experiments of BCLL and monocytes cultures that we conducted and that were the basis for this model produced daily dynamics of cell survival and total cell concentration in the medium. With these data and the help of model exploration techniques such as sensitivity analyses and calibration profiles, we have tested and validated our ABM.

We were able to reproduce via simulation the daily dynamics from the cultures. We gained knowledge on a few key parameters such as the initial density of cells that is needed, and the durations for which the apoptosis-blocking signal will last or the cancer cells can look for the signal. This model is a first step to a better understanding of monocyte differentiation in a tumoral environment, and in particular of the way in which cancer cells can influence monocytes to differentiate into pro-tumoral macrophages. A more complex model of the entire tumour micro-environment, taking into account different kinds of immune cells (for instance T cells, which are usually needed for immunotherapy success) and integrating the signaling pathways that lead to monocyte differentiation, is the next step.

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P309

The extracellular domain of E cadherin linked to invasiveness in Colorectal Cancer: a new resistance and relapses monitoring serum-bio marker?

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Background: Multiple studies have tried to demonstrate the interest of the cell adhesion marker, E cadherin, as a diagnostic and prognosis marker in colorectal cancer (CRC). However, it was considered non specific.

Materials and methods: Studies were carried out with CRC cell lines and patients' cohort operated for CRC. The expression of E cadherin was studied after 5 fluorouracil (5FU) treatment and correlated to CRC relapse, chemoresistance and survival.

Results: In CRC cell lines derived from high tumor stages, extracellular domain of E cadherin expression decreased after 5FU treatment whereas it increased in supernatants. Interestingly, only specific cleaved forms at 55 kDa of E cadherin were detected in supernatants. In CRC surgical patients, more importantly concerning extracellular E cadherin domain, a decreased expression was observed in tissues in function of CRC stages whereas an increased expression was found in sera. Moreover, there is an increasing trend of survival with weak serum E cadherin secretion, reinforcing the implication of this protein in CRC evolution.

Conclusion: The extracellular domain can be defined as a 5FU resistance marker and allows CRC monitoring.

P310

Mutations of the B-cell receptor pathway confer chemoresistance in primary cutaneous diffuse large B-cell lymphoma leg-type

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Background

Primary cutaneous diffuse large B-cell lymphoma leg-type (PCLBCL-LT) is the most aggressive cutaneous B-cell lymphoma requiring
a combination of poly-chemotherapy with Rituximab as first line therapy. About 50% of patients will experience progression or relapse without so far any predictive biologic marker. We previously characterized the specific mutational profile of PLCBCL-LT of activated B-cells leading to constitutive activation of the NF-κB and B-cell receptor (BCR) signaling pathways, as reported for central nervous system or testicular lymphoma (Mareschal et al., 2017).

Aims

Here, we tried to determine if the genomic profile may predict therapeutic response and help to design personalized second-line therapy. Using lymphopanel next generation sequencing, we analyzed 14 PCLBCL-LT cases with complete response and 18 with relapsing/refractory disease. Among the latter, 14 tumor pairs at diagnosis and relapse/progression were analyzed to assess genetic changes.

Results

PCLBCL-LT patients harboring one mutation that targets one of the following BCR signaling genes (CD79A/B or CARD11) displayed a reduced progression-free survival and specific survival (median 18 months, P=0.002 and 51 months, P=0.03 respectively, whereas median duration in the wild type group was not reached) and were associated with therapeutic resistance (P=0.0006). Longitudinal analyses showed that both MYD88 and CD79B were the earliest and among the most conserved mutated genes. Evaluating the genomic profile of cutaneous large B-cell lymphoma has not only a descriptive/diagnostic interest but may also help to predict therapeutic resistance in patients with BCR mutations who may benefit from adjuvant or second-line selected therapy (Ducharme et al., 2019).

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P311

Expression by immunohistochemistry of Anaplastic Lymphoma Kinase (ALK) in Glioblastoma Multiforme : Foreshadow of clinical implications (GLIMAL1 study)

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Introduction : ALK gene rearrangement has implications in a variety of cancers and show clinical and therapeutic advantages in lung cancer with ALK expression. Fundamental research on glioblastoma (GBM) models pinpoint pleiotrophin (PTN) signaling via ALK in the development of GBM. Furthermore, ALK inhibitors show tumor control in xenograft models prefiguring their use as targeted therapy of GBM.

Methods : Fifty seven consecutive biopsy or surgery samples of human GBM were tested for ALK expression by immunohistochemistry (IHC) treated at our university hospital between november 2018 and june 2019.

Results : ALK expression was detected in 16 samples of 57 consecutive patients (28.07%). The 95% exact confidence limits being 16.97% and 41.54%. This confidence interval is wide accounting for the small number of tissue samples, though the minimum frequency of ALK expression (16.97%) remains an important indicator foreshadowing clinical implications of therapies targetting ALK in GBM.

Conclusions : ALK expression in GBM seems to be a promissing finding for clinical and therapeutic implications. Consequently, more GBM samples are being included in order to correlate the prevalence of ALK to clinical features, prognostic significance and outcomes after standard primary treatment. Future perspectives include a multicenter clinical trial of ALK inhibition in recurrent cases after standard primary treatment in cases with ALK expression.

P312

Targeting proteolytic notch activation inhibits PD-1 expression and improves cytotoxic T lymphocytes (CTL) cytotoxicity against MSI and MSS tumor cells and enhances tumor-infiltrated CTLs and tumor regression.

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Notch is synthesized as a proprotein (ProNotch-1) that requires proteolytic maturation by the proprotein convertases (PCs) to generate a transmembrane form (NTM). The latter is then cleaved by ADAM17 at a second site to generate the Notch extracellular truncation (NEXT) domain and finally by γ-secretase to generate the Notch intracellular cytoplasmic domain (NICD). We found that inhibition of PCs represses PD-1 expression in cytotoxic T lymphocytes (CTL), and their exhausted phenotype by preventing their proliferation impairment and progression to apoptosis and improves their efficacy against microsatellite instable (MSI) and stable (MSS) colon cancer cells. In vivo PCs inhibition enhances CTL infiltration in tumors induced in mice and mediates more tumor clearance in syngeneic mice while compared to immunodeficient mice. Immunoblotting analysis revealed that while NTM form and ProNotch-1 form are observed in control T cells, ProNotch-1 was the major form observed in cells with repressed PCs activity. PD-1 expression in activated T cells was repressed by DAPT. While the presence of PCs inhibitor repressed PD-1 expression, the lentiviral-mediated expression of NICD induced PD-1 expression. The intracellular calcium concentration in activated T cells was inhibited by DAPT. Similarly, nuclear accumulation of NFAT in activated T cells was reduced following DAPT treatment as assessed by western blotting analysis and following cells transfection with the EGFP-based reporter plasmid that contained an NFAT promoter. Further analysis revealed that cells treatment with DAPT had no effect on NF-κB and ERK phosphorylation in activated T cells. These findings indicate that Notch cleavage is required for calcium mobilization and NFAT activation, pathways involved in PD-1 and other immune checkpoint molecules expression. Altogether, we propose a mechanism of action in which PCs inhibition disrupts PD-1 and other immune checkpoint molecules expression in T cells through Notch processing (probably other precursors), calcium/NFAT and NFκB pathway blockade. In consequence, the reduced expression of these molecules, particularly PD-1 receptor at the cellular membrane of T cells, allows these cells to bypass the PD-L1/PD-1 mechanism developed by cancer cells to avoid the immune response.

P313

Preclinical xenograft and culture models of Sézary syndrome reveal cell of origin diversity and subclonal heterogeneity

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Sézary Syndrome (SS) is a rare but an aggressive epidermotropic cutaneous T-cell lymphoma (CTCL) defined by erythroderma, pruritis and a circulating atypical CD4+ T-cell clonal population. The diversity of Sézary cells (SC) phenotype and genotype possibly reflects either plasticity or heterogeneity that is difficult to assess, as SC are difficult to expand with very few cell lines available. Therefore, we developed six new defined culture conditions allowing the amplification of SC defined by their phenotype and monoclonality in 4 of 7 patients. The SC expansion in response to different culture conditions by addition of several cytokines and stromal cells is heterogeneous between patients. This shows the importance of microenvironment for tumor SC cell growth. Engraftment of SC into immunodeficient NOD.Cg-Prkdc(scid)Il2rg(tm1Wjll)/SzJ (NSG) mice was achieved in 2 of 14 cases. Secondary xenograft by subcutaneous injection mimicked several clinical features of SS with dermal infiltration, epidermotropism and blood spreading. Such models permitted to assess the intra-individual heterogeneity of patient SC. Such subclones sharing the same TCR gene rearrangement evolved independently according to culture condition and/or after xenografting. This clonal selection was associated with phenotypic differences and limited genomic evolution both *in vitro* and *in vivo*. The long-term amplification of SC allowed the development of eight new SC lines derived from four different patients. They represent the cell of origin diversity of SC cells and new tools to evaluate their functional properties. Indeed, SC lines demonstrate differential responses to therapies according to the cells of origin of SC. The new *in vivo* model we developed mimicking both skin and blood involvement of SS represents a new preclinical model to test therapeutic agents as well as the mechanisms regulating the balance between blood and skin compartments of SC cells.

P314

Towards Precision Medicine using Tumor-adapted H-1PV oncolytic virus in Preclinical Models of PDAC

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The rat parvovirus H-1 (H-1PV) is nonpathogenic in humans and has a natural oncolytic activity, as it kills a wide spectrum of cancer cells by activating several cell death pathways. The safety and tolerability of H-1PV treatment was recently demonstrated during early clinical studies in glioma and pancreatic adenocarcinoma (PDAC) patients. However, H-1PV is often unable to completely eradicate cancer cells cultured in vitro, and tumors in vivo, including in patients. The aim of this project was to better characterize the oncolytic activity of H-1PV in primary models of PDAC, a cancer with no cure. During this work, we first found that H-1PV is poorly oncolytic in PDAC-derived cellular models, as compared to the highly permissive NB324K control cells. H-1PV could hardly induce apoptosis of PDAC cancer cell lines in vitro, even at very high multiplicities of infection, as monitored non-invasively using the Incucyte Zoom technology; moreover, we found using qPCR analysis that H-1PV amplification is very limited in PDAC cells. To address this concern, wild-type (wt) H-1PV was tumor-adapted in a semi-permissive PDAC cell line as well as a patient-derived primary PDAC cell (PDPC), using a serial passaging protocol. In vitro, we managed to produce clonal, tumor-adapted (TA) H-1PVs at similar titers than wt H-1PV. Remarkably, TA-H1PVs induced rapid lysis of their target cells in vitro, when wt H-1PV had only very limited effect. The PDPC-adapted virus showed a much wider oncolytism than the wt during a screening of various PDPCs and PDAC cells lines, while infection of normal pancreatic cells remained similar to the one of the wt H-1PV. In vivo, the PDPC-adapted H1PV demonstrated greater anti-tumor effect than wt H-1PV, following intraveneous administration in an experimental model of orthotopic pancreatic tumors engrafted in immunodeficient mice. Taken together, these results demonstrate for the first time that H-1PV can be adapted to primary cultures of patients with pancreatic cancer, and that TA-H1PV replicates and kills cancer cells with a high efficacy both in vitro and vivo, while sparing normal cells. This study represents the first step for precision medicine strategies based on patient-tailored oncolytic viruses.

P315
A simple core model of metabolism. The interplay between glutamine and glucose

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Genome-scale models of metabolism (GEM) are now used to study how metabolism works/changes in different physiological conditions or environment. However, the great number of reactions involved in GEM makes it difficult to understand the results which are obtained in these studies. In order to have a more understandable tool, we develop a reduced metabolic model of central carbon metabolism and nitrogen, C2M2N with 77 reactions, 53 internal metabolites and 3 compartments, taking into account the true stoichiometry of the reactions, including the stoichiometric role of the cofactors and the irreversibility of some reactions. In order to model OXPHOS functioning, the proton gradient through the inner mitochondrial membrane is represented by two pseudo-metabolites DPH (ΔpH) and DPSI (Δψ).

To illustrate the interest of such a reduced model of metabolism in mammalian cell, we use Flux Balance Analysis (FBA), to systematically study all the possible fates of glutamine in central carbon metabolism. We demonstrate that glutamine can supply other sources of carbon for cell energy production and as carbon source to synthesize the different essential metabolites thus sustaining cell proliferation. We also show the role of reductive glutamine pathway to the rescue of oxphos defect and hypoxia. We show how C2M2N can also be used to explore the results of more complex metabolic models in comparing our results with those of a medium size model MitoCore.

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

P401

Les cancers du sein du colon et les mélanomes malins sont diagnostiqués tardivement chez les personnes déficientes intellectuelles. Résultats préliminaires d'une expérience en Hérault.

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Objectif et contexte : Les personnes en situation de déficience intellectuelles (DI) développent autant de cancers que les personnes dans la population générale, mais ces cancers sont mal connus et on suspecte des diagnostics posés tardivement. Ces retards diagnostiques n'ont jamais été documentés. L'objectif de l'étude est d'évaluer les stades au diagnostic pour les cancers du sein, du colon et les mélanomes malins cutanés par comparaison aux personnes non DI.
Population et méthode : Les cancers du sein, du colon et mélanomes malins ont été obtenus par croisement de la base de l'étude CHAID (Cancer-Herault-Adultes-Intellectual-Disability) avec la base du Registre des Tumeurs de l'Hérault. La comparaison des stades au moment du diagnostic entre les personnes DI et non DI a été faite par test de Fisher.
Résultats : Les 21 cancers du sein ont été diagnostiqués à un stade avancé (IIb-IV) pour 57% des femmes DI en comparaison des femmes non DI (44%) (p=0.38). Sur 10 cancers du côlon-rectum, 9 (90%) ont été découverts à un stade tardif (III-IV) contre 47% chez les non DI (p=0.03). Les mélanomes malins ont été découverts à un stade avancé (>IIB) plus souvent (57%) chez les personnes DI en comparaison des non DI (11,4%) (p= 0.005). De plus, 28,6% étaient ulcérés chez les personnes DI contre 20,9% chez les non DI.

Discussion : Ces trois tumeurs ont été choisies pour l'importance pronostique du stade au diagnostic, et pour deux d'entre-elles du fait de leur grande fréquence en population générale. Il y a pour deux tumeurs un retard statistiquement significatif. Pour les cancers du sein il y a une plus grande fréquence de stades avancés, mais non statistiquement significative. Il est nécessaire d'accroitre le nombre de patientes pour évaluer précisément les délais diagnostiques. Les retards diagnostiques peuvent être liés aux difficultés de communication des personnes DI, à une présentation particulière des symptômes et à leur moindre participation au dépistage organisé des cancers.
Conclusion : Les cancers du sein, du colon-rectum, et des mélanomes cutanés malins, sont découverts à un stade plus avancé chez les personnes DI, impliquant des traitements plus lourds et de moins bons résultats thérapeutiques. Ces données préliminaires doivent-être confortées par des études incluant un plus grand nombre de patients. Il est souhaitable d'augmenter la participation des adultes avec DI au dépistage systématique des cancers du sein et du colon-rectum, et de favoriser la détection précoce des tumeurs pigmentaires cutanées.
L'étude est soutenue par l'Institut National du Cancer INCa, la Fondation Obélisque et l'Association Française d'Epargne et de Retraite AFER.

P402

Impact psychologique de la différence de parcours de soins des patients traités par anticancéreux à domicile

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Les patients traités à domicile bénéficient d'une prise en charge différente en fonction de la forme du traitement : les anticancéreux administrés par voie périphérique impliquent un contact régulier avec le personnel soignant alors que, ue fois l'ordonnance rédigée, les patients traités par voie orale se trouvent seuls à gérer la prise de leur traitement, la prévention et la gestion des effets secondaires sans compter les boulversements psychiques induits par la maladie et les traitements.

Cette recherche transversale a une finalité comparative entre les représentations de la maladie et des traitements, le sentiment d'auto-efficacité et la qualité de vie des patients traités par anticancéreux oraux et ceux traités par voie périphérique.

L'échantillon se compose de 130 participants atteints de cancer dont 72 sont traités par chimiothérapie intraveineuse et 48 par voie orale. Le protocole est composé d'un questionnaire de représentations de la maladie (IPQ-r), de représentations des traitements (BMQ), de sentiment d'auto-efficacité (GSES-10) et de qualité de vie (QLQ-C30).

Les résultats de notre étude montrent que la voie d'administration du traitement anticancéreux impacte directement les représentations de la maladie avec un phénomène de banalisation du cancer. A l'inverse, un traitement intraveineux, par son caractère invasif et chronophage, implique une gêne cognitive et plus de difficultés dans l'accomplissement des rôles familiaux et professionnels malgré une meilleure compréhension de la maladie. Par ailleurs, le poids des effets secondaires est corrélé avec la dangerosité perçue du traitement et avec le sentiment d'auto-efficacité.

Ces résultats montrent que la différence de forme du traitement implique un remaniement profond du parcours de soins impliquant des conséquences psychologiques différentes que les prescripteurs doivent prendre en considération dans leurs choix thérapeutiques.

P403

Contemplative ou active : quelle réalité virtuelle plébisciter pour une meilleure efficacité en cancérologie ?

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De nombreux travaux, réalisés dans différents domaines en santé, ont confirmé que la réalité virtuelle (RV) a un atout fondamental : son fabuleux pouvoir de distraction. Ce pouvoir se solde par de véritables bénéfices oncologie puisqu'il permet de détourner l'attention du patient lors des soins (par ex la chimiothérapie) tout en réduisant l'anxiété. Si la RV est efficace pour soutenir les patients dans ces situations complexes, reste maintenant à définir quelles sont les conditions pour une application optimale de la RV en cancérologie. Son efficacité est- elle dépendante du degré d'immersion ? Ce degré d'immersion dépend t- il de l'implication du patient dans l'exploration de l'environnement virtuel ? Ces questions nous ont amené à réaliser une étude dans un service d'oncologie auprès de femmes atteintes d'un cancer du sein en situation de chimiothérapie. Pour les besoins de cette recherche, nous avons mis au point un questionnaire qui rassemble des outils classiquement utilisés pour évaluer d'une part, la propension à l'immersion (ITC-SOPI, Cybermalaises, Propension à l'immersion) et d'autre part, l'état émotionnel (SAM, STAI). Nous avons comparé deux conditions d'immersion virtuelle : les patientes étaient placées soit dans une situation contemplative d'un environnement naturel exploré via le casque de réalité virtuelle (n=20) soit dans une situation d'exploration active de cet environnement (utilisation des manettes pour effectuer des actions dans l'environnement) (n=20). Les résultats obtenus confirment l'efficacité de la RV pour abaisser le niveau d'anxiété et apaiser l'état de tension émotionnel des patientes sans pour autant révéler de différence significative entre les deux conditions (RV active vs. RV passive). S'agissant de la propension à l'immersion, à nouveau, aucune différence significative n'est constatée entre les deux conditions. Deux contributions majeures sont à retenir : premièrement, le pouvoir de distraction de la RV s'accompagne d'un meilleur confort émotionnel pour les patientes, deuxièmement le caractère purement contemplatif qu'offre la RV s'avère tout aussi efficace pour réguler les émotions et favoriser le sentiment de présence qu'une stimulation virtuelle qui requiert des actions motrices répétées pour interagir avec l'environnement.

P404

Recherche interventionnelle d'un dispositif de médiation auprès des étudiants atteints d'un cancer pédiatrique

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Peu d'enquêtes renseignent les effets des altérités singulières des jeunes et jeunes adultes suivis pour un cancer sur leur parcours biographique, en particulier leur trajectoire universitaire. Du fait de leur rareté et de leur méconnaissance, les cancers pédiatriques augmentent le risque d'isolement et de décrochage universitaire. L'enjeu est donc de favoriser la création de liens entre les instances et de fluidifier les démarches à l'aide d'un professionnel extérieur neutre (hors institution universitaire) afin de favoriser l'inclusion de ces étudiants. L'objectif est de comprendre les obstacles et les leviers à l'inclusion des jeunes adultes suivis pour un cancer. L'étude menée porte sur l'analyse d'entretiens réalisée auprès des étudiants concernés, de leurs parents et des professionnels de l'enseignement supérieur. Une observation ethnographique vient compléter l'enquête initiale en proposant une mise à l'épreuve de la médiation comme outil facilitateur des interactions plurielles. Cette recherche-intervention s'articule particulièrement autour des sciences de l'éducation et de la sociologie. Ce travail considère l'étudiant malade comme étant indissociable de son contexte et s'intéresse ainsi au groupe d'individus gravitant autour de lui, notamment sa famille et les professionnels de l'établissement universitaire dans lequel il est inscrit. Sur l'ensemble des résultats recueillis, on relève notamment que les acteurs éducatifs témoignent d'un manque de légitimité à intervenir auprès d'une population présentant un cancer, pathologie à laquelle ils ne sont pas formés. Les étudiants suivis pour un cancer et leurs parents expriment le besoin d'un accompagnement régulier et continu.

L'analyse des observations recueillies *in situ* du suivi d'une médiatrice en santé apporte une meilleure compréhension des parcours estudiantins et des positionnements professionnels à travers le prisme du cancer. Ces résultats permettent d'envisager la mise en place d'interventions médiatrices prenant en compte l'organisation actuelle des services et impliquant l'ensemble des acteurs participant à l'accompagnement des jeunes adultes atteints d'un cancer.

P405

Le « Grand Défi Vivez Bougez » et la promotion de l'activité physique auprès des enfants : Résultats d'un essai randomisé contrôlé en cluster

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Contexte et objectifs

Les recommandations internationales suggèrent un niveau de pratique quotidien d'activité physique (AP) chez l'enfant d'au moins 60 minutes d'AP modérée à vigoureuse. Néanmoins, des études réalisées en France et en Europe rapportent qu'une majorité des enfants d'âge scolaire ne sont pas suffisamment actifs pour atteindre les recommandations internationales. Les interventions ancrées théoriquement impliquant à la fois les sphères scolaire, familiale et territoriale peuvent considérablement augmenter le niveau d'AP des enfants d'âge scolaire. Le « Grand Défi Vivez Bougez » (GDVB) est un programme de promotion de l'AP des enfants âgés de 7 à 11 ans basé sur la théorie du comportement planifié (TCP; Ajzen, 2011). Cette étude avait pour objectif (1) d'évaluer l'impact du GDVB sur l'AP et les variables de la TCP des enfants, et (2) de déterminer dans quelle mesure l'impact du GDVB sur l'AP était médiatisé par l'évolution des variables de la TCP.

Méthode

Un essai randomisé en clusters a été initié afin de comparer un groupe intervention et un groupe contrôle, randomisés en clusters (communauté de communes) et stratifiés par département (Hérault, Gard, Aude) et type d'environnement (urbain, rural). L'action du GDVB dure un mois et demi et cible à la fois les variables centrales de la TCP et la pratique concrète d'AP. Les enfants ont été interrogés sur leur niveau d'AP et les variables de la TCP sur 4 temps de mesure répartis sur les 2 années de suivi. Un sous échantillon de 198 enfants a également porté un accéléromètre Actigraph GT3x+.

Résultats

Un total de 3121 enfants (âge moyen = 9,07; ET = 0,85) répartis dans 202 classes a participé à cette étude. En ce qui concerne l'objectif 1, les modèles linéaires généralisés mixtes réalisés indiquent qu'en comparaison des enfants du groupe contrôle, ceux du groupe intervention rapportent une augmentation significativement plus importante de leur niveau d'AP (auto-rapporté et actimétrie) au cours de la première et deuxième année de suivi ($ps < .01$). Les analyses indiquent également qu'en comparaison des enfants du groupe contrôle, ceux du groupe intervention rapportent une augmentation significative de leur niveau d'attitudes envers l'AP au cours de la première année de suivi ($p < .001$). En ce qui concerne l'objectif 2, les analyses en pistes causales réalisées indiquent que l'impact du GDVB sur l'AP est partiellement médiatisé par l'évolution des attitudes et des intentions durant la première année de suivi ($.06 \leq \beta s \leq .18$, $ps < .01$).

Conclusions et perspectives

Le GDVB est une intervention efficace pour promouvoir l'AP auprès des enfants âgés de 7 à 11 ans. Néanmoins, les processus psychosociaux impliqués dans l'efficacité de ce programme restent globalement encore à identifier. Il parait également nécessaire d'évaluer à l'avenir la transférabilité du GDVB dans d'autres territoires.

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Les comorbidités identifiées dans les registres des cancers sont elles identifiables de manière fiable dans les bases de données médico-administratives

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Objectif:
L'objectif de ce travail est de comparer la distribution des comorbidités identifiées dans les registres des cancers, à partir des dossiers médicaux, à celles identifiées à partir des bases de données médico-administratives (BDMA), à partir d'un algorithme d'identification des comorbidités, afin d'étudier la possibilité d'utiliser les BDMA en routine pour collecter ces informations.
Méthodes:
La population d'étude était constituée des cas incidents de cancer de la prostate et de cancer du sein issues des études hautes résolutions de respectivement 2008 et 2011 et de l'Echantillon Généraliste des Bénéficiaires (EGB), un échantillon représentatif en termes d'âges et de sexe à l'échelle 1/97 des données nationales du Système National des Données de Santé. Les patients dans l'EGB ont été identifiés à partir d'algorithmes développés par la caisse nationale de l'assurance maladie. Des populations témoins indemnes du cancer étudié et appariées sur l'âge et le sexe ont également extraites de l'EGB, à raison de 4 témoins pour un cas. Les comorbidités d'intérêts étaient celles utilisées dans le calcul du score de Charlson et ont été identifiées à partir des diagnostics hospitaliers, des procédures médicales, des médicaments et des codes diagnostics d'Affection Longue Durée. Elles ont été recherchées un an avant la date de diagnostic. Chaque individus témoins s'est vu assigné le même suivis que son cas associé. Les distributions des comorbidités ont été comparées à partir d'un test de Fisher exact.
Résultats:
L'échantillon provenant des registres comportait 2077 cancers de la prostate et 1821 cancers du sein. Respectivement entre 2011 et 2016, 2216 cancers de la prostate et 2701 cancers du sein diagnostiqués ont été issus de l'EGB. L'âge moyen des patients atteints d'un cancer de la prostate était 68.69 ans pour les registres et 70.24 ans pour l'EGB et de 61.25 ans et 61.83 ans pour les patientes atteintes d'un cancer du sein.
Pour les deux pathologies d'intérêts, nous avons identifiés les mêmes différences entre les proportions de comorbidités caractérisées à partir des registres et à partir de l'EGB. Les registres retrouvent significativement plus d'insuffisances cardiaques que l'EGB (resp. prostate et sein, 7.8% vs 3.07% et 4.06% vs 1.85%), d'ulcères (resp. prostate et sein, 2.21% vs 0.32% et 1.48% vs 0.15%). En revanche l'EGB, retrouve significativement plus de maladies pulmonaires chroniques que dans les registres (resp. prostate et sein, 7.17% vs 11.28% et 3.95% vs 7.92%). De plus, dans le cas du cancer de la prostate, les registres ont identifié davantage de maladies systémiques et moins de diabètes avec et sans complications. Aucune différence significative n'a été trouvée entre les cas et les contrôles issues de l'EGB. Ainsi, les différences entre l'identification des comorbidités entre l'EGB et les registres ne proviennent pas des populations mais des définitions des comorbidités et de la méthode d'identification utilisée.
Discussion:
Nos résultats peuvent être expliqués par les différentes sources utilisées, le type de données et les définitions des comorbidités mais aussi par le fait que les registres sont davantage centrés sur la période du diagnostic du cancer.Cette étude met en exergues les possibilités grandissantes apportées par les BDMA, notamment dans les cas où il est nécessaire de récupérer des informations à postériori, mais rappelle également l'importance de se questionner sur la provenance, la qualité et la définition des informations recherchées pour parvenir à des résultats cohérents et valides.
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Etude ETIOSARC : Etiologie environnementale des sarcomes à partir d'une étude cas-témoins multicentrique française en population générale

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Les sarcomes sont des tumeurs rares du tissu conjonctif. L'incidence exacte des sarcomes est mal connue liée aux difficultés diagnostiques et aux nombreux types histologiques (plus de 80 types). Néanmoins, une augmentation de l'incidence qui semble être en faveur de causes environnementales comme les pesticides, est suggérée. En dehors des radiations ionisantes et des prédispositions génétiques, la littérature scientifique portant sur l'étiologie des sarcomes est pauvre et contradictoire. La France est un pays particulièrement approprié pour mettre en place une étude sur l'étiologie des sarcomes grâce à son organisation de la prise en charge clinique, anatomopathologique et biologique des patients qui est très structurée et organisée autour de réseaux experts nationaux. L'objectif principal du projet ETIOSARC est d'étudier le rôle des facteurs environnementaux et professionnels et des habitudes de vie, dans la survenue des sarcomes à partir d'une étude cas-témoins multicentrique en population générale.

Les cas sont tous les cas incidents (âgés de plus de 18 ans) identifiés dans 15 zones françaises (régions, département ou métropole) couverts par un registre général des cancers et/ou un centre de référence des sarcomes (centre NetSarc/RRePS) et diagnostiqué à partir du 1er février 2019. Deux témoins par cas sont individuellement appariés sur le sexe, l'âge, le département de résidence et aléatoirement sélectionnés à partir des listes électorales. Un questionnaire standardisé est administré par un ARC pour collecter des informations sur l'historique des emplois et des domiciles, les caractéristiques socio-démographiques et les habitudes de vie. A la fin de l'entretien, un prélèvement salivaire est systématiquement proposé. Le promoteur de l'étude est l'Inserm (n°C17-03). L'étude a reçu un avis favorable du CPP Sud Méditerranée I (n°18-31) et de la Cnil (n°918171) et est enregistrée sur ClinicalTrials (n° NCT03670927).
A ce jour, Etiosarc a démarré dans 5 zones géographiques: Gironde, Lille, Haut-Rhin, Rhône et Isère. L'inclusion des cas et des témoins a débuté le 25/04/2019. Entre le 1er février 2019 et le 26 septembre 2019: 117 cas ont été signalés. Parmi eux, 42 cas ont été enquêtés, 45 sont en cours de recrutement et 30 cas n'ont pas été enquêtés. Concernant les témoins, 28 sujets ont été enquêtés. A ce jour, nous enregistrons un taux de participation de 58% parmi les cas et pour recruter 2 témoins, 6 contacts sont nécessaires en moyenne. Concernant le délai moyen entre le diagnostic et l'enquête des cas, il s'écoule environ 4 mois (45 jours en moyenne entre le diagnostic et le signalement et environ 64 jours entre le signalement et l'enquête) ce qui est en accord avec le protocole. Enfin, la durée moyenne d'enquête est de 2h38 ce qui représente un écart au protocole.
Ces premiers résultats semblent indiquer que les procédures de recrutement des cas et des témoins sont efficaces ce qui est encourageant pour la suite de l'étude. Les principales difficultés rencontrées jusqu'à ce jour sont le recrutement des ARC rattachés aux registres généraux des cancers, l'aide financière pour l'ouverture de la totalité des zones géographiques participantes et la lenteur du processus d'obtention des accords réglementaires. Toutes ces difficultés expliquent le retard pris dans le lancement des inclusions. Néanmoins, avant la fin de l'année 2019, 3 nouvelles zones françaises devraient ouvrir: Poitou-Charentes, Val de Marne et Haut-Rhin. De plus, nous répondrons bientôt à d'autres appels à projets pour l'ouverture de 7 nouvelles zones.
Cette étude permettra de valider et plus généralement d'aborder de façon plus systématique les facteurs de risques possiblement associés aux sarcomes (exemple des phénoxyherbicides et chlorophénols). Ce projet contribuera à générer de nouvelles hypothèses pour améliorer notre compréhension de la contribution génétique et environnementale dans la sarcomagenèse.

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Automated classification of French pathology reports: application to a population based cancer registry

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Introduction: Pathology reports are one of the main data sources in a cancer registry. These documents are unstructured free-text format and available in a digital form. Information in pathology reports can be coded according to ADICAP terminology or not. When pathology reports are not coded, a manual task performed by the cancer registries consists in the pathology report annotation i) to classify a pathology report with histological evidence of cancer and ii) to code the type of cancer according to International Classification of Disease for Oncology (ICD-O3). The aim of this study is to propose supervised machine learning process for the classification of non-coded pathology reports using automatic textual categorization models.

Methods: Data from 84,745 non-coded pathology reports is extracted from the general cancer registry of Gironde Department over the 2005-2016 period and is used for training and validation of classifiers. We use a "bag of words" representation of the reports and the classification is performed with Support Vector Machine, Random Forest and Logistic Regression. Then, different approaches are tested with changes in input data, data transformation and the number of features. The evaluation measures used are recall, precision and F-measure. A binary classification model is used to distinguish the pathology reports related to a cancer or related to a benign lesion. A multiclass classification is used to classify pathology reports with cancer according to ICD-O3 topography.

Results : Regarding to binary classification model, empirical results show a 0.964 F-measure. For the cancer topography transcription, the results for the best performing model are a 0.703 micro F-measure and a 0.633 macro F-measure. An analysis of errors show two main causes of mistakes: i) imprecise annotations of reports, leading to a biased Gold Standard for training and validation of models, especially for binary classification, and ii) linguistics ambiguities that cannot be treated by a bag of words representation, like syntactic or semantic ambiguities.

Conclusion : In this work we addressed the task of automatically classifying pathology reports written in French. Preliminary results show that this is a promising direction and suggest the possibility of using such models to automate the processing of non-coded pathology reports. Moreover, classification errors of the binary model show that we can achieve a F-measure close to 100% for this task consisting to distinguish pathology reports related to cancer, solely using better annotations. Nevertheless, improvements are necessary to increase multiclass model 's specifications for being used in a cancer registry. Thereby, we suggest i) to develop more complex data representation by treating linguistics ambiguities, and ii) to use other domain of artificial intelligence (AI) instead of basic machine learning, particularly deep learning models.

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Effect of PSA-based screening on prostate cancer mortality: results from two departements with cancer registry (French section of ERSPC)

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Objectives: Prostate cancer (PCa) remains a major public health problem and represents the most common cancer in men worldwide. Two large trials (ERSPC and PLCO) evaluated the effect of screening with PSA on PCa mortality, but their results were discordents.

Main objective: to assess the PCa-specific mortality based on two departments (Tarn and Hérault) of southern France which have a cancer registry necessary to carry out such as trial.

Material and methods: This randomised controled trial started in 2001, it involved 80 696 aged 50-69 yr (including 38 474 in screening group). Screening group was invited to a PSA testing after their written and informed consent. Positive tests were defined as a PSA >= 3.0ng/mL. Biopsy was recommended for subjects having positive PSA. Participants were followed until diagnosis of PCa, death or end date (December 31, 2013). Primary outcome was mortality from Prostate cancer. Poisson regression analysis was used to estimate Rate Ratio (RR) in the screening vs. the control group.

Results: In the screening group, compliance rate of PSA was 31.3%. After a median follow-up of 9 years, incidence of PCa increased by 10% in the screening arm compared to the control (RR=1.10; IC95%=[1.04-1.16], p=0.0014).PCa Mortality was 0.222 and 0.215 deaths per 1000 person-year, respectively in the screening and control group, showing a non-statistically difference between the two group (RR=1.03 [0.75-1.41], p=0.88) even after stratification on PSA compliance (RR=0.76 [0.44-1.24], p=0.29).

Discussion and conclusions: Results didn't confirm the significant reduction of PCa mortality in screening group when compared to the control group. This can partly explained by the fact that the beginning of this trial was concomitant with the national screening recommendation which promote a PSA screening for men 50-75 years which probably lead to high contamination in control group. Further follow up was needed to evaluate the potential long-term effects of screening.

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Hématologie-post greffe. Education thérapeutique du patient- apport d'une psychologue

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Education thérapeutique du patient en post greffe « on en discute »- apport d'une psychologue.
Agnes Ruscassie-Florence Carantois

Dans le cadre de la PEC des patients allogreffés, le service hématologie de l'iuct-o propose aux patients sortant de greffe des ateliers d'éducation thérapeutique. Plusieurs thèmes sont abordés pour renforcer la continuité de la PEC et permettre aux patients de rester acteurs du parcours de soins.

Sur ce programme éducatif, l'atelier « on en discute » propose aux patients un espace de parole pour exprimer leur vécu de la maladie, de la greffe, du retour à domicile. Cette séance éducative collective (4 à 6 patients) favorise l'utilisation d'une production individuelle pour nourrir une réflexion collective. Le matériel utilisé est la photo-expression. Le processus va permettre l'accès à une élaboration psychique commune afin de structurer la pensée individuelle et collective.

Cet atelier est co-animé par une psychologue et une IDE membres de l'équipe ETP ; les échanges vont favoriser les apprentissages de stratégies d'ajustement et apporter des connaissances en lien avec la pathologie ou le traitement ; une complémentarité au service d'un patient partenaire.

Posters – Axis 5 “Health Technologies”

P501
Imaging of cancer cell death induced by magnetic hyperthermia

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Thermotherapies use heat as therapeutic tools. For cancer treatment, according to the thermal dose delivered to tissues, temperature increase may induce thermo-ablation, indirect cell death by potentiation of other therapeutic agents or thermo-induced phenomena like gene expression or drug release. Magnetic nanoparticles (MNPs) placed in an alternative magnetic field (AMF) induce local hyperthermia. The present project examines the potential of MNPs for tumor thermotherapies.

MNPs are multicore iron oxide particles (18nm), with a high heat power (Specific Absorption Rate: 230W/g). They were coated with a thin silica layer doped by red and near infrared dyes and chemically surface-modified so as to make them positively charged in physiological conditions (patent pending). Human glioblastoma cells (U87) and mouse prostate cancer cells (RM1) are genetically modified for constitutive expression of Firefly luciferase (LucF) for both cells or nanoluciferase (Nluc) for RM1 cells. For *in vitro* studies, cells were plated in 16-wells Nunc™ LabTek® microscopy chambers. MNPs were added in the culture medium at different concentrations and for different incubation times. For *in vivo*studies, cells (MNP-loaded or not) were injected subcutaneously into mice. Three mice species were used: ID mice are immunodificient NOG mice for U87-CMV-LucF cells, IC mice are immunocompetent C57bl6 albinos mice for RM1-CMV-LucF cells and thermosensitive mice are immunocompetent C57bl6 albinos mice genetically modified for thermo-induced LucF gene expression (Hsp70 promoter) for RM1-CMV-Nluc. AMF were generated using an *in vitro/in vivo* setup working at 4 different frequencies. During AMF application, temperature raise was monitored using optical probes and infrared camera. Cells viability was followed by bioluminescence imaging (BLI). MNPs internalization was quantified *in vivo* by reflectance fluorescence imaging (FRI) or *in vitro* by flow cytometry.
Fluorescence and electronic microscopies were performed to determine the MNPs localization into cells.

For *in vitro* studies, cells were incubated with increasing MNPs amount and followed in time for loading and viability. Higher internalization level was reached at 24h of MNPs incubation for concentrations equal and more than 250µg Fe/mL (300pg Fe/cell). MNPs alone did not affect cell viability and were mainly found in cytosol. MNPs-loaded cells were submitted to AMF, *in vitro*, or subcutaneously injected before AMF applications and in both cases, cells viability was not affected.
Then, MNPs were injected into subcutaneous tumors (1.3 or 0.6mg Fe/tumor) and submitted to 4 AMF applications (473.5kHz; 15mT; 15min) which resulted in temperature raise in the tumor. The decrease of BLI signal were observed 24h after AMF in regions corresponding to the MNPs location and maximum heating. For small tumors, MNPs injection and AMF applications resulted in complete disappearance of the BLI signal, which correspond to a total tumor thermo-ablation.
Magnetic hyperthermia effects on the tumor microenvironment (µE) was studied by thermo-activation of Hsp70 promoter. MNPs were injected into subcutaneous tumors (0.6mg Fe/tumor) implanted in thermosensitive mice and submitted at AMF. MNPs and AMF induced raise of temperature in the tumor, leading to a decrease of Nluc BLI signal of the tumor and an increase of thermo-induced LucF BLI signal of the µE. All together, these results show combined thermo-ablation of the tumor and thermo-modulation of the µE.
To conclude, cell-loaded MNPs were unable to induce cell death even at maximum internalization concentration, *in vitro* and *in vivo*. However, MNPs injected into the tumor followed by AMF application induce both cell death in the tumor and Hsp70 promoter activation into the µE. These data establish the proof of concept of combined tumor thermo-ablation and µE thermo-modulation induced by magnetic hyperthermia for synergetic therapies.

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Imaging of tumor heating by MRgHIFU for thermo-ablation and thermo-modulation

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Among the cancer treatment options, selective temperature increase of pathologic tissues by physical means (radiofrequency, laser) is widely used clinically. Local heat deposition may result in cell death by thermo-ablation. Under less aggressive heating conditions, non-lethal processes (thermo-modulation) can take place like thermo-induced gene expression or drug delivery from thermo-sensitive nanocarriers. Thus, combining thermo-ablation in the tumor with tumor microenvironment (TµE) thermo-modulation may be exploited to both improve therapeutic efficacy while sparing surrounding tissues. In this study, local temperature raise was generated in mice tumors by high intensity focused ultrasounds (HIFU) guided by real-time magnetic resonance imaging (MRI) thermometry (MRgHIFU). The physiological response was assessed by bioluminescence imaging (BLI) on different types of genetically modified cells. The aim was to establish *in vivo* the proof of concept of combined MRgHIFU-induced thermo-ablation and thermo-modulation in solid tumors.

BLI signal was performed using Firefly luciferase (LucF). A mice prostate cancer cells (RM1) was modified for constitutive expression (RM1-CMV/LucF) or heat-inducible expression of LucF (RM1-HSP/LucF). Two different mice models were used: Group 1 was mice bearing RM1-CMV/LucF tumors and Group 2 was mice bearing RM1-HSP/LucF.
Anesthetized mice laid on a thermo-regulated bed and monitored for respiration and body temperature.
HIFU heating (2.5 MHz) was performed using a dedicated platform (IGT) installed into a 9.4 T preclinical MRI scanner. The software integrated an automatic feedback control algorithm that regulated the electrical power delivered to the transducer to force local temperature at the focal point to follow a predefined time-temperature profile.

To induce tumor thermo-ablation, RM1-CMV/LucF tumors were grown on WT mice. Tumors were heated 1 min at 60°C. Incomplete or total disappearance of the BLI signal in the heated area were observed 24 hours after MRgHIFU heating.
To assess tumor thermo-modulation, RM1-HSP/LucF tumors were grown on WT mice. Tumors were heated 5 min at 43°C, 45°C or 47°C. A low BLI signal was observed at both 43°C and 47°C while a strong signal was observed for 45°C, consistent with insufficient (5 min at 43°C), excessive (5 min at 47°C) and optimal (5 min at 45°C) thermal doses for HSP promoter activation in tumor cells.
Not shown in the current abstract, experiments were also performed to assess thermo-modulation of the TµE using a transgenic mouse expressing LucF under control of the HSP70 promoter and tumors expressing nanoluciferase. Thermo-ablation of the tumor resulted in disappearance of the BLI signal in the tumor but ring-shape BLI signal from the host TµE.

To conclude, we demonstrated that MRgHIFU allows for precise tumor heating making possible both thermo-ablation and thermo-modulation depending of the accumulated thermal dose. It make possible to combine tumor cells destruction in the core with thermo-modulation in the TµE (on going experiments). The thermo-modulation allowed for adjuvant therapies by local drug release from thermo-sensitive nanoparticles or thermo-induced expression of therapeutic genes or miRNA including non-lethal-strategies targeting the TµE.

P503
Targeting prostate cancer with specific nanoparticles

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Introduction
Theranostic aims to combine diagnostic with therapy for example, by combining a specific diagnostic probe with a drug nano-container for a specific local release. Fluorescent-labelled anti-PSMA scFv (single chain antibody fragment) was reported as an efficient probe for specific prostate cancer imaging in a mouse model, thanks to PSMA mediated internalization process1. Silica nanoparticles (NPs) are attractive porous nanoparticles for drug loading. Injected in the blood stream, PEGylated forms of silica NPs accumulated into prostate cancer tumors in mice by nonspecific accumulation processes2. The aim of this project is to functionalize the silica NPs with anti-PSMA scFv to improve the specific targeting to prostate cancer for theranostic purpose.

Methods
Human prostate cancer cell line PC3 were genetically modified for constitutive expression of PSMA protein and firefly luciferase (Fluc) (PC3-Fluc-PSMA+). A control cell line only express Fluc (PC3-Fluc-PSMA-). NIR/red dually fluorescent silica NPs of 19 nm covered by a PEG layer was synthesized and characterized as reported2. Anti-PSMA scFv fragment was grafted on silica NPs (scFv-NPs). The optimal condition for grafting was determined in vitro by flux cytometry analyses on PC3-Fluc-PSMA+ cell line. PC3-Fluc-PSMA+ and PC3-Fluc-PSMA- were injected either subcutaneously or in mouse prostate. Tumor growth was monitored by bioluminescence imaging (BLI). NPs or scFv/NPs were injected in mice via the tail vein and fluorescence was followed by Fluorescence Reflectance Imaging (FRI) and Fluorescence Molecular Tomography (FMT®). Excised prostates were imaged by BLI and FRI and then processed for histological analyses.

Results
Flux cytometry analysis showed that grafting 4 anti-PSMA scFv on silica NPs permits optimal increase of scFv/NPs internalization into PC3-Fluc-PSMA+ cells. According to these results, a batch of silica NPs decorated with 4 anti-PSMA scFv was synthesized (4scFv/NPs) and fully characterized. After injection of NPs or 4scFv/NPs via the tail vein, fluorescent signal accumulated into both PSMA- and PSMA+ tumors but fluorescent signal from 4scFv/NPs specifically increases in PSMA+ tumors. BLI and FRI imaging of excised prostates confirmed colocalization of accumulated NPs with prostate cancer cells. Internalization of NPs in cancer cells is further confirmed by histology.

Conclusions
Grafting anti-PSMA scFv on silica NPs significantly enhance accumulation of NPs in PSMA expressing tumors but did not abolish non-specific accumulation in tumors that do no express PSMA.

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P504

Pulsed electric fields as key element overcoming cold-atmospheric plasma limits in cancer therapy

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This last decade, **cold atmospheric plasma** (CAP), an ionized gas composed of heat, reactive species, charged particles and photons, has been proposed as a new tool for several biomedical applications. Among them, the anti-cancer effect of CAP and more recently, **plasma-activated liquids** (PALs), such as culture media, water or buffered saline solutions, previously exposed to plasma has been reported on different types of cancer *in vitro* and *in vivo*. Nevertheless, in vitro tests show that this novel approach is sometimes less efficient than expected and displays penetration limits when tested on **three-dimensional multicellular tumor spheroids** (MCTS) that mimic small avascular tumors architecture.
In parallel, **pulsed electric fields** (PEF) are well-known in the literature for their potential to reversibly or irreversibly permeabilize the cell membrane. This technique is based on the capacity of PEF to modulate the cell electric transmembrane potential inducing transient pores at the cell membranes without disturbing cellular homeostasis. Interestingly, cell electropermeabilization (EP) is used in clinics for either anti-cancer drugs delivery (electrochemotherapy) or gene electrotransfer (electrogenotherapy). Currently, new EP strategies are under development to extend its applicability to different histological hallmarks tumors. EP combined with injection of supraphysiological doses of calcium has been recently proposed as a simple and inexpensive tool for anti-cancer therapy. This emerging therapeutic approach supports the theory that noncomplex chemical drugs can be combined with EP to cure cancer. We thus proposed to use EP in combination with PALs with the aim to potentiate its cytotoxic effect and enhance their delivery within 3D models in vitro or tumor in vivo.

In the present study, we evaluated the response to single treatment with **plasma-activated phosphate buffered saline**(P-A PBS) compared to dual-mode treatments (P-A PBS combined with EP) using colorectal cancer cells MCTS. For this purpose, we checked for MCTS growth, viability, and global morphological changes by live cell video-microscopy. In addition, the induction of caspases activation, appearance of DNA damages, as well as the early modifications in the cellular ultrastructure, were investigated. Our results showed that P-A PBS could penetrate deeper in the MCTS when EP was performed, spreading the cytotoxic effects to the entire MCTS. The in-depth spheroid death was correlated with an earlier onset of DNA damages and caspases activation, leading to mitochondrial stress and nuclear damages, which completely abolished MCTS growth. This work evidenced that**electropermeabilization greatly potentiates the cytotoxic effect of P-A PBS** *in vitro* on a three-dimensional cancer cell model. This first *in vitro* proof-of-concept will be further study on tumors *in vivo* where a more complex microenvironment is present including the immune system.

P505

Photodynamic therapy activity of new porphyrin-xylan-coated silica nanoparticles in a human colorectal cancer in vivo model

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Photodynamic therapy (PDT) using porphyrins has been approved in treatment of several solid tumors thanks to generation of cytotoxic reactive oxygen species (ROS). However, low physiological solubility and lack of selectivity towards tumors sites are the main limitations of their clinical use. Indeed, targeted drug delivery is an important issue for tumor therapy. Nanoparticles are able to spontaneously accumulate in solid tumors through the enhanced permeability and retention (EPR) effect due to leaky vasculature, poor lymphatic drainage and increased vessel permeability. The purpose of our study was to demonstrate added value of nanoparticles vectorization strategy on anticancer efficacy and tumor-targeting of the 5-(4-hydroxyphenyl)-10,15,20-triphenylporphyrin (TPPOH). Using the 80 nm silica nanoparticles (SNPs) coated with xylan-TPPOH conjugate (TPPOH-X), we first showed very significant phototoxic effects of TPPOH-X SNPs in HT-29 human colorectal cancer cell line compared to TPPOH free. Then, on HT-29 tumor-bearing nude mice, we highlighted without toxicity, a high anticancer efficacy of TPPOH-X SNPs through an improvement of tumor-targeting compared to TPPOH free.

P506

Radiation doses from terbium-161 compared to lutetium-177 in single tumor cells and micrometastases

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Aim/Introduction

Targeted radionuclide therapy is a very promising modality for treating minimal residual disease, occult micrometastases and single tumor cells. However, the radionuclide needs to be appropriately selected. Indeed, radiation doses delivered with traditional beta emitters decrease as the size of tumors decreases (Hindié *et al.*, 2016). Terbium-161 is a medium-energy beta radionuclide like lutetium-177 and with similar chemistry (Müller*et al.*, 2018). However, terbium-161 abundantly emits conversion and Auger electrons which may increase the dose to micrometastases.

Materials and Methods

We used the Monte Carlo code CELLDOSE to compare the effectiveness of lutetium-177 and terbium-161 in irradiating single cells (14 µm cell diameter with 10 µm nucleus diameter) or small tumor clusters consisting in a central cell surrounded by 18 neighboring cells. We studied the dose to the nucleus of the single cell according to various distributions of the radionuclides: either located in the cell membrane, in the cytoplasm, homogeneously distributed in the cell, or only intranuclear location. For the tumor cluster, we studied the dose to the nucleus of the central cell considering the various distributions of the radionuclides. For both radionuclides, the simulations were run assuming that 1 MeV was released per μm^3 (1436 MeV/cell).

Results

For the single cell, the dose to the nucleus was substantially higher with terbium-161 compared to lutetium-177, whatever the radionuclide distribution: 5.0 Gy vs 1.9 Gy in the case of cell membrane distribution; 8.3 Gy vs 3.0 Gy for intracytoplasmic distribution; 19.5 Gy vs 5.8 Gy in the case of homogeneous distribution in the whole cell; and 38.6 Gy vs 10.7 Gy in the case of intranuclear location. The dose to the central cell increased with the addition of the 18 neighbors, but remained higher for terbium-161 compared to lutetium-177. For example, in the case of cell membrane distribution, the dose to the nucleus of the central cell was 15.1 Gy with terbium-161 and 7.2 Gy with lutetium-177.

Conclusion

Terbium-161 should be a better candidate than lutetium-177 for irradiating single tumor cells and micrometastases, whatever the radionuclide distribution is.

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P507

Comparison of iron oxide particles for theranostic: MRI cell monitoring and anti-cancer thermoablation

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INTRODUCTION

Magnetic Field Hyperthermia (MFH) is one of the new approaches for treating cancer by specifically targeting the rise in temperature within the tumor region. To do so, iron oxide particles (IOP) are employed because of their high Specific Absorption Rate (SAR), and their ability to dissipate energy to the local surrounding. They can be injected either intra-tumorally or intravenously to specifically accumulate within tumors through targeting moieties. This therapy is of great interest for tumors that are inaccessible or very invasive like glioblastoma. Unfortunately MFH can not cure glioblastoma, but the lifetime of patients can be extended by several months. This motivates the intensification of research in this field.

Nevertheless, synthesizing iron oxide particles that can generate a high MR detection sensitivity and a high heat power is challenging. Indeed, the smaller IOPs, the higher heating power. Nevertheless, the T2* effect weakened when the amount of iron oxide decrease. Consequently, the goal of this study was to evaluate the abilities of two large-sized commercial IOPs to be good theranostic agents. The final purpose was to determine the ideal particle to monitor cancer cells in vivo by MRI and subsequently induce radio-frequency (RF) thermal ablation.

MATERIEL & METHODS

Two commercial micron-sized particles MPIO (Bangs Laboratories) and ScreenMAG (Chemicell) were characterized by transmission electron microscopy (TEM). Then, these particles were incubated 4h on human glioma cells (MG-U87 cells). In order to study their intracellular trafficking, an approach of correlative microscopy was used. Subsequently, the endocytotic pathway of each particle was analyzed by flow cytometry and also on thin cell slices by TEM. A RF field was applied on these two particles and on labeled-cell pellets using a commercial magnetic inductor (DM3, Nanoscale Biomagnetics) operated at 473kHz. Finally, in vitro MRI experiments of MPIO- and ScreenMAG-labeled U87 cells trapped in agarose gels and in vivo mouse brain implantations of ScreenMAG-labeled cells were investigated. The T2 relaxivities were measured at 7T (Bruker) using a Multi-Slice Multi Spin Echo sequence.

RESULTS

TEM demonstrated that these particles are different in size and shape. MPIO are polydisperse particles with a size range of 50nm to 1.5µm whereas ScreenMAG are monodisperse particles with a mean size of 900nm.

After checking by correlative microscopy that these particles have been internalized into cells, their energy-dependant pathways were studied. The macropinocytosis and caveolae-dependant pathways were involved in the internalization of MPIO whereas ScreenMAG was internalized through the clathrin-dependant pathway.

After application of a RF field, only ScreenMAG induced a rise in temperature. An elevation of 28°C was observed in 6min. An increase of temperature was also measured on the ScreenMAG-labeled cells, whereas no elevation of temperature was observed in unlabeled cells. After application of the RF during 1h at 42-43°C, a strong cytotoxicity (59% ± 1%) was noted, compared to labeled cells not submitted to the RF field.

Moreover, the transversal relaxation times significantly lengthened after application of magnetic hyperthermia on the ScreenMAG-labeled cells (24ms ±10ms to 38ms ± 23ms).

CONCLUSION

We characterized and identified the endocytotic pathways of two IOPs. Flow cytometry data were confirmed by TEM and are in agreement with the particle sizes. Application of a RF field on ScreenMAG-labeled cells induced heating and lead to a strong cell death. These particles generated also a high sensitivity of detection. These data justify the use of ScreenMAG particles for tracking cells in vivo by MRI and perform MFH.

ScreenMAG particles could be used to non-invasively monitor the efficiency of the MFH treatment through relaxation times measurements.

P508

Evaluation of biological effects after exposure of 3D multicellular models to radio frequencies

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This project involves the study of cellular and molecular responses induced by exposure to radiofrequency emissions on 3D multicellular microtissue models through the development of a metrology system that provides calibrated and systematized electromagnetic field application conditions. The objective was to develop and validate a metrological approach that accurately assesses the effects of RF waves on DNA integrity and membrane permeabilization. This work aims to provide precise and quantitative data on the potential impact of electromagnetic field (Bluetooth and WIFI applications in particular) on the general public and on the military personnel.

Results: The exposure of micro-tissues to radiofrequency signals does not affect membrane permeability of the cells, which constitute the model. Nevertheless, when micro-tissues, made of cancerous cells, are exposed to continuous wave signals during a period of 15 minutes and at extremely high specific absorption rates (SAR) (from 2.4 kW/kg to 37 kW/kg), we observe the occurrence of micronuclei.

These results will be analyzed further to see it clastogenic or aneugenic effects occur. In addition, analogous experiments will be performed on normal non-cancerous cells, from healthy skin biopsy (human dermal fibroblasts).

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

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SUMCASTEC* explores new approach for cancer stem cells (CSCs) real time and neutralization, by developing a micro-optofluidic lab-on-chip (LOC) platform. Cancer Stem Cells or CSCs appear as major biological and therapeutic targets, in particular for Glioblastoma (GBM). Heterogeneity of tumor cell populations, leads to optimize characterization and sorting methods.

Actually, analysis are based on efficiently targeting of a set of biological markers, which are used to validate the cell stemness properties. Besides the biological properties, biophysical properties of CSCs are expected to be a potential way to discriminate, sort and finally neutralize CSC populations. Our data summarize first's results glioblastoma cell lines' and GBM primary cultures characterization; measuring their crossover frequencies by di-electrophoresis (DEP) technics using Ultra High frequency (UHF) range (above 50 MHz).

In order to establish the proof of concept, GBM cell lines are cultured following different conditions, in order to achieve an enrichment of CSCs. In other hand, CD133 marker-based sorting is assessed to discriminate CSC of GBM primary cultures subpopulations and characterize their crossover frequencies. Using microfluidic lab-on-chip systems implemented on Bipolar-Complementary Oxide Semiconductor (BiCMOS) technology (allowing single cell handling and analysis), and following DEP electrokinetic method, these CSCs were discriminated from the differentiated cells. Based on measurements of their own intracellular specificities, the enriched CSCs subpopulations have shown clear differences of DEP crossover frequency signatures of CSC enriched populations compared to differentiated cells.

That demonstrates the concept and validates the technique efficiency for CSCs discrimination. Confirming a high potential of the LOC platform in the diagnosis and development of new glioblastoma therapeutics.

*SUMCASTEC (Semiconductor-based Ultrawideband Micromanipulation of Cancer STEm Cells)

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Structural Insights into hDM2 protein Recognition by Oligourea Foldamers

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The p53 protein is a transcription factor that regulates the expression of many genes coding for proteins involved in various biological functions. This protein is the guarantor of cellular integrity. The level of p53 expression is highly controlled and kept low by a negative regulatory mechanism driven by the hDM2 protein.[1] The overexpression of the hDM2 protein has been observed in many cases of cancer. Thus, inhibiting the interaction between these proteins, in order to restore the activity of the wild-type p53 is a strategy to fight against cancer.[2] The interaction between these two proteins is mediated by a short α-helix located at the N-terminal extremity of the p53 protein.[3] However, short, isolated peptide helices are generally only weakly populated in aqueous environment and are susceptible to proteolytic degradation, thus limiting their therapeutic potential. A variety of chemical strategies have been proposed to increase the helix folding propensity and stability of α-peptides among which foldamer-based approaches have recently emerged.[4]

In this context, we became interested by the possibility to combine peptide and foldamer helical backbones in a single strand to generate new generations of α-helix mimics. We have shown that oligourea foldamer/peptide chimeras form well-defined helical structures in polar organic solvents with the propagation of a continuous intramolecular H-bond network spanning the entire sequence.[5]

In this presentation, we describe the design of peptide/oligourea hybrid compounds with the ability to modulate the p53/hDM2 interaction, and report our efforts to structurally characterize the interactions between the most potent foldamers in this series and the target protein as a mean to improve design principles and generalize the discovery of foldamer-based inhibitors of protein-protein interactions.

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Colon-on-chip development to model epithelial-stromal relationship during colorectal cancer initiation

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Detection of lipid droplets by MCARS microspectroscopy in cells expressing TrkB

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Cancer is characterized by uncontrolled cell growth, and cells spread to other sites in the organism, to generate metastasis [1]. In fact, specific markers are associated to cancer processes [1,2]. Among them, TrkB receptor, a member of the neurotrophin family, seems to be of particular interest. Surprisingly, this receptor family has been discovered in central and peripheral nervous systems, thereby regulating the growth and differentiation of neurons [3].

Expressed in other cells and activated by its ligand (BDNF), it is associated to tumorigenesis and metastasis [4]. Mainly, the BDNF/TrkB complex is strongly associated to colorectal cancer (CRC) allowing a cell growth, metastasis formation leading to a poor prognosis [5]. Lipid accumulation has already been observed in several human cancers such as brain, colon, breast, prostate, and is associated to the aggressiveness of cancer cells [6].

The aim of our study is to establish a link between the activation of TrkB and the accumulation of lipids in cells. For this purpose, we evaluated lipid metabolism changes by multiplex coherent anti-Stokes Raman scattering (MCARS) microspectroscopy, which is a label-free and non-destructive vibrational imaging technology, allowing the visualisation of lipids in cells with high sensitivity [7,8]. Cells were mapped by means of high spectral resolution (< 1 cm^{-1}) MCARS microspectroscopy in the 2500-3200 cm^{-1} range and images were reconstructed for the CH_2 (2850 cm^{-1}) vibrational signature, mainly associated to lipids.

We analysed three CRC cell lines (HCT-116, HT-29 and SW-620), which represent three stages of CRC, and differently express TrkB. Cell images at 2850 cm^{-1} show the presence of lipid droplets, mainly for HT-29 cells, which have the highest TrkB expression level.

To correlate the expression of TrkB receptor with lipid metabolism, we used HEK cell line, which does not express TrkB receptor. Cells were stably transfected in order to obtain a cell clone with a high expression of this receptor. When analysing HEK-Clones by MCARS microspectroscopy, we observed a higher intensity of CH_2 signature in cytoplasm for cells treated with BDNF. Moreover, CH_2 signature increases for longer treatment time and appears punctiform. It corresponds mainly to endoplasmic reticulum (ER) [9] where neutral lipids are synthesized. This shows that lipid metabolism increase observed in HEK-Clones depends on the presence of activated TrkB receptor. More specifically, we highlight the two major steps of biogenesis of lipid droplets: accumulation of neutral lipids in ER bilayer (diffuse signal) and generation of lipid droplets (punctiform signal) in function of time [10].

As a conclusion, we show that a high level of TrkB receptor expression in cells and its activation by BDNF foster an increase of lipid metabolism leading to lipid droplet accumulation in cytoplasm. This variation of lipid content was easily monitored by MCARS microspectroscopy. Thus, MCARS imaging proves to be a helpful tool to detect cancer cells without preliminary staining, and to set up a treatment since the presence of lipid droplets is associated to chemotherapy resistance [11].

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Posters – “Technological facilities & Industrial partnerships”

P601

TBM Core: Vivoptic, an optical imaging platform for in vivo evaluation of diagnostic and therapeutic strategies

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TBM Core - University of Bordeaux, Inserm US-005, CNRS UMS-3427

1- Vivoptic an optical imaging platform
Optical imaging is widely used in cancer research and it's a convenient tool for evaluation of nanoparticles and new therapies. After an initial training, Vivoptic offers you free access to optical imaging machines for bioluminescence and fluorescence imaging:
- Lumina LT (PE) for 2D bioluminescence and fluorescence 2D imaging
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- Fluobeam (Fluoptic) a per-operatory probe for free and live monitoring of fluorescence signals including during surgery
- Probe-based confocal laser endo-microscopy (Cellvizio)
Vivoptic is a France Life Imaging (FLI) labelled platform.

2- Vivoptic, a complete offer for in vivo evaluation of your diagnostic and therapeutic agents or your innovative therapeutic strategy.
Vivoptic can provide you a library of optical imaging reporter genes (luciferase, NIR fluorescent proteins), vectors, and modified cell lines. Vivoptic also provide immunocompetent and immunocompromised mouse models of sub-cutaneous, orthotopic and metastasis solid tumors especially dedicated for optical imaging monitoring.
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Vect'UB : Vectorology expertise at the service of research

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INSERM US 005 - CNRS 3427 - TBMCore, Université de Bordeaux

The vectorology platform is an academic structure for the production of viral particles for gene transfer. The main activities are the production of viral vectors such as lentivirus, AAV and Adenovirus for over-expression of gene or knock-down of gene expression.

Lentiviral vectors are tools of choice for gene transfer. They have the qualities of efficiently transducing a large panel of cells including primary stem cells (neurons, retina, HSC). They allow stable and efficient integration of DNA sequences into the cell genome.

Adeno-associated virus (AAV) is a versatile viral vector technology that can be used in a wide range of clinical applications in multiple diseases due its unique biological and biophysical properties.

The most important step in viral vector production is the proper design of vector. We will help you to find the best construction that will fit to your future experiments. Our platform can assist you in choosing the best viral vectors for your specific application and target cells. Once the choice of viral vector is done, our platform can also help you to design, construct and product the viral vector containing your gene of interest (or shRNA or CRISPR). This service includes viral vector production, concentration, clarification and titration. We have also different ready-to-use viral vector systems (with different pseudotype/serotype and promoters) carrying fluorescent or resistant proteins. The platform offers a large choice of vectors for constitutive or inducible expression and continues to develop new vectors to propose innovative tools. Vect'UB provides also, stable cell line generation and cell immortalization service, manipulations that require a biosafety level # 3.

Vect'UB is a powerful platform that produces more than 400 lots of viruses a year. The power of these tools in gene transfer and its plasticity explain the success of this platform.
Do you need to express a specific protein in your cells of interest? Do you need to inhibit or KO specific protein expression in your target cells? The Vect'UB platform can help you !

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Mechano-chemical driving of EMT in pancreatic cancer

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Pancreatic ductal adenocarcinoma cancer (PDAC) is a particularly aggressive cancer, with a death toll of 99% after 5 years. As of today, there is no efficient treatment or targeted therapy. Cells from this cancer undergo a large series of genetic modifications such KRas activation mutations and p53 silencing which, concomitant with alterations of the interactions between the cells and the stroma, leading to tumor progression. Notably, the rapid cell proliferation in a confined environment, along with the remodeling of the extracellular matrix, leads to growth-induced mechanical compressive stresses that eventually accumulate in PDAC. Although mechanical stresses alter cellular physiology and cancer treatments, we further hypothesize that cancer cells could modulate their response to chemical signals in presence of mechanical stresses. In this context, it is not known if specific mechanical stresses can either promote or restrain tumor progression.

To address these questions, we are developing one of the first experimental platform based on microfluidics that permits the study of cancer cells in a perfectly controlled environment. More specifically, we can alter the intensity of the mechanical environment of a spatially confined population of cells. Our microfluidic platform also enables the coupling between mechanical and biochemical signals through the dynamic mixing of chemicals of interests such as drugs or cytokines. Moreover, innovative microfabrication approaches allow us to bring co-culture of a stromal compartment with cancer cells and even recover the sample of interest (such as patient-derived organoid) to perform subsequent analysis. We are currently using this experimental platform to determine how a cellular biological response is altered following a variation of both the chemical and mechanical environments. In particular, we focus on the characterization of how a specific set of mechano-chemical conditions can drive the epithelial-to-mesenchymal transition, a phenomenon critical to the dissemination of PDAC and known to be dependent on mechanical cues and chemical signaling. This determination will be performed in cells of various and defined genetic alterations characterizing PDAC progression.

Altogether, our work can bridge the biochemical, genetic and mechanical characteristics of cancer cells. Our device can eventually be used to understand cancer progression and explore novel therapeutic strategies incorporating mechanics.

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CellOxia Core facility: modeling the hypoxic niche

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While air is composed of 21% O_2 (159 mmHg), the physiological O_2 concentration in body tissues is much lower. For instance, in murine bone marrow, Spencer et al. measured an average O_2 concentration of only 1.8% (13.3 mmHg) in the extravascular environment. In some pathological contexts such as tumors, O_2 concentrations are strongly modified leading to drastic effects.

The cellular O_2 effects are mediated by oxygenases. The most studied are PHDs (Prolyl Hydroxylase Domain) which, in the presence of oxygen, induce the degradation of HIF (Hypoxia Inducible Factors) transcription factors. In physiological and pathological hypoxia, HIFs are responsible for the transcription of several hundreds of genes with various roles in cellular homeostasis (energy metabolism, cytokine synthesis, signalling pathways, epigenetics, etc...).

In tissue culture laboratories, the O_2 parameter is very often underestimated/misregarded and many cultures/experiments remain performed under so-called normoxic conditions (~21%) which are actually hyperoxic conditions and therefore not physiologically relevant. Hence, some published *in vitro* results unfortunately present an experimental bias, that can compromise their *in vivo* validation.

Our platform CellOxia offers both expertise and equipment to incubate mammalian cells and/or perform experiments under controlled atmospheric conditions (O_2, CO_2, temperature) to academic and private laboratories. Through its "PAULA" imager (Leica), users are able to monitor their cell cultures without perturbing the culture conditions.

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CRISP'edit core facility

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The new CRISP'edit core facility, part of the UMS-TBMcore at the University of Bordeaux, provides service to researchers who want to perform genome editing using CRISPR technology. From a basic frameshift knock-out mutation to complex knock-in genetic changes, our dedicated scientific team will work collaboratively with you to design the right CRISPR tools to accelerate your research programs. We can create stable cell lines with a homozygous or heterozygous gene knock-out. Primary cells can also be engineered. More sophisticated genetic modifications such as the removal of specific exons, insertion of tags in a coding sequence or targeted base mutations are also feasible. Used on a larger scale with sgRNA CRISPR libraries, this technology can also be adapted for genetic screening experiments. The CRISP'edit platform provides service according to your needs: we can advise you in the design of your experiment or we can take the experiment from start to finish in-house, for example performing screen design, cell line selection and bioinformatic analysis of screen results.

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