FORUM
DE LA RECHERCHE EN CANCÉROLOGIE

FORUM DE LA RECHERCHE EN CANCÉROLOGIE AUVERGNE-RHÔNE-ALPES 2018

BOOK DES COMMUNICATIONS

ORALES ET POSTERS

2003—2018

CLARA
CANCÉROPÔLE LYON AUVERGNE RHÔNE - ALPES

Table des matières

Bioinformatics, Modeling

Poster # 1

A Meta-Analysis of Breast Cancer Cell Lines Transcriptomic Profiles: Finding the Right Cell Line Model

Konstantinn BONNET[1], Sylvain PICARD[1], Claire BARDEL[1,2], Mathieu GABUT[3], François DUCRAY[1,3], David MEYRONET[1,3], Marc BARRITAULT[1,3]

1. Hospices Civiles de Lyon – Université Lyon 1 Claude Bernard
2. UMR CNRS 5558 – LBBE, "Biométrie et Biologie Evolutive", UCB Lyon 1 , Service de Biostatistique 162 avenue Lacassagne, 69424 Lyon cedex 03
3. UMR inserm 1052 CNRS5286 Centre Léon Bérard, « Diversité du transcriptome des cellules souches », Cheney A, 4e étage, Centre Léon Bérard, 28 rue Laennec, 69008 Lyon

Contact: marc.barritault@chu-lyon.fr

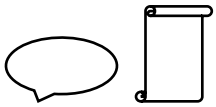
Keywords: breast cancer cell lines, transcriptomic profile, meta-analysis, microarray, gene set enrichment analysis.

Introduction: Cell lines is one of the mostly used tool for cancer studies. Many international institutions have independently carried out gene expression profile (GEP) characterization of numerous breast cancer cell lines in order to study cancer signaling pathways. However the GEP of a cell line may differ between studies and lead to uncertainty on which cell line model an experimenter should choose. Here we compare in a meta-analysis the GEP of over 100 breast cancer cell lines coming from independent studies and cell banks.

Methods: 433 Affymetrix U133plus2 chips GEP corresponding to 106 different breast cancer cell lines from 7 independent Gene Expression Omnibus and ArrayExoress datasets were selected. GEP were first normalized using robust multi-array average (RMA) normalization and dataset batch effect was adjusted . Unsupervised hierarchical cluster analysis (UHCA) and principal component analysis (PCA) were then performed. An average reference GEP was calculated for highly represented cell lines.
Cell lines GEP were classified according to two published breast cancer molecular classification tools (CITBCMST and TNBCtype). Gene set enrichment analysis with the main breast and cancer pathways was performed.

Results: UHCA and PCA showed that identical cell lines from different datasets clustered together. For the 33 cell lines that were present in at least 4 of 7 datasets, an average reference GEP could be calculated and plausible outliers' profiles highlighted.

Conclusion: This is the first GEP breast cancer line. For 33 of the most frequently used breast cancer cell lines, we computed a cell line specific reference GEP that can be used to:
1/ identify an abnormal GEP (e.g. contamination).
2/ determine which cell line(s) would be the best models to study a specific molecular pathway.
3/ molecularly classify cell lines in a study-independent manner.



Poster # 2

Detection of Genetically Altered Proteins in Cancer by Proteogenomics

Georges BEDRAN[1,2,3], Eric BONNET[2], Yves VANDENBROUCK[1], Lucid BELMUDES[1], Jean-François DELEUZE[2], Delphine PFLIEGER[1,4*] and Christophe BATTAIL[1*]

1. CEA/DRF/BIG/BGE/EDYP, 17 rue des Martyrs, 38054, Grenoble, France
2. CEA/DRF/JACOB/CNRGH, 2 rue Gaston Crémieux, 91057, Evry, France
3. Master Bioinformatique - Université de Rouen, Place Emile Blondel, 76821, Mont-Saint-Aignan, France
4. CNRS, 25 rue des Martyrs, Grenoble, 38042, France

∗ Co-senior authors

Contact: christophe.battail@cea.fr

Keywords: proteogenomics, RNA-seq, proteomics, genetic variants

In recent years, high-throughput DNA sequencing technologies allowed consortia such as The Cancer Genome Atlas (TCGA) Research Network to map genetic alterations from hundreds of tumor biopsies of different cancers. However, among the thousands of variants identified by genomic profiling, only a portion of them impact significantly protein expression or function. Computational approaches were developed to evaluate the pathogenicity of mutations to distinguish between deleterious and neutral ones. These methods are useful to prioritize variants but they obviously cannot capture the complexity of post-transcriptional regulations, which result notably in low correlation between transcript and protein abundances, and could attenuate or favor the cellular impact of altered proteins. Indeed, beyond the genome information, the Clinical Proteomic Tumor Analysis Consortium (CPTAC) has recently demonstrated on tumor biopsies that the integration of proteome profiling revealed perturbations of signaling pathways and new tumor subtypes inaccessible to genomics alone.

To improve the interpretation of intragenic variants in cancers, we developed a proteogenomic computational workflow which combines transcriptomic and proteomic data to assess whether mutations detected at the nucleotide level are translated and to measure their effect on protein abundance. Our methodology implements two complementary approaches dedicated to the discovery and the targeted analysis of peptides carrying single amino acid variations, insertions/deletions or aberrant splicing junctions. We tested our tool on a colorectal cancer cell line and found that 130 intragenic mutations identified by RNA-seq, were also harbored by expressed proteins. Moreover, we provide a computational toolbox dedicated to the exploration of mutated peptides: to annotate them using online cancer resources, to predict their pathogenicity, to visualize there fragmentation spectra and their mapping on the genes they belong to.

Poster # 3

Interaction des radiations ionisantes avec les systèmes biologiques : modélisation multi-échelle pour comprendre et optimiser les radiothérapies innovantes

G. ALPHONSE, M. CHANRION, M. CUNHA, C. MONINI, F. POIGNANT, C. RODRIGUEZ-LAFRASSE, E. TESTA, M.BEUVE

1IPNL, Université Lyon 1, UMR 5822, CNRS/IN2P3, Lyon, France
Contact : m.beuve@ipnl.in2p3.fr

Mots clés : modélisation multi-échelle, radiothérapies innovantes, hadronthérapie, nannoparticules

L'interaction entre un rayon ionisant et la matière vivante est un domaine complexe. Modéliser ce phénomène consiste à mieux comprendre les mécanismes physiques, chimiques et biologiques fondamentaux impliqués, à prédire les observables utiles à l'amélioration de la radiothérapie du cancer, et estimer les effets des radiations sur la santé.

Comme les effets tardifs de la radiation (contrôle de la tumeur, complications, cancers radio-induits) sont déterminés par des phénomènes précoces situés sur des échelles très petites de temps (<<fs) et d'espace (nm), une telle modélisation multidisciplinaire nécessite de fournir une description globale allant des effets quantiques à la réponse cellulaire.

Le groupe « PRISME » à l'IPNL est la fusion d'équipes de physiciens (PhaBio) et de biologistes (LRCM). Ses membres travaillent ensemble depuis plusieurs années en hadronthérapie, s'intéressant à différentes échelles et divers phénomènes (interactions primaires des radiations sur la matière, dosimétrie multi-échelle, production de radicaux, mort cellulaire radio-induite, et contrôle de la tumeur). Ils ont aussi développé des modèles biophysiques et des simulations Monte Carlo. L'expertise du groupe PRISME a récemment été étendue aux radiothérapies innovantes, telle la photo-activation de nanoparticules.

Poster # 4

Circadian Clock and Cancer: A Network Biology Perspective Sheds Light on Adhesion Signaling

Cyril BOYAULT, Ingrid BOURRIN-REYNARD, Sandra MANET-DUPE, Christiane ODDOU, Daphné VANNIER, Anne-Pascale BOUIN, Emmanuelle PLANUS, Olivier DESTAING, Eva FAUROBERT, Corinne ALBIGES-RIZO

DYSAD, Institut for Advanced Biosciences (IAB), Centre de Recherche UGA / Inserm U 1209 / CNRS UMR 5309, La Tronche
Contact: cyril.boyault@univ-grenoble-alpes.fr

Keywords: Signaling Network, Circadian clock, Chronotherapy,

During evolution, most of living organisms have evolved an internal time keeping device, a circadian clock, to be able to synchronize and anticipate daily oscillatory cues, such as variation in light, temperature or nutrient abundance (1). In mammals, although the sleep/wake cycle being the most prominent illustration, the last two decades also revealed that it is involved in an exquisite periodical regulation of the endocrine and cardiovascular systems, body temperature regulation or brain activity (1).

At the tissular or cellular level, we and others reported that the circadian clock controls a wide amount of cellular processes which encompass apoptosis, DNA damage response, differentiation and proliferation (2-4). Accordingly, many reports associated circadian clock disruptions and occurrence of cancer (4). Also, it is clear that our understanding of the relationship between the clock and carcinogenesis or metastatic processes will benefit to set up chronotherapies designed to fight cancer. We developed a network biology pipeline to model the relationships between the circadian clock, oncogenes and tumor suppressors. In addition to predict numerous cross-talks between pathways, together with previous data (5, 6), we hypothesized and demonstrated that a circadian clock disruption affects the cellular adhesion, migration and invasion signaling in vivo. Finally, although our network biology pipeline predicts cellular signaling cross-talks, we will present how it could be used to set up future chronotherapies.

References

1. Cuninkova L, Brown SA. Ann N Y Acad Sci. 2008;1129:358-70.
2. Lande-Diner L, Boyault C* et al., Proc Natl Acad Sci U S A. 2013 Oct 1;110(40):16021-6. (*Co-first author)
3. Robles MS, Boyault C* et al., Science. 2010 Jan 22;327(5964):463-6. (*Co-first author)
4. Lamia KA. F1000Res. 2017 Oct 30;6:1910.
5. Yang N, et al., Nat Commun. 2017 Jan 30;8:14287.
6. Hoyle NP, et al., Sci Transl Med. 2017 Nov 8;9(415.

Poster # 5

Personalized Oncology with Artificial Intelligence: The Case of Temozolomide

Nicolas HOUY[1] and **François LE GRAND[2]**

1. University of Lyon, Lyon, F-69007, France; CNRS, GATE Lyon Saint-Etienne, F-69130, France.
2. emlyon business school, Écully, F-69130, France.
Contact: legrand@em-lyon.com

Keywords: Pharmacokinetics, Pharmacodynamics, Optimization, Personalized Oncology, Artificial Intelligence.

Purpose: Using artificial intelligence techniques, we compute optimal personalized protocols for temozolomide administration in a population of patients with variability.

Methods: Our optimizations are based on a Pharmacokinetics / Pharmacodynamics (PK/PD) model with population variability for temozolomide, inspired by Faivre et al. (Apr. 2013) and Panetta et al. (Nov. 2003 and Dec. 2003). The patient pharmacokinetic parameters can only be partially observed at admission and are progressively learned by Bayesian inference during treatment. For every patient, we seek to minimize tumor size while avoiding severe toxicity, i.e. maintaining an acceptable toxicity level. The optimization algorithm we rely on borrows from the field of artificial intelligence.

Results: Optimal personalized protocols (OPP) achieve a sizable decrease in tumor size at the population level but also patient-wise. The tumor size is on average 67.2 grams lighter than with the standard maximum-tolerated dose protocol (MTD) after 336 days (12 MTD cycles). The corresponding 90% confidence interval for tumor size reduction amounts to [58.6−82.7] (grams). When treated with OPP, less patients experience severe toxicity in comparison to MTD.

Poster # 6

NanOx, a New Multiscale Model to Predict Ion RBE in Hadrontherapy

Caterina MONINI, Etienne TESTA, Michael BEUVE

IPNL, Université Claude Bernard Lyon 1
Contact: monini@ipnl.in2p3.fr

Keywords: Hadrontherapy, modeling, survival curves, biological dose, RBE

Object: Hadrontherapy is becoming an increasingly attractive modality for cancer treatment due to the favourable depth-dose profile of ions and high relative biological effectiveness (RBE) in the tumour region. Since RBE depends on multiple parameters related both to the irradiation beam and the cell properties, biophysical models are essential to comply with the demands of a clinical environment. NanOx addresses some of the flaws in the models currently implemented in the treatment planning systems, and presents many innovative features.

Method: The model takes into account the fully stochastic nature of ionizing radiation by considering dose fluctuations both at nanometric and micrometric scales, and introduces the concept of chemical dose. The latter represents the induction of cell death by “non-local” events as the accumulation of cellular oxidative stress or sub-lethal lesions induced by radical species. Such “non-local” events are complementary to the “local” events, which take place at a very localized scale and are considered as lethal since can singly cause cell death.

Results: NanOx predictions for V79, CHO and HSG cell lines irradiated by photons, protons and carbon ions are in good agreement with the experimental data. The model is able to describe the effectiveness of ions, including the overkill effect at high LET values. Moreover, the typical shoulder in cell survival curves is reproduced owing to the introduction of the chemical dose which varies with LET.

Conclusion: The promising results obtained with NanOx stress its potential in the context of hadrontherapy, and may lead in the future to apply it to neutron beam therapy or photoactivation of nanoparticles. Despite a rigorous mathematical approach, its implementation remains simple and compatible with the constraints of clinical application. The model relies in fact on the fit of five parameters, and its pragmatic architecture facilitates improvements and optimizations.

Poster # 7

Modélisation physique, chimique et biologique pour la radiothérapie améliorée par les nanoparticules à fort-Z : vers une meilleure compréhension de l'effet radiosensibilisant

F. POIGNANT[1], B. GERVAIS[2], A. IPATOV[1], H. CHARFI[1], E. TESTA[1], M. BEUVE[1]

1. Institut de physique nucléaire de Lyon, Rhône, Lyon, France
2. CIMAP, Calvados, Caen, France
Contact: poignant@ipnl.in2p3.fr

Mots clés : Nanoparticules, Effet radiosensibilisant, Modélisation

L'enjeu majeur de la radiothérapie est de concentrer la dose d'irradiation dans les cellules cancéreuses tout en épargnant au mieux les cellules saines. Parmi les stratégies envisagées, l'utilisation de radiosensibilisants vise à amplifier les effets destructeurs de dose dans la tumeur. Les nanoparticules (NPs) de métaux lourds tels que l'or, ont montré des propriétés radiosensibilisantes et ont des résultats prometteurs. Si leur effet est connu depuis une vingtaine d'années, l'origine de ce phénomène est encore mal comprise et peu quantifiée.

La littérature suggère que, interagissant avec les NPs, les radiations génèreraient un effet physique appelé cascade Auger. Cet effet aurait pour conséquence de déposer davantage de dose localement, amplifiant les dommages cellulaires critiques par cassure directe de molécules sensibles (ADN) ou par boost de radicaux libres. Ces effets sont produits à des échelles nanométriques et dans des temps extrêmement courts (à partir de 10-18 seconde) mais ont des conséquences à échelle du patient. Parce que ce phénomène n'est pas observable, l'outil de simulation est indispensable pour mieux comprendre les processus initiaux.

Notre objectif est dans un premier temps de développer une simulation permettant de calculer les distributions spatiales de dose et de radicaux libres autour des NPs et de quantifier le boost induit. Dans un second temps, nous allons injecter ces résultats dans le modèle NanOx, développé dans le cadre de l'optimisation de soin par hadronthérapie, pour traduire ces effets en termes d'augmentation de dose biologique et de mort cellulaire.

Ces deux étapes feront l'objet d'une confrontation avec des données expérimentales pour évaluer la qualité des modèles et de la pertinence des scénarios proposés dans la littérature. L'objectif final serait de guider le développement des NPs et si possible d'aider à la planification clinique de traitements radiothérapeutiques basés sur les NPs.

Poster # 8

DNA Methylation-Wide Deregulation by Estrogen Hormones in Breast Cancer

Athena SKLIAS, Zdenko HERCEG

Epigenetics Group, International Agency for Research on Cancer, Lyon, France.
Contact: skliasa@students.iarc.com

Keywords: DNA methylation, microarray, estrogen receptor

Breast cancer (BC) is the most common cancer in women worldwide. Among established risk factors, the steroid hormones (such as estrogens) have been recognized as critical players in a large fraction of breast cancer cases and current chemotherapeutic strategies target hormonally responsive breast tumours. While only 7% of normal epithelial breast cells expresses estrogen receptor (ER), a majority of BCs (around 70%) are ER+, suggesting that ER plays a central role in BC development in response to exogenous and endogenous steroid-like and hormone exposures. Because the unique transcriptional response to estrogen hormone can be mediated by epigenetic mechanisms, we hypothesized that ER ligand-activation contributes to the modulation of the methylation landscape in collaboration with other epigenetic and transcription factors in response to exposure to estrogenic compounds. In this work we examined the impact of deprivation of and stimulation with estadiol (E2), ER's most common physiologic ligand, on genome-wide DNA methylation (DNAm). ER+ breast cancer cell line MCF-7 exposed to and deprived of E2 was subjected to methylome profiling using an Infinium MethylationEPIC array (that interrogates over 850 000 CpG sites). Our results show a large number of CpG sites that are differentially methylated between E2 exposed and E2 deprived, a majority of which gained methylation after 14 days of E2 deprivation. It is noteworthy that after incubation of E2-deprived cells in the presence of E2, only a small minority of differentially methylated CpGs reacquired their initial methylation levels. These results indicate that DNAm is modulated in response to ER's inactivation but once DNAm changes have taken place, they are irreversible, this observation being consistent with the existence of epigenetic memory. The experiments that are currently underway will allow testing if ER recruits other transcription factors, thereby modifying DNAm states and the results will be reported.

Poster # 9

Mise en place d'un pipeline d'analyse de puce Affymetrix Cytoscan dans le cadre du projet IMODI

Emilie SOHIER[1], Séverine TABONE-EGLINGER[2], Sandrine BOYAULT[3], Janice KIELBASSA[1], Emilie THOMAS$_1$, Olivier DUCHAMP[4], Alain BRUNO[5], Fabien CAVASINO[6], Juan IOVANNA[7], Autres membres du consortium IMODI[8]

1. Plateforme Gilles Thomas, CLB/Synergie Lyon cancer
2. Plateforme de Gestion des Echantillons Biologiques CLB
3. Département de Recherche Translationnelle et de l'Innovation, Génomique des Cancers CLB
4. Oncodesign, Dijon
5. Servier institut de recherche, Suresnes
6. Modul-Bio, Marseille
7. INSERM U1068, Marseille
8. http://www.imodi-cancer.org/

Contact : emilie.sohier@lyon.unicancer.fr

Mots clés : pipeline, analyse, cytoscan, PDX, IMODI

Le projet IMODI est un projet collaboratif dont le but est de générer des modèles de souris PDX (Patient Derived Xenograft), fidèles aux tumeurs des patients et caractérisés au niveau anatomopathologique, génomique et pharmacologique. La caractérisation génomique, réalisée par la Plateforme a pour objectif d'identifier les altérations de la tumeur et vérifier qu'il n'y a pas de dérive au cours des passages. Pour cela, différentes collections de PDX ont été analysées (71 tumeurs de sein, 28 d'ovaire et 38 de pancréas) sur des puces Cytoscan (Affymetrix), qui permettent de déterminer le nombre de copies d'ADN et le génotype sur l'ensemble du génome. Pour chaque modèle un passage précoce (P0 à P3) et un passage tardif (P4 à P10) ont été comparés.
Cependant, devant le peu de méthodes d'analyses décrites dans la communauté scientifique, nous avons développé un pipeline bioinformatique automatisé.
Après avoir vérifié que les sondes de Cytoscan étaient spécifiques du génome humain, chaque étape de l'analyse a été optimisée : normalisation, segmentation et détermination du nombre de copies, génotype des segments d'ADN, ploïdie des tumeurs, contamination par d'autres ADN et enfin l'étiquetage déterminant le statut normal, gagné ou perdu des segments génomique. Puis nous avons comparé la méthode de normalisation fournie par Affymetrix (Affymetrix Power Tool) avec une méthode rawCopy, plus récente et décrite dans la littérature comme plus efficace (Mayrhofer et al, Scientific Reports 2016). Deux méthodes ont également été testées pour l'étape de segmentation et de détermination du nombre de copies et du génotype, avant de choisir et d'optimiser la méthode ASCAT (Van Loo et all, PNAS 2010). Enfin nous avons mis en place des outils qui permettent de comparer 2 passages du même modèle : une corrélation des SNP d'une part pour vérifier que les 2 échantillons proviennent bien du même individu, et un score de similarité d'autre part qui correspond au pourcentage de génome avec le même statut (normal, gain, perte) entre les 2 profils. Nous avons ainsi observé que malgré une diversité de résultats, pouvant dépendre du type tumoral et de la qualité des ADN, une grande majorité des couples sont similaires à plus de 70%.
La mise en place de ce pipeline a été complexe du fait de la nouveauté de ce type de puces avec très peu de logiciel bioinformatique existant et réellement testé sur ce type de puce. Ce pipeline est utilisé depuis près de 2 ans dans le cadre du projet IMODI, avec plus de 170 échantillons analysés.
Pour compléter le travail, nous allons nous intéresser aux différences observées entre 2 passages. Nous allons également faire des tests de variabilité intra passage, nous pensons qu'il est intéressant d'étudier si des clones cellulaires différents peuvent émerger car nous savons qu'il y a de l'hétérogénéité clonales dans certaines tumeurs.

Poster # 10

NGS et France Génomique 2025 - quels challenges en pratique ?

Séverine COQUERELLE, Isabelle DURAND-ZALESKI

URC-Eco - Unité de Recherche Clinique en Economie de la santé d'Ile-de-France
Contact : severine.coquerelle@urc-eco.fr

Mots clés : NGS, pratique clinique

La médecine stratifiée offrent aux professionnels de santé de nouvelles possibilités diagnostiques et thérapeutiques. Parmi les enjeux médicaux et économiques principaux figure celui d'adapter les traitements aux patients sur la base de leurs résultats d'analyse biomoléculaire (NGS).
Le plan France Genomique 2025 prévoit le déploiement d'une offre génomique nationale et définit des objectifs pour construire une médecine génomique de qualité sur l'ensemble du territoire.
Or le volume important d'informations ainsi généré suppose aussi de développer des méthodes de traitement de l'information, d'analyse, d'évaluation... qui impactent le parcours de soins et requièrent une mutualisation des expertises.
Nous utiliserons les données issues d'un projet financé par l'INCa portant sur l'impact du séquençage haut débit sur la pratique clinique mené auprès de 7 plateformes de biologie moléculaire et des centres qui les alimentent.
Nous présenterons quelques challenges qui se posent aux professionnels de santé dans l'exploitation des résultats de séquençage haut débit.
Pour conclure nous présenterons quelques axes de développement possible pour atteindre les objectifs de France Génomique 2025.

Clinical Research

Poster # 11

Intérêt d'une réflexion anticipée du la limitation des soins dans un service d'oncologie thoracique : une étude prospective

Natacha DENIS[1], Anne-Claire TOFFART[1], Matteo GIAJ LEVRA[1], Linda SAKHRI[2], Michaël DURUISSEAUX3, Julian PINSOLLE[1], Léonie FERRER[1], Jean-François TIMSIT[4], Denis MORO-SIBILOT[1]

1. Service de pneumologie, CHU Grenoble Alpes, boulevard de la Chantourne, CS10217, 38043 Grenoble cedex 9
2. Service d'oncologie, Institut Daniel Hollard, Groupe Hospitalier Mutualiste, 21 rue Dr Hermitte 38000 Grenoble
3. Service de pneumologie, Hôpital Louis Pradel, 59 Boulevard PINEL 69677 Bron cedex
4. Réanimation médicale et infectieuse, Hôpital Bichat Claude Bernard, 46 Rue Henri Huchard, 75877 Paris

Contact : ndenis@chu-grenoble.fr

Mots clés : oncologie, oncologie thoracique, limitation de soins, proposition anticipée de soins, intensité des soins,

Contexte : L'objectif de cette étude est d'évaluer l'intérêt d'une réflexion anticipée sur la limitation des soins chez des patients atteints d'un cancer thoracique.

Méthode : Cette étude prospective a été menée au Centre Hospitalo-Universitaire de Grenoble. Les patients hospitalisés du service d'oncologie thoracique entre le 28/01/2014 et le 31/03/2016 étaient inclus. A l'admission, une proposition d'intensité de soins en cas d'épisode aigu était notée par écrit. Ces propositions de soins pouvaient être modifiées au cours de l'hospitalisation. Le consentement des patients devait être recueilli. Le critère de jugement principal était d'évaluer si les propositions de soins anticipées étaient respectées en cas de défaillance d'organe.

Résultats : Les données de 715 hospitalisations correspondant à 473 patients ont été recueillies. Lors de la 1ère admission, 247 (52%) patients présentaient un Performance status entre 0 et 2, 188 (40%) n'étaient pas encore traités pour leur cancer et 163 (34%) étaient en progression. Les principaux motifs d'hospitalisation étaient la survenue d'une pathologie aigüe (n=209, 44%) et la prise en charge de symptômes liés au cancer (n=167, 35%). Le souhait des patients n'a été rapporté que pour 67 (16%) patients. En cas de défaillance d'organes, une prise en charge en réanimation était proposée pour 331 (70%) patients et une prise en charge maximaliste dans le service pour 140 (30%). 64 patients (14%) ont bénéficié d'une réévaluation de cette proposition pendant l'hospitalisation. 138 (29%) patients ont présenté une défaillance d'organes. Les malades ont tous bénéficié de soins d'intensité inférieure ou égale à l'intensité proposée.

Conclusion : En cas de défaillance d'organes, la planification préalable des soins semble utile pour en proposer une intensité raisonnable. Il apparait que l'avis du patient est insuffisamment recueilli. C'est sur ce point qu'il est important de travailler. Financements dans le cadre du projet OncoStarter 2013.

Poster # 12

Métastase cutanée ombilicale (ou nodule de Sœur Marie-Joseph) révélant un carcinome gastrique : à propos d'un cas

A.ETCHIALI[1,3], L. HENAOUI[2,3], K.MEGUENNI[2,3]

1. Service Hépato-Gastroentérologie CHU Tlemcen Algérie ;
2. Unité Epidémiologique Clinique Faculté Médecine Tlemcen Algérie ;
3. Laboratoire CancerLab N°30 Faculté de Médecine Tlemcen Algérie

Contact : etchialiamel@gmail.com

Mots clés : carcinome gastrique, métastase ombilicale, Nodules de Sœur Marie-Josèphe, nodule cutanée

Introduction : Les métastases ombilicales des tumeurs viscérales sont très rares. Elles représentent 3 à 4% de l'ensemble des localisations tumorales secondaires cutanées. Elles posent un problème de diagnostique étiologique. Elles révèlent un mauvais pronostic.

Objectif : Ces métastases ombilicales des tumeurs viscérales constituent parfois le seul signe d'appel vers la tumeur primitive ce qui rend la démarche diagnostique difficile. A cet égard il nous semble intéressant de vous rapporter un cas de métastase cutanée ombilicale de tumeur gastrique colligé dans le service d'Hépato-gastroentérologie au CHU en février 2014.

Observation : Patient H.K âgé de 37 ans originaire et demeurant à Saida marié, agriculteur de profession, sans antécédents pathologiques hospitalisé dans notre service pour complément d'exploration des epigastralgies chroniques évoluant depuis deux ans sur une tuméfaction ombilicale, dont l'enquête étiologique à la recherche de la tumeur primitive à savoir une gastroscopie et une iléo-colonoscopie ont retrouvé un double aspect infiltrant de la muqueuse gastrique, et de la muqueuse rectale ;l'étude anatomopathologique des biopsies a conclut a un carcinome gastrique à cellules indépendantes en bague a chaton. Le bilan d'extension a retrouvé de plus de l'envahissement cutané ombilical une carcinose péritonéale et des adénopathies profondes. Le patient a été confié à un traitement palliatif.

Discussion : Les métastases ombilicales des tumeurs gastriques sont très rares. On a retrouvé un cas au stade de carcinose péritonéale chez un sujet jeune sans antécédents pathologiques dont le pronostic est péjoratif vue le diagnostique tardive a un stade avancés de la maladie.

Conclusion : Le nodule cutanée de la sœur marié Joseph n'a pas de symptomatologie spécifique, son expression clinique dépend plutôt de l'expression de la tumeur primitive. Cette métastase ombilicale cutanée pose un double problème diagnostique étiologique et pronostique d'où l'intérêt de la prise en charge thérapeutique précoce après une enquête étiologique bien approfondie.

Poster # 13

Registre et profil des cancers en République Démocratique du Congo : cas du centre d'anatomopathologie LEBOMA

Charles N MBENDI[1], Aliocha NKODILA N[2], Majoie SEWOSOLO B[3], Bienvenu M LEBWAZE[4], Eric M MADIATA[5]

1. Cliniques Universitaires de Kinshasa, RDC
2. Centre Médical Moyo, RDC
3. Médecins des Hôpitaux, RDC
4. Centre d'Anatomopathologie LEBOMA
5. Cancérologie clinique, centre hospitalier de Soissons, France

Contact : maderic_doc@yahoo.fr

Mots clés : cancer, registre, LEBOMA, histopathologie, Kinshasa, RDC

Contexte : Le cancer est aujourd'hui devenu un problème de santé publique dans les pays en développement. Il est aggravé par la difficulté supplémentaire d'un diagnostic qui est beaucoup plus tardif.

Objectif : faire un état des lieux sur les cancers les plus fréquents à Kinshasa.

Méthodologie : étude documentaire et descriptive, 284 protocoles d'examen d'anapath au Centre inclus d'Anatomopathologie LEBOMA durant la période allant du 01/01 au 30/08/2017.

Résultats : Sur un échantillon de convenance de 284 protocoles d'anapath sélectionnés, on a dénombré 59,2% des femmes (ratio 2F/1H), l'âge moyen des patients était de 55,1±14,6 ans. Le carcinome épidermoïde (23,9%), le carcinome canalaire (23,9%), l'adénocarcinome (21,1%) et le carcinome prostatique (14,8%) sont les cancers les plus fréquents. Selon les organes, le cancer de sein (26,4%), de la prostate (15,1%), du col utérin et colorectal(12,7% respectivement) étaient plus fréquents. Chez l'homme le cancer de la prostate (37,1%) et chez la femme le cancer du sein (43,5%) prédominaient. 50,4% de ces cancers étaient bien différenciés, avec 57,7% de cas infiltrant d'autres organes. Seuls 10,6% des cancers avaient des métastases à distance.

Conclusion : Le cancer est plus fréquent chez la femme âgée avec une prédominance des carcinomes épidermoide et canalaire. La présence d'un registre de cancer national est nécessaire dans le pays pour un bon suivi des cas de cancer.

Poster # 14

Profil épidémiologique, clinique et évolutif du Sarcome de Kaposi chez les personnes vivant avec le VIH/SIDA de janvier 2000 à janvier 2003

Charles N MBENDI[1], Aliocha N NKODILA[2], Fifi K KANGUFU[3], Eric M MADIATA[4]

1. Cliniques Universitaires de Kinshasa, RDC
2. Centre Médical Moyo, RDC
3. Médecins des Hôpitaux, RDC
4. Cancérologie clinique, Centre Hospitalier de Soissons, France

Contact : chmbendi@yahoo.fr

Mots clés : Fréquence, Clinique, Evolution, Sarcome de Kaposi, VIH, HMC.

Contexte et objectif : Cette étude veut évaluer le profil épidémiologique clinique et évolution de Sarcome de Kaposi à l'Hôpital Militaire Central/ Camp Kokolo.

Matériel et méthodes : C'est une étude rétrospective des patients suivis dans le service de médecine interne de l'HMC pour Sarcome de Kaposi durant la période allant de janvier 2000 à janvier 2003 basée sur les dossiers médicaux.

Résultats : Sur les 80 PVVIH suivies à l'HMC, 38 avaient présenté un Sarcome de Kaposi soit une fréquence de 47,5% ; les hommes sont plus atteints que les femmes (62,5% vs 37,5%) avec un sexe ratio de 1,6 à prédominance masculine. La tranche d'âge de de 31-50 ans chez les hommes et de 22-30 ans chez les femmes est la plus atteinte (50,0% / 50,0%). Les macules sont les lésions cutanées les plus fréquentes (34,2%) suivies des papulonodules pigmentés (28,9%) et les nodules angiomateux (23,6%). La fièvre est la plainte la plus fréquente (44,7%). Le paludisme est la comorbidité associée la plus fréquente (47,3 %) suivie de la tuberculose (34,2 %). Le traitement reçu par nos PVV avec sarcome de Kaposi comprenait essentiellement les ARV (47,4%), le Cotrimoxazole (21,1%) et les soins locaux (18,4%).
Il n'y a eu aucun cas de décès.

Conclusion : Le Sarcome de Kaposi était fréquent durant ces années avec une mortalité nulle bien que la prise en charge n'était pas optimale.

Poster # 15

Evaluation du polymorphisme génétique des régions régulatrices du gène EGFR dans les carcinomes pulmonaires

Amal MESLI[1], Katia SOLCHURCH[2], Deborah STABLEY[2], Ahmed KACIMI[3], Nacera BELBLIDIA[3], Bahia MERAD[4], Tewfik SAHRAOUI[1], Fatima Zohra EL KEBIR[1]

1. Laboratoire de Biologie du Développement et de la Différenciation/Université Oran 1, Ahmed Ben Bella, Algérie
2. Laboratoire de Biologie Moléculaire BCL, Nemours /Alfred I duPont, USA
3. Laboratoire de Diagnostique Anatomopathologique, Hôpital Mohamed Sghir Nekkache, Algérie
4. Laboratoire de Diagnostique Anatomopathologique, Oran, Algérie

Contact : meslimesliamel@yahoo.com

Mots clés : CBNPC, CBPC, EGFR, carcinomes épidémies, Sp1 , G216T , C191A , dinucléotide CA

Le carcinome pulmonaire représente la première cause de mortalité par cancer au monde. Il est hautement agressif et de faible pronostic minimisant ainsi les chances de survie des patients qui se présentent souvent à un stade avancé.

Cette étude a été réalisée sur 20 patients atteints de carcinomes pulmonaires non à petites cellules CBNPC et à petites cellules CBPC afin d'établir un diagnostic différentiel. La recherche d'éventuels polymorphismes génétiques situés dans le gène du récepteur de facteurs de croissance épidermique EGFR, pouvant être incriminés en cancérogenèse, a été réalisée par électrophorèse capillaire sur un ABI 3100. Le séquençage de la région du promoteur et d'une partie de l'exon 1 du gène EGFR, a révélé la présence d'un polymorphisme G216T dans le site de fixation du facteur de transcription Sp1 chez 64.70% des patients atteints de CBNPC, accompagné d'une nette prédominance dans les carcinomes épidermoïdes. Cette variation induit le changement d'une guanine en thymine (-216G/T) et permet ainsi d'augmenter son activité transcriptionnelle de 30% (Liu et al, 2005). Une autre variation nucléotidique C191A a été également retrouvée dans la région du promoteur induisant le changement d'une cytosine vers une adénine. Elle est située en amont de nombreux sites initiateurs de la transcription pouvant exercer un rôle régulateur sur le promoteur de l'EGFR (Johnson et al, 1988; Kageyama et al, 1988). L'analyse de distribution des quatre haplotypes (G-C, G-A, T-C et T-A) et du diplotype (G-C/T-C) des polymorphismes G216T et C191A, a été effectuée pour analyser d'éventuelles corrélations fonctionnelles. L'analyse de la région de l'intron 1, a révélée la présence d'une séquence répétitive (CA)n, située en aval de l'enhancer du gène EGFR et un nombre de variation reliée significativement au type histologique. Néanmoins, aucune relation fonctionnelle n'a été reportée concernant le polymorphisme G216T et le dinucléotide CA.

Poster # 16

Stratification of Head and Neck Cancers: DNA Repair Enzyme Signature to Identify Resistance and Toxicity Biomarkers

Giovanna MUGGIOLU[1], Sarah LIBERT[1], Alexandra LAURET[2], Philippe CERUSE[3], Christian Adrien RIGHINI[4], Claire RODRIGUEZ-LAFRASSE[5], Sylvie SAUVAIGO[1]

1. LXRepair, 7 parvis Louis Néel, 38000 Grenoble Cedex 9
2. CNRS/UMR 5822, Cellular and Molecular Radiobiology Laboratory, University of Medicine Lyon-Sud, BP12 69921 Oullins Cedex
3. Head Neck Department, Civil Hospital of Lyon, University Claude Bernard Lyon 1, 69000 Lyon
4. Head Neck Surgery Department, Michalon Hospital, CHU of Grenoble, 38000 Grenoble
5. Civil Hospital of Lyon, Biochemistry and Molecular Biology Service, Lyon-Sud Hospital, 69495 Pierre-Bénite

Contact: sylvie.sauvaigo@lxrepair.com

Keywords: DNA repair, biomarker, resistance, toxicity

Head&Neck squamous cell carcinomas are highly heterogeneous tumors. Despite extensive research there are no prognostic and predictive biomarkers widely accepted for routine use in managing patients. In particular there is a critical need to identify patients who will benefit from radio and/or chemotherapy without developing resistance or sufferin from adverse effects.

Indeed DNA is the principal target of these agents and the presence of defects in the DNA repair machinery can be associated with tumors resistance and individual sensitivity. Defining sub-group of patients according to their sensitivity/resistance is one of the main developments for increasing therapeutic effects.

Tobacco consumption, a known carcinogen, is a strong risk factor for H&N cancer. Interestingly, its carcinogenic effect is directly linked to mutations associated with unrepaired DNA lesions it induces. The objective of this project was to characterize the effective individuals DNA repair capacity of tumor and blood samples obtained from patients treated for H&N cancer. Peripheral Blood Mononuclear Cells and tumor biopsies of patients were collected before and during the time course of chemo and/or radiotherapy. Whole cell extracts were prepared and tested for their DNA repair capacity toward a panel of different DNA lesions. In particular, we evaluated glycosylases/AP endonucleases and excision/synthesis repair activities with the patented Glyco-SPOT and ExSy-SPOT assays, respectively.

Preliminary results revealed an inter-individual variability in DNA repair capacities at basal level and after treatment in both PBMCs and tumor cells which could be associated with treatment resistance or hypersensitivity.

We believe the DNA Repair Enzyme signature could be a relevant strategy to stratify patients and tumours for a better personalisation of the treatments.

The study was partly supported by the « Preuve du Concept » program from Cancéropôle Lyon Auvergne-Rhône-Alpes CLARA.

Poster # 17

Stratification of Melanoma Patients Based on DNA Repair Enzyme Signature: Relationship with Driver Genes Mutations and Insights into DNA Repair Defects

Sylvie SAUVAIGO[1], Sarah LIBERT[1], Florence de FRAIPONT[2], Stéphane MOURET[3], Marie-Thérèse LECCIA[3]

1. LXRepair, 7 parvis Louis Néel, Grenoble, France
2. Génétique moléculaire, maladies héréditaires et oncologie, CHU Grenoble, France
3. Clinique de Dermatologie et Photobiologie, CHU Grenoble, France

Contact: sylvie.sauvaigo@lxrepair.com

Melanoma resistance to radiotherapy and chemotherapy is commonly attributed to specific DNA Repair regulation in this tumor type. Recent progress in our understanding of the molecular factors that drive malignant transformation have led to the classification of melanoma according to mutations in specific genes in parallel with the development of targeted therapies. Notably, DNA Repair mechanisms are regulated by the MAPK/PI3K/AKT signaling pathway.

The success of immunotherapy has further changed the clinical management of metastatic melanoma. But patients' response to these treatments are highly heterogeneous and there is a critical need to identify biomarkers which could predict who will benefit from which therapy.

Exposure to UV radiation is a major risk factor for melanoma. Carcinogens promote elevated mutation frequencies in tumors and impact DNA Repair pathways. Defective DNA Repair could be responsible for the observed elevated mutation frequencies in these tumors. Interestingly mutational load predict clinical benefit of immunotherapy in various cancers.

Because we believe a unified strategy is required to stratify metastatic melanoma to choose the best therapeutic option, and because of the central role played by DNA Repair in this carcinogen-induced tumor, we propose a new classification of melanoma based on functional DNA Repair analysis.

In a prospective clinical study, we used a multiplex functional excision/synthesis assay to characterize 12 melanoma samples removed from patients suffering from metastatic melanoma.

Interestingly we found that specific DNA Repair signatures were associated with distinct mutations in the MAPK pathway known to drive tumor development. Alternative versions of the assay allowed identifying several DNA repair defects possibly at the origin of elevated mutational load.

Further evaluation on a larger cohort could confirm these results and allow establishing correlations with clinical parameters and other candidate biomarkers.

Poster # 18

La qualité des données du registre du cancer de Batna ? 2010 – 2014

M OUDJEHIH, I NOURANI, F BEICHI, H BOUNECEUR, ML BOUHIDEL, A BOUHIDEL

Université Batna 2 Algérie, CHU Batna Algérie
Contact : messa18@yahoo.fr

Mots clés : exhaustivité, validité, registre, cancer, Algérie, Batna

Introduction : En Algérie les registres du cancer reconnus par les instances nationales et internationales constituent un outil pour les programmes de lutte contre le cancer. L'objectif était d'évaluer la qualité des données du registre du cancer de Batna entre 2010 et 2014, proposées par le Centre International de Recherche sur le Cancer (CIRC).

Méthodes : L'évaluation des données s'était basée sur des indicateurs d'exhaustivité et de validité tel, que le nombre de sources d'information, le pourcentage de vérification histologique, les taux standardisés par âge et les tendances temporelles. Les indicateurs de validité étaient le pourcentage des valeurs manquantes.

Résultats : Les indicateurs d'exhaustivité étaient une seule source d'information par cas pour l'ensemble des enregistrements, un pourcentage de vérification histologique faible de l'ordre de 30% pour quelques localisations. Des taux standardisés par âge comparés à ceux du registre de Sétif ainsi que les tendances temporelles qui n'allaient pas dans le même sens. Les indicateurs de validité étaient assez bons, avec des taux de vérification histologique élevés qui dépassent 80 % et des taux de valeurs manquantes nul.

Conclusion : Des efforts sont à fournir pour améliorer la qualité des données du registre de Batna. Un registre de cancers est une opération à long terme ; les premiers résultats valides peuvent n'apparaître que de nombreuses années après le début de son fonctionnement

Poster # 19

Tabac et cancers du larynx, étude cas-témoins à Batna,Algérie,2008-2011

M OUDJEHIH[1], H BOUNECEUR[1], I DELTOUR[2], ML BOUHIDEL[1], A BOUHIDEL[1], J SCHUZ[2], M LEON ROUX E[2]

1. Université Batna 2 Algérie, CHU Batna Algérie
2. Section of Environment and Radiation,IARC cours Albert Thomas Lyon,France

Contact : messa18@yahoo.fr

Mots clés : tabac fumé, cancer, larynx, Algérie, Batna

Introduction La consommation du tabac est reconnue comme cancérigène pour les cancers du larynx. Compte tenu de la diversité des produits consommés dans la Wilaya de Batna, il convient de rechercher l'existence d'un éventuel impact de la consommation de tabac sur la survenue de ces cancers. Matériel et méthodes Il s'agit d'une étude cas-témoins, portant sur 50 cas de cancer du larynx survenus entre janvier 2008 et décembre 2011. Chaque cas a été apparié à deux témoins, sur les critères de sexe, âge (± 5 ans) pour le témoin hospitalier et le sexe. Age et commune de résidence pour le témoin communautaire. La mesure de l'association a été estimée par des odds ratio (OR) obtenus par régression logistique conditionnelle. Résultats La consommation du tabac était liée au cancer du larynx [OR = 4,08 ; IC 95 % :1,17–14,19](p=0,02) . Le risque augmentait avec la durée de la consommation, la consommation quotidienne, le nombre de paquets-année, la consommation de tabac sans filtre et de tabac traditionnel et le jeune âge à l'initiation du tabac. Une durée depuis l'arrêt du tabagisme excédant les 15 ans par rapport aux fumeurs actuels semblait réduire le risque du cancer du larynx en analyse univariée [OR = 0,31 ; IC 95 :0,10–0,95] (p=0,04) Conclusion L'étude montrait une augmentation du risque avec les produits de tabac consommés à Batna. Nos résultats, devront être complétés par l'étude de la composition chimique de ces produits.

Nanomedicine, Health Technologies

Poster # 20

Targeting Cancer Cells by Membrane Physicochemical Properties: An Alternative Way to Improve Drug Delivery

Julien BOMPARD, Jihen ZOUAOUI, Leyre BRIZUELA, Saïda MEBAREK, Thierry GRANJON, Agnès GIRARD-EGROT, Ofelia MANITI

Equipes Génie Enzymatique, Membranes Biomimétiques et Assemblages Supramoléculaires (GEMBAS) et Métabolisme, Enzymes et Mécanismes Moléculaires (MEM2)
Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), UMR CNRS 5246, Université Lyon 1, Université de Lyon, Villeurbanne, France
Contact: julien.bompard@etu.univ-lyon1.fr

Keywords: liposome, targeted drug delivery, prostate cancer, nanomedicine

Aim: While liposomes are commonly used in drug delivery, they often rely on the coupling with a small ligand-like molecule to bind specifically to their target. Although changes in membrane physicochemical properties between tumoral and healthy cells may exist, they have never been used for drug delivery purposes. Our aim is then to develop a way to use lipid-based carriers to target cells based on membrane physicochemical parameters, instead of a ligand-receptor interaction.

Methods: Liposomes made of six different phospholipid compositions have been used, containing 2% of a fluorescent lipid (NBD-PE), 20 % of DiOleoylPE (a fusogenic lipid) and 78% of PC with varying chain length, resulting in the creation of a range of membrane fluidity. After incubation with human prostate cells coming either from a normal cell line or from a cancer cell line, the cells were visualized with an epifluorescence microscope to determine if the liposomes were able to interact with them. We also characterized the mechanism of the liposome – membrane interaction, by using two kind of fluorophores (NBD-PE and calcein).

Results: We found that low Tm liposomes constituted of POPC or DOPC interacted with PC-3 cells, but not with the non-tumoral WPMY-1 cells. Inversely, while high Tm liposomes made of DSPC showed no interaction with PC-3 cells, they interacted strongly with WPMY-1 cells. By comparing results obtained with the two types of fluorescent probes, we found that the interaction between liposomes and cells is more likely a membrane fusion, and not an endocytosis phenomenon.

Conclusions: We present a significant difference between tumoral and non-tumoral cells interaction with liposomes of varying lipid composition, as low Tm liposomes fuse with the membrane of tumoral cells while high Tm liposomes fuse with the membrane of control cells. This shows that variation in lipid composition could be used in drug delivery to target tumoral cells rather than healthy cells.

Poster # 21

Nanoscintillators-Induced Deep-Tissue Photodynamic Therapy Upon X-Rays Irradiation

Anne-Laure BULIN[1,2], Mans BROEKGAARDEN[1,3], Hélène ELLEAUME[2], Jean-Luc RAVANAT[4], Lucie SANCEY[3], Frédéric CHAPUT[5] and Tayyaba HASAN[1]

1. Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, 40 Blossom Street, Boston, MA-02114, USA
2. EA 7442 UGA Grenoble, équipe "Rayonnement Synchrotron et Recherche Médicale", 71 avenue des Martyrs CS40220, 38043 Grenoble cedex
3. Institute for Advanced Biosciences, UGA/Inserm/CNRS, 38706 La Tronche cedex
4. UMR 5819 CEA/CNRS/UGA, CEA Grenoble, 17 rue des Martyrs, 38054 Grenoble Cedex 9
5. Laboratoire de Chimie, ENS de Lyon

Contact: anne-laure.bulin@esrf.fr

Keywords: photodynamic therapy, radiation therapy, nanoscintillators

Photodynamic therapy (PDT) is a cancer therapy that demonstrates promising results for the treatment of several cancers including brain, gastrointestinal and ovarian cancers, diseases associated with a dismal prognosis. The PDT efficacy derives from non-toxic molecules (photosensitizers) that generate reactive oxygen species upon light irradiation, inducing cytotoxicity. Although promising, PDT is limited by the shallow penetration of light in tissue and its application remains restricted to small and/or superficial tumors. Recently, it has been proposed to use nanoscintillators to induce deep tissue PDT. Nanoscintillators are down-converting nanoparticles that absorb high energy X-ray photons and emit visible light, that can subsequently excite nearby photosensitizers and induce PDT in deep tissue embedded tumors and across large tumor volumes. Through this mechanism, the RT/PDT combination efficacy is likely to benefit from three contributions: the RT, the PDT and the radiation dose enhancement effect that is observed when high-Z elements are accumulated within a tumor before the RT. Since the introduction of this idea, proofs of concept have been reported, yet many questions remain to be answered.

In this communication, we will discuss the effect of low dose PDT combined with RT applied to 3D heterocellular models of pancreatic cancer. We will also present the ongoing project we are developing around X-PDT for brain and ovarian cancers using synchrotron radiation to deliver RT.

Poster # 22

Nanotechological Strategies for Pentamidine Delivery in Cancer Treatment

CARTON F[1,2], CHEVALIER Y.[2], JORDHEIM LP.[3], MALATESTA M[1], BRIANÇON S[2], ARPICCO S[4], STELLA B[4], AND LOLLO G[2]

1. University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences, Anatomy and Histology Section, Verona, Italy
2. Univ Lyon, Université Claude Bernard Lyon 1, CNRS, LAGEP UMR 5007, VILLEURBANNE, France
3. Centre Léon Bérard (CLB), Centre de Recherche en Cancérologie de Lyon (CRCL), Univ. de Lyon, INSERM, CNRS, Lyon, France
4. Department of Drug Science and Technology, Università degli Studi di Torino, Italy

Contact: flavia.carton@univr.it

Keywords: pentamidine, nanotechnology, biomaterial, anticancer treatment, intravenous administration

Nanomedicine applied to cancer therapy has provide a wide range of new delivery systems able to target tumor cells. However, there is a recognized need to improve the design and development of nanocarriers that should be able to improve the therapeutic benefits of oncologicals. Among the biomaterials used in the development of nanomedicines, polysaccharides as hyaluronic acid (HA), and polyaminoacids as poly(L-arginine) (PArg) have raised great expectancy because of their biodegradability and acceptable regulatory profile. The aim of the work presented here has been to formulate a new type of polymeric nanostructures made of HA and PArg for the encapsulation of pentamidine. Recent works showed that pentamidine has a strong antiproliferative effect both in *in-vitro* and *in-vivo* models of solid tumors. Despite its already proven efficacy, the systemic administration of pentamidine is compromised by its serious toxicities, particularly renal. Thus, to overcome this problem and to enhance the uptake by cancer cells, a new drug delivery system has been developed. Moreover, HA based carrier could also increase the cellular uptake of the drug thanks to the presence of a specific HA receptor namely CD44, overexpressed on human cancer cells. Using ionic gelation technique we obtained biocompatible nanoparticles with an average size between 150 nm and 200 nm and a negative zeta potential, around -30 mV. We optimized the system in order to load pentamidine which was associated in a high amount (84 %). Morphological analysis carried out using transmission electron microscopy (TEM) shown a monodispersed population with a round regular shape. Moreover, these particles were lyophilized in order to improve their stability. After resuspension the nanoparticles recovered their initial physicochemical properties in terms of size and association efficiency. *In vitro* viability studies performed on A549 lung and MDA-MB-231 human breast cancer cell lines evidenced that PTM-loaded nanoparticles have a similar effect on the reduction of cell viability while blank nanoparticles were not toxic.

Poster # 23

New siRNA-Based Nanotherapy for Inflammatory Bowel Diseases, Targeting Janus Kinase 1/3

Flora CLEMENT, Stéphanie COMBE, Frédérique KERMARREC, Xavier GIDROL and Eric SULPICE

INSERM 1038 – UGA – CEA Grenoble BIG BGE Biomics
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 720905.
Contact: clement.flora@hotmail.fr

Keywords: nanoformulation, siRNA, inflammatory bowel diseases, JAK pathway

Inflammatory bowel diseases (IBDs), such as Crohn's disease (CD) and ulcerative colitis (US) are chronic and immune-mediated disorders of the gastrointestinal tract, affecting especially young people. The incidence of IBDs is increasing, affecting about 3 million people in Europe, and many patients do not benefit from available therapies at all. Moreover, conventional IBDs therapies including 5-aminosaliycilates, corticosteroids or immunosuppressants show side-effects and patients often relapse. Biological therapy (monoclonal antibodies against cytokines or adhesion molecules) still leaves a large number of IBD patients insufficiently treated, thereby leading to the need of new therapeutics development, such as Janus Kinases (JAKs) chemical inhibition. In this context, Tofacitinib (pan-JAK inhibitor) and Filgotinib (JAK1-specific inhibitor) have been assayed in clinical trials, showing strong benefit for patients. Nevertheless, both molecules also display important side-effects, raising up the urgent clinical need of new safest and more specific therapies. More specifically, it is crucial to inhibit JAK1/3 without affecting JAK2 signalization that is mandatory for hematopoiesis, therefore a more selective JAK3 will greatly improve the clinical response of future IBD therapy. In this context, a consortium (named New Deal) granted by the European Commission proposed a new therapeutic approach. New Deal project aims at providing a radically improved IBD therapy targeting specifically Jak1/3 inhibition using RNAi interference. The siRNA would be complexed to lipid nanoparticles encapsulated to deliver siRNA directly to the locally inflamed gut. We have designed a collection of 85 different siRNA to target either JAK1 or JAK3 using available commercial siRNA or home-made designed sequences, and ranked their efficacy and specificity. We provide two best siRNA targeting either JAK1 or JAK3.

Poster # 24

Developement of a Beam Tagging Diamond Hodoscope for Online Ion Range Verification in Hadrontherapy

S CURTONI[1], L ABBASSI[4], A BES[1], G BOSSON[1], J COLLOT[1], W de NOLF[3], D DAUVERGNE[1], M FONTANA[2], L GALLIN-MARTEL[1], M-L GALLIN-MARTEL[1], A GHIMOUZ[1], J-Y HOSTACHY[1], A LACOSTE[1], S MARCATILI[1], J-F MOTTE[4], J-F MURAZ[1], F.E RARBI[1], M SALOME[3], E TESTA[4], M YAMOUNI[1]

1. Univ. Grenoble Alpes, CNRS, Grenoble INP, LPSC-IN2P3, 38000 Grenoble
2. Institut de Physique Nucléaire de Lyon, Université de Lyon, CNRS-IN2P3, Bâtiment Paul Dirac, Rue Enrico Fermi, 69622 Villeurbanne, France
3. European Synchrotron Radiation Facility (ESRF), 71 Avenue des Martyrs, 38000 Grenoble, France
4. Institut Néel, CNRS, 25 Avenue des Martyrs, 38042 Grenoble

Contact: sebastien.curtoni@lpsc.in2p3.fr

Keywords: Diamond detector, hodoscope, online ion range verification, prompt-gamma imaging, hadrontherapy, beam tagging, Time-Of-Flight

Hadrontherapy enables a highly localized dose deposition and better organ-at-risk protection, compared to conventional photon radiotherapy. Therefore, the treatment quality strongly relies on the control of the effective ion range in vivo. However, the ballistics makes this technique sensitive to various ion range uncertainties induced by the dose calculation, patient set-up and morphological changes between sessions. In this context, the French CLaRyS collaboration aims to develop various online ion range verification techniques by detecting secondary particles emitted by the patient following nuclear interactions along the ion path. Among them, Prompt-Gamma Imaging consists in the detection of gamma rays by either a collimated- or a Compton-camera. Indeed, the emission profile of prompt-gamma photons is spatially correlated to the ion range. The performances of such detection systems can be improved by Time-of-Flight discrimination. A high-count-rate beam hodoscope may be necessary to measure the arrival time of ions on the patient. The MoniDiam project at LPSC is developing an ultra-fast beam tagging hodoscope, based on large area diamond sensors. Diamonds exhibit a fast time response, high resistivity and radiation hardness that make them good candidates for such a detector concept. Polycristalline, single crystal and heteroepitaxially grown on Iridium diamond samples with full planar metallization have been characterized, under different irradiation conditions (α and ß particles, 95 MeV/u 12C ions at GANIL, 8.5 keV photons at ESRF and 68 MeV protons at ARRONAX). Characterization results demonstrating time resolution below 100 ps, energy resolution between 7% and 10% and a good charge collection efficiency will be presented. In order to build a 2D position tagging hodoscope, we are also developing double-side stripped diamond sensors. We will present current mapping and time resolution recently obtained with first samples at ESRF (ID21).

Poster # 25

Anti-Tumor Efficacy of Hyaluronan-Based Nanoparticles for the Co-Delivery of Drugs in Lung Cancer

Victor JEANNOT[1], Cony GAUCHE[2], Silvia MAZZAFERO[2], Morgane COUVET[1], Laetitia VANWONTERGHEM[1], Maxime HENRY[1], Chloé DIDIER[1], Julien VOLLAIRE[1], Véronique JOSSERAND[1], Jean-Luc COLL[1], Christophe SCHATZ[2], Sébastien LECOMMANDOUX[2], Amandine HURBIN[1]

1. Cancer Target and Experimental Therapeutics, Institute for Advanced Biosciences, INSERM U1209, CNRS UMR5309, Univ. Grenoble Alpes, Grenoble, France
2. Laboratoire de Chimie des Polymères Organiques, CNRS UMR5629, Pessac, France

Contact: amandine.hurbin@inserm.fr

Keywords: lung cancer, drug delivery system, hyaluronan-based nanoparticles

Combinations of therapeutic agents could synergistically overcome resistance of lung cancer cells. Co-delivery systems capable of transporting chemotherapeutics with different physicochemical properties and with simultaneous release of drugs remain elusive. Here, we assess the ability of nanoparticles of 30 nm diameter obtained from the self-assembly of hyaluronan-based copolymer targeting CD44 receptors to encapsulate both gefitinib and vorinostat for effective combinational lung cancer treatment. Drug loading was performed by nanoprecipitation method. Drug release experiments evidenced a slow release of both drugs. Nanoparticles uptake and antitumor effect were measured into two and three-dimensional lung adenocarcinoma cells culture systems, and in vivo in lung tumor bearing mice. Nanoparticles were mostly found at the periphery of the spheroids and correlated to CD44 expression. In both monolayer cell culture and three dimensional spheroids, drug-loaded nanoparticles elicited a strong cytotoxic effect and induced apoptosis in lung cancer cells as efficiently as free drugs. Intravenous injection of hyaluronan-based nanoparticles in mice showed selective delivery to subcutaneous CD44 overexpressing tumors, despite a significant liver capture, besides a decrease of systemic drug side effects compared to free drug combination. Drug-loaded nanoparticles showed better orthotopic lung tumor growth inhibition than free drugs after intrapulmonary administration, and were well tolerated. Hyaluronan-based nanoparticles account for the effective co-delivery of chemotherapeutics with different physicochemical properties within tumor cells, reducing lung tumor growth.

These nanoparticles provide both CD44-mediated active targeting and protection from undesired drug release during circulation.

Poster # 26

Preclinical Evaluation of an Innovative Drug Delivery System Based on Immunostimulant Nanoparticles against Chronic HBV Infections

Myriam LAMRAYAH[1], Capucine PHELIP[1], Laura DIMIER[2], Julie LUCIFORA[2], David DURANTEL[2], Bernard VERRIER[1]

1. Colloidal vectors and tissue transport - LBTI - UMR 5305 CNRS – Lyon
2. INSERM U1052 – Cancer Research Center of Lyon (CRCL) – Lyon

Contact: myriam.lamrayah@ibcp.fr

Keywords: : HBV, ccc DNA, hepatocellular carcinoma, in vitro studies, mouse model, biodistribution

Object: Around 400 million worldwide people are HBV carriers and one million people die of HBV-related causes annually. This is mainly due to complications of the infection: chronic liver disease, fibrosis, cirrhosis and hepatocellular carcinoma (HCC). In HBV-endemic regions, chronic hepatitis B (CHB) is even a primary risk for HCC. Despite current therapies, the HBV infection is still a global scourge of public health with an important cost for medical care because they do not lead to viral eradication. Today, drug discovery efforts are focused on the novel strategic target against CHB: cccDNA. This viral minichromosome is responsible for chronicity and drug-resistance aspects of the infection because of its intra-nucleus location. Toll-Like-Receptor (TLR) agonists, a family of immune-stimulatory molecules have showed promising results in this way. Our overall aim was to explore the anti-HBV effect of free or particulated TLR1/2 agonists in vitro and in vivo in monotherapy approaches. In order to protect the active substance, and reciprocally to protect the organism of side effects, that is especially crucial in oncology therapeutic, we are developing an innovative delivery system based on poly(lactic) acid (PLA) nanoparticles (NPs).

Method: NPs are produced by nanoprecipitation with active substance into the core. The immunostimulatory activity of the encapsulated ligand is quantified by in vitro studies in non-infected (HEK-Blue hTLR2) and infected cell lines (dHepaRG, PHH). Furthermore, by in vivo biodistribution studies, we have controlled the body diffusion of the NPs to anticipate their action sites, the optimal administration routes and the need of surface functionalization. Then, AAV-HBV transduced mouse model have been established, which is stable during one year and expresses cccDNA.

Results: NPs are preferentially accumulated in the liver after iv administration. In vitro, loaded TLR1/2 ligand led to a stronger antiviral activity as compared to free form in vitro.

Poster # 27

MRI-Based Radiomic to Assess Lipomatous Soft Tissue Tumors Malignancy: A Pilot Study

B. LEPORQ[1], A. BOUHAMAMA[2], F. LAME[2], C. BIHANE[2], M. SDIKA[1], J.Y. BLAY[3], O. BEUF[1], F. PILLEUL[1,2]

1. CREATIS (CNRS UMR 5220, Inserm U1206, INSA-Lyon, UCBL Lyon 1)
2. Centre de lutte contre le cancer Léon Bérard, Department of Radiology
3. Centre de lutte contre le cancer Léon Bérard, Department of Oncology

Contact: benjamin.leporq2@gmail.com

Keywords: Liposarcomas, Lipomatous soft tissue tumors, MRI, Radiomic

Introduction: Among lipomatous soft tissue tumor, the noninvasive diagnosis between benign lipomas, borderline well differentiated liposarcomas (WDL)/atypical lipomatous tumors (ALT) and high grade subtype of liposarcomas is crucial since it directly drive the therapy strategy. Our aim is to develop a MRI-based radiomic method to classify between these three forms of tumors.

Methods: 105 subjects with lipomatous soft tissue tumors with histology and fat-suppressed T1w contrast enhanced MR images available were retrospectively enrolled to constitute the database. According to histology, 3 groups have been constituted: benign (including deep lipomas, n = 23); intermediate (including ALT and WDL, n = 41); and malignant (including high grade liposarcomas: myxoid, dedifferentiated, and pleomorphic, n = 41). MR images were obtained from 56 different centers with non-uniform protocols (3 fields: 1.0T, 1.5T, and 3.0T, with 18 different MR systems commercialized by 4 vendors). Images were automatically loaded on an in-house software and tumor was manually segmented by two observers blinded to histology to extract the radiome. The radiome included 87 features (size, shape, intensity distribution, image domain and frequency domain textures features). Radiomes were next mined with a supervised machine learning approach to build a decisional algorithm based on two radiomic models.

Results: To classify between benign and (intermediate + malignant) groups, the 12th order model gave the best performance (AUROC: 0.959; sensitivity: 89%; specificity: 95.7). To classify between intermediate and malignant groups the 17th order model gave the best diagnosis performances (AUROC: 0.907; sensitivity: 85.4%; specificity: 90.2%).

Conclusion: These results show that the evaluation of lipomatous tumor malignancy is feasible using a routinely used MRI acquisition in clinical practice. These encouraging results need to be further confirmed on another prospective or existing application cohort.

Poster # 28

Photoactivation of Iron Nanoparticles for the Improvement of Glioma Treatment

S REYMOND[1,2], P GIMENEZ[1, 2], M FLAENDER[1], R DELORME[6], C BISSARDON[1] , J-K KIM [4], S BOHIC[1, 3], J ARNAUD[5], R SERDUC[1] , J-L RAVANAT[2], H ELLEAUME[1]

1. Université Grenoble Alpes EA 7442 RSRM, Grenobe, France;
2. INAC/SCIB LAN CEA-Grenoble, France;
3. European Synchrotron Radiation Facility, Grenoble, France;
4. Catholic University of Daegu, Daegu City, Korea;
5. Centre Hospitalier Universitaire, Grenoble, France;
6. IMNC -Groupe Nouvelles Approches en Radiothérapie, Orsay, France

Contact: sreymond@esrf.fr

Keywords: nanoparticle, dose enhancement, radiotherapy

Rationale : An alternative approach for the improvement of radiotherapy consists in increasing differentially the radiation dose between tumors and normal tissues using nanoparticles (NPs) that have been beforehand internalized into the tumor. These high-Z NPs can be photo-activated by monochromatic synchrotron X-rays, leading to a local dose enhancement delivered to the neighbouring tumor cells. In this study, we evaluated the ability of iron NPs to act as radiosensitizers in vitro and through simulations.

Materials and Methods : The radiosensitizing effect of Fe NPs was assessed through Monte Carlo simulations (PENELOPE) and in vitro experiments: F98 tumor cells were incubated for 24h with Fe NPs before being irradiated at 30 keV, 51 keV or 80 keV. The cell survival was measured by clonogenicity and MTT assays. Subsequently, the iron intake after a 24h incubation with NPs was characterized using ICP-MS and the iron distribution was studied thanks to X-ray fluorescence microscopy.

Results : F98 are able to endocytose NPs: we measured ~20±4pg of internalized iron per cell (initial iron concentration: 0.06mg/mL in culture medium). The Fe NPs are located in vacuoles in the cytoplasm. The presence of Fe NPs in the cells caused a 1.6±0.4 enhancement of cell death with 30 keV irradiation (initial iron concentrations in culture medium 0.06 mg/mL).

Conclusion : F98 tumor cells were able to endocytose and retain Fe NPs in their cytoplasm, and a significative effect of the NPs was observed for a 30 keV irradiation. Our following studies will attempt to better characterize and optimize the radio-sensitizer properties of Fe NPs and shed light on another way to distribute them into the tumor site.

This work was supported by the LabEx PRIMES Lyon, France. We thank ESRF for the beamtime and technical support.

Poster # 29

Calcitriol-Loaded Nanoparticle Development for Cancer Therapy Applications

Sabrina NICOLAS[1], Eyad ALMOUAZEN[1], Lars Petter JORDHEIM[2], Hatem FESSI[1], Marie-Alexandrine BOLZINGER[1]

1. Univ Lyon, Université Claude Bernard Lyon 1, CNRS, LAGEP UMR 5007, F-69100, Villeurbanne, France
2. Univ Lyon, Université Claude Bernard Lyon 1, CRCL, UMR INSERM U1052, CNRS 5286, F-69000 Lyon, France

Contact: sabrina.nicolas@univ-lyon1.fr

Keywords: calcitriol, nanoparticles, vectorization, cancer

Calcitriol, the active metabolite of vitamin D3, plays a role in many types of cancer including breast and prostate cancer [1]. However, calcitriol anticancer activity requires supraphysiological doses associated with a high risk of hypercalcemia, which led to failure of clinical studies [2]. Vectorization could be an interesting strategy to avoid calcitriol calcemic side effects and extend its activity on cancer cells.

In this line, we prepared several biodegradable formulations using nanoprecipitation. By varying polymer:oil ratio, different formulations with a monodisperse size close to 200 nm, a high encapsulation efficiency of calcitriol (>70%) and various release profiles were obtained. The growth inhibitory efficiency of the calcitriol-loaded formulations was evaluated in vitro on human breast adenocarcinoma cells (MCF-7) using an MTT assay. Incubation for 24 hours with 10−6 M of calcitriol showed a significant difference at day 10 between free (100% cell viability) and encapsulated calcitriol (≥60% cell viability) which depends on the nanoparticles release profile. Preliminary in vivo toxicity assays were performed by administering calcitriol-loaded NP to mice. A good tolerance of treatment was found as the initial calcemia (10.5 mg/dL) was recovered at day 7, allowing repeated dose administration to go forward with in vivo efficacy evaluation of developed nanosystems.

In conclusion, calcitriol encapsulation enhances its antiproliferative activity in vitro. These findings will be investigated in vivo on a xenograft mouse model in order to confirm calcitriol vectorization benefit.

References

[1] Feldman, D., Krishnan, A.V., Swami, S., Giovannucci, E., Feldman, B.J., 2014. The role of vitamin D in reducing cancer risk and progression. Nature Reviews Cancer 14, 342–357.
[2] Woloszynska-Read, A., Johnson, C.S., Trump, D.L., 2011. Vitamin D and cancer: Clinical aspects. Best Practice & Research Clinical Endocrinology & Metabolism 25, 605–615.

Poster # 30

Development of New RF sensor for Early Diagnosis of Breast Cancer

Latifa FAKRI-BOUCHET, Abel RANGEL TREJO

Institut des Sciences Analytiques (ISA), Université de Lyon 1, UMR 5280, CNRS, F-69100 Villeurbanne, France
Contact: latifa.fakri-bouchet@insa-lyon.fr

Keywords: Breast cancer; Radio frequency sensor, microwave-sensing, microwave imaging.

Breast cancer is the most commonly diagnosed cancer among women [1] According to the American Cancer Society, approximately 252,710 breast cancer deaths are expected in 2017 in the United States [2].

An early diagnosis will increase the survival chance among patients and they will require less expensive treatment [3]. Many breast imaging techniques were been studied and are commonly used for diagnosing early-stage breast cancer, like Mammography, Contrast-enhanced (CE) digital mammography MRI, ultrasonography, PET, CT and biopsy. However all these techniques are expensive methods that require trained people and have respective limitations [4] that imply complementary investigation.

Over the past years, several Breast Cancer Non-Invasive Detection Techniques have been started to develop using different equipment and materials, confirming that one of the most efficient ones is Microwave Imaging (MI).

MI techniques can be grouped as passive and active approaches. Passive MI uses radiometry to measure the temperature differences between normal and malignant tissues Active one concerns microwave tomographic and radar-based MI. It measures the dielectric properties (DPs) contrast between healthy tissue and malignant tissue in the high-MHz to low-GHz regime. Active MI is an emerging mammography technique for diagnosing breast cancer.

Our project focuses on the development of the RF sensors, and more particularly on the development of the RF sensor array configuration that plays an important role in MI systems. Our RF sensor array system is chosen in order to improve resolution and to enhance the sensitivity and selectivity with new innovative and flexible microstrip antennas that might allow one of the first possible underwear-integrated, optimal signal, low cost, and easy-use prototypes.

[1] Mohebian, M.R. et al. Comput. Struct. Biotechnol. J. 2017.
[2] www.breastcancer.org
[3] Migowski, A.et al. Cienc. Saude Coletiva, 2015.
[4] Abel, E.J. et al. BJU Int. 2013.

Poster # 31

Pretargeted Imaging of Peritoneal Carcinomatosis Using Bioorthogonal Chemistry

A RONDON[1,3]*, N TY[1]*, J-B BEQUIGNAT[1], M QUINTANA[1], A BRIAT[1], T WITKOWSKI[1], B BOUCHON[1], C BOUCHEIX[2], E MIOT-NOIRAULT[1], J-P POUGET[3], J-M CHEZAL[1], I NAVARRO-TEULON[3], E MOREAU[1]*, F DEGOUL[1]*

1. Clermont Université, Université d'Auvergne, U1240 Imagerie Moléculaire et Stratégies Théranostiques, F-63000 Clermont Ferrand, France
2. Université Paris Sud, U935, Bâtiment Lavoisier, 14 Avenue Paul-Vaillant-Couturier, 94800 Villejuif
3. Institut de Recherche en Cancérologie (IRCM), U1194 – Université Montpellier – ICM, Radiobiology and Targeted Radiotherapy, 34298 Montpellier cedex 5

*Co-authors
Contact: francoise.degoul@inserm.fr

Keywords: Pretargeted Radioimmunotherapy, Bioorthogonal Chemistry, Peritoneal Carcinomatosis .

Aim: Bioorthogonal chemistry represents a challenging approach in pretargeted radioimmunotherapy (PRIT) based on fast, strong and biocompatible covalent interaction between trans-cyclooctene (TCO) conjugated antibodies (mAbs) and radiolabelled probes linked to tetrazine (TZ). However, both the number of TCO engrafted per mAb and the linker length between mAbs and TCO can influence the efficiency of PRIT. We thus studied the influence of the number of TCO conjugated per mAb and the effect of several PEGylated linkers in order to determine the optimal mAb-(PEG)n-TCO structure.

Methods: Two models of colorectal cancer were used, a subcutaneous model of colon (HT29) using Ts29.2 mAb specific for tetraspanin 8 (Maisonial et al., 2017) and an orthotopic peritoneal carcinomatosis model (A431-CEA-Luc) using mAb 35A7 targeting CEA (Boudousq et al., 2013). Different amount of TCO (0, 5, 10, 15, 20 and 30 equivalents) were incubated with mAbs, and the corresponding number of linked TCO quantified using MALDI-TOF MS. mAbs-(PEG)n-TCO functionality was evaluated in immunofluorescence assays. Three PEG lengths were compared (i.e. PEG0, PEG4 and PEG12) through in vitro and in vivo experiments using a fluorescent TZ probe.

Results: In vitro immunofluorescence showed that Ts29.2 and 35A7 labeling intensity is correlated with the number of TCO when using PEG0,12 while signals reach a maximum at 10 equivalents when using PEG4. Under 10 equivalents conditions, the capacity of resulting mAbs- PEG0,4,12 for antigen recognition is similar when reported per grafted TCO and comparable to mAbs without TCO. In vivo, on both models, pretargeting with mAbs- PEG4, PEG12 followed by TZ injection induced a fluorescent signal two times lower than with mAbs- PEG0.

Conclusion: These findings suggest that while PEG linkers allow a better accessibility for TCO grafting, it might decrease the number of reactive TCO. In conclusion, mAb-PEG0 represents the best candidate for PRIT.

Poster # 32

Mapping Drug Mechano-Sensitivity in Tumour Spheroids with Brillouin Light Scattering

Thomas DEHOUX[1], Jérémie MARGUERITAT[1], Angélique CARLOTTA[1], Hichem MERTANI[2], Alice BERTHELOT[1], Quentin MARTINET[1], Xavier DAGANY[1], Charlotte RIVIERE[1], Jean-Paul RIEU[1]

1. Univ Lyon, Université Claude Bernard Lyon 1, CNRS, Institut Lumière Matière, F-69622, Villeurbanne, France
2. Université de Lyon, Université Lyon 1, INSERM U1052, CNRS UMR 5286, Centre de Recherche en Cancérologie de Lyon, Centre Léon Bérard, Lyon, France

Contact: thomas.dehoux@univ-lyon1.fr

Keywords: cancer, mechanobiology

Aims and/or Background: Mechanical properties are key players in tumour physiology, but their exact role in growth, invasivity and response to drugs remains largely unknown due to the lack of characterisation techniques. Standard microscopy techniques are limited by the use of fluorophores or tags that alter normal cell functions. Most importantly, they provide a contrast that does not reveal mechanical properties. In this work we implement a novel quantitative, label-free microscopy technique based on Brillouin light scattering (BLS) to decipher the link between mechanical properties and drug efficacy.

Methods: Multicellular spheroids (MS) are an apt tumour model that recapitulate closely the complex mechanics of tumours and captures the spatial gradient distribution of mechanics and biological factors, and resistance to drug penetration. For demonstration, we monitored with BLS the mechanical properties of MS formed from a colorectal cancer cell line HCT116 during a 3-days chemotherapy with 5-fluorouracil (5-FU).

Results: We captured BLS maps with 10 µm resolution in the MS. Our images reveal a clear variation in the rigidity and viscosity from the outer rim to the core of the untreated MS. In addition, the mechanics across the centre of the spheroid during the 5-FU therapy show the radial action of the drug starting in the outer regions of the MS from the first day of exposure to reach the core in about 3 days.

Conclusion: Such results, which cannot be observed by any other existing modality, demonstrate the ability of BLS to image quantitatively drug efficacy on in vitro models using mechanical properties as the contrast mechanism, without tags, and with an unprecedented imaging depth in ~300-500 µm objects. Our approach should shed light on the link between mechanics, structure and biological functionality, thereby offering innovating solutions for the understanding and control of tumors and design of anti-cancer drugs.

Poster # 33

Multi-Scale Mechanical Characterization of Prostate Cancer Cell Lines: Relevant Biological Markers to Evaluate the Cell Metastatic Potential

J ZOUAOUI[1,4], A.M TRUNFIO-SFARGHIU[2], L BRIZUELA[1], A PIEDNOIR[3], O MANITI[1], B MUNTEANU[2], S MEBAREK[1], A GIRARD-EGROT[1], A LANDOULSI[4] and T GRANJON[1]

1. Univ Lyon, CNRS, Molecular and Supramolecular Chemistry and Biochemistry Institute ICBMS UMR 5246, F-69622 Lyon, France
2. Univ Lyon, INSA, Mechanics of Contacts and Structures Laboratory LaMCoS, UMR 5259, F-69621 Lyon, France
3. Univ Lyon, CNRS, Institut Lumière Matière IML UMR 5306, F-69622 Lyon, France
4. Laboratory of Biochemistry and Molecular Biology, FSB TUNISIA

Contact: thierry.granjon@univ-lyon1.fr

Keywords: cell mechanical characterization, cell membranes, membrane dynamics

Considering the importance of cellular mechanics in the birth and evolution of cancer towards increasingly aggressive stages, nano-mechanical properties of non-tumoral (WPMY-1) and highly aggressive metastatic (PC-3) prostate cell lines were compared both on cell aggregates, single cells, and membrane lipids.

Cell aggregate rheological properties were analyzed during dynamic compression stress performed on a homemade rheometer. Single cell visco-elasticity measurements were performed by Atomic Force Microscopy (AFM) using a cantilever with round tip on surface-attached cells, whereas at a molecular level, the lateral diffusion coefficient of total extracted lipids deposited as a Langmuir monolayer on an air-water interface was measured by Fluorescence Recovery After Photobleaching (FRAP).

At cellular pellet scale, and at single cell scale, PC-3 cells were less stiff, less viscous, and thus more prone to deformation than the WPMY-1 control. Interestingly, stress-relaxation curves obtained by AFM indicated a two-step response, which we attributed to a differential response coming from two cell elements, successively stressed, namely plasma membrane and actin cytoskeleton. Both responses are faster for PC-3 cells. At a molecular scale, the dynamics of the PC-3 lipid extracts are also faster than that of WPMY-1 lipid extracts.

As the evolution of cancer towards increasingly aggressive stages is accompanied by alterations both in membrane composition and in cytoskeleton dynamical properties, we attribute differences in visco-elasticity between PC-3 and WPMY-1 cells to modifications of both elements. A decrease in stiffness and a less viscous behavior may be one of the diverse mechanisms that cancer cells adopt to cope with the various physiological conditions that they encounter.

Poster # 34

Infiltrative Glioma Detected by Fast Field Cycling NMR: A Nuclear Magnetic Resonance Technology of Low and Variable Magnetic Fields

Manuel PETIT, Sandra PIERRE, Maxime LECLERCQ, François BERGER and Hana LAHRECH

BrainTech Lab - INSERM U1025 – Grenoble, France
Contact: hana.lahrech@univ-grenoble-alpes.fr

Keywords: Fast-Field-Cycling NMR, T1-dispersion curve, glioma models, glioma cell infiltration, power model, quadrupolar peaks

Purpose: Fast Field Cycling Nuclear Magnetic Resonance (FFC-NMR), which measures relaxation times T1 at different magnetic fields (T1-dispersion profiles) in low regime (0.1mT-1T) is used in physics and chemistry to characterize the molecular dynamics of materials. Here our aim is to highlight the role of FFC-NMR in detecting glioma cell infiltration in brain tissue. Using mathematical models, we aim to find how the numerical parameters derived either from T1-dispersion profiles or from quadrupolar peaks that result from the nuclei interactions of 14N-1H (i.e. from proteins and water) could be exploited as biomarkers in glioma.

Subjects and Methods: 3 mouse models of glioma were studied: U87, a solid glioma model and Glio6 and the Glio96 a tumour cell migration/invasion models. T1-dispersion profiles of biopsy samples were acquired on a Stelar FFC-NMR relaxometer at CEA Grenoble and were analyzed using two mathematical models: the power model giving information on molecular dynamics and the QP model related to the immobilized protein content.

Result: T1-dispersion profiles of Glio6 and Glio96 were well separated from those of U87. The curves showed a power-law shapes ($R>0.98$) indicating dominant relaxation by protein matrix. Parameters of the power model and of QPs amplitude were found to discriminate between solid and infiltrative glioma. Using Kruskal–Wallis test, the amplitude and the slope at low field were found the most discriminant parameters.

Conclusion/Discussion: Peritumoural regions invaded by infiltrative glioma cells are not early diagnosed by MRI. This study highlights the interest of FFC-NMR in cancer to exploit molecular dynamics that are not visible by any other methods. These results were also observed in human resection and highlight the interest to develop FFC-MRI for clinical investigations, an European H2020 project (IDentIFY: Improving Diagnosis by Fast Field Cycling MRI) which is under progress.

Poster # 35

In Vivo and Ex Vivo Multimodal Imaging Tracking of Gold Quantum Clusters for Cancer Applications

Xavier LE GUEVEL[1]*, Danjin SHEN[1], Vincent MOTTO-ROS[2], Estelle PORRET[1], Véronique JOSSERAND[1], Lucie SANCEY[1], Jean-Luc COLL[1]

1. Cancer Targets & Experimental Therapeutics, Institute for Advanced Biosciences, University of Grenoble Alpes (UGA)/INSERM-U1209/CNRS-UMR 5309-38000 Grenoble, France
2. Institut lumière matière, UMR5306, Université Claude Bernard Lyon1-CNRS, University Lyon 69622 Villeurbanne cedex, France

Contact: xavier.le-guevel@univ-grenoble-alpes.fr

Keywords: metal nanoclusters; multimodal imaging; cancer

Gold quantum clusters (Au NCs) are an emerging class of nanoparticles with size smaller than 5 nm filling the gap between the molecules and the plasmonic nanoparticles. In this sub-size regime, these species exhibit molecular-like properties with photoluminescence signal in the red-near infrared region enabling in vivo monitoring. Recent studies have shown the strong influence of Au NC size and nature of the ligand stabilizing the metal core to the pharmacokinetics and the tumor accumulation of these particles in mice[1]. For instance, it was demonstrated that Au NCs exhibit renal clearance but with passive tumor uptake higher than small molecules such as IR800Cw[2].

In this context, Au NCs were synthesized using two different small zwitterionic molecules: glutathione (Au NCs-GSH) or thioctic sulfobetaine (Au NCs-Zw). Thanks to their photoluminescence properties and high electronic density, we could track these Au NCs using a wide library of imaging technics in animal models. Studies performed in nude mice demonstrated the pivotal role of the ligand to tune the half-life of Au NCs at 2 min and 6.5 min using GSH and Zw respectively keeping a relatively high renal clearance[3]. Studies on glioblastoma model suggested a high passive uptake and retention of Au NCs-Zw in the periphery of the tumor while no significant accumulation in the reticuloendothelial system had been observed.

References

[1] a) B. Du, X. Jiang, A. Das, Q. Zhou, M. Yu, R. Jin, J. Zheng, Nature Nanotechnology 2017, 12, 1096; b) X. D. Zhang, Z. Luo, J. Chen, X. Shen, S. Song, Y. Sun, S. Fan, F. Fan, D. T. Leong, J. Xie, Advanced Materials 2014, 26, 4565.

[2] J. Liu, M. Yu, C. Zhou, S. Yang, X. Ning, J. Zheng, Journal of the American Chemical Society 2013, 135, 4978.

[3] D. Shen, M. Henry, V. Trouillet, C. Comby-Zerbino, F. Bertorelle, L. Sancey, R. Antoine, J. L. Coll, V. Josserand, X. Le Guével, APL Materials 2017, 5, 053404.

Poster # 36

Evaluation of the Efficacy of 5FU-Loaded Lipid Nanoparticles Using 2D and 3D In Vitro Models

G LOLLO[1], K MATHA[2], T DEHOUX[3], A CARLOTTA[3], J-P RIEU[3], S BRIANÇON[1] and J-P BENOIT[2]

1. Univ Lyon, Université Claude Bernard Lyon 1, CNRS, LAGEP UMR 5007, Villeurbanne, France
2. MINT, Université d'Angers, INSERM U1066, CNRS UMR 6021, Angers F-49933, France
3. Univ Lyon, Université Claude Bernard Lyon 1, CNRS, Institut Lumière Matière, Villeurbanne, France

Contact: giovanna.lollo@univ-lyon1.fr

Keywords: Nanotechnology, 2D cell culture, 3D MultiCellular Tumor Spheroids (MCTS), anticancer treatment 5FU

Nanomedicines have raised extensive interest as promising drug-delivery systems for cancer treatment. To demonstrate the efficacy of drug-loaded nanosystems relevant in vitro models, well representative of the human disease and good predictors of the therapeutic response in patients, need to be developed. The first step towards this process is the in vitro testing on 2D cell culture. 2D cell culture does not show the structural architecture of tumor tissues and lack of the complex physiology of the real tumor tissues. Recently, 3D models based on spheroids have been developed as a powerful in vitro model that mimic solid tumors. These three-dimensional tumor models have been used to assess the diffusion, distribution and drug efficacy of nanotherapeutics. In this work, we developed lipid nanocapsules (LNC) loaded with a modified 5FU derivative (5FUC12) and we tested their effect on tumor cell viability using 2D and 3D derived from HCT116 cell line. Blank and 5FUC12-loaded-LNC showed an average size of 60nm, a neutral surface charge and a high drug encapsulation efficiency. In a 2D model, we evaluate the cell viability using the resazurine test. After 24h of incubation, we found that 5FUC12-loaded-LNC exerted a toxic effect at a lower doses (5 µM) in comparison with 5FU alone or 5FUC12 (15µM and 20µM respectively). Blank LNC also showed an important toxicity at a concentration above 1.3mg/ml. Then, we prepared MultiCellular Tumor Spheroids and we used the epifluorescence microscopies techniques to measure their volume as a readout of toxicity. As in the case of the 2D model, blank LNC were toxic only at high concentration above 1.3mg/ml. While, loaded LNC, 5FU or 5FUC12 were able to reduce the volume of the spheroids at lower drug doses (2µM) showing a similar anticancer activity. This first set of experiment will allow us to set up the parameters in order to study tumor penetration capacity of nanosystems for generating predictive results for in vivo evaluation.

Poster # 37

Evaluation of Self-Assembled Nanogels Containing Boron for Tumor Imaging and Therapy

L SANCEY*, R POIROT[#], B BUSSER*, F GARCIA[#], R AUZELY-VELTY[#], J-L COLL*

* IAB INSERM U1209 CNRS UMR5309 UAG - Grenoble
# CERMAV - Grenoble
Contact: lucie.sancey@univ-grenoble-alpes.fr

Keywords: AB-NCT, innovative radiotherapy, nanomedicine, vectorization

Biopolymers made of hyaluronic acid (HA) are interesting for tumor targeting and delivery of anti-cancer drugs. Such nanostructures might be used for optimization of accelerator based-neutron capture therapy (AB-NCT), an emerging radiotherapeutic modality, due to their efficient tumor-targeting. We investigated the properties of innovative nanogels based on self-assembly of HA derivatives for efficient tumor targeting.

The biological behavior and tumor-targeting properties of the native and boron-rich nanogels were determined using optical imaging for cell expressing low (TS/A-pc cells) and high-levels of CD44 (HeLa cells), the natural receptor of the HA. The tumor-to-liver ratios were quantified and compared to the one of the native HA, labeled with Cy5.5, until 48 hours post injection. Cell internalization was evaluated and AB-NCT was performed at the iLL facility. In vivo, the precise distribution of boron was determined using laser-induced breakdown spectrometry.

In vitro, the nanogels were efficiently internalized, independently of the CD44 status. After IV injection, the nanogels circulated in the bloodstream, were eliminated through the liver, and strongly accumulated into the tumor tissues. The tumor targeting was not driven by the CD44 expression, but rather relies on the passive enhanced permeability and retention (EPR) effect. The tumor-to-muscle ratios were determined for both tumor types. For TS/A-pc, this ratio reached 25-30 at 24 to 48 hr pi, respectively. After incorporation of boron into the nanogel, the cell internalization was still highly efficient, leading to efficient cell death after AB-NCT.

The incorporation of boron into the nanogel allowed the vectorization boron-atoms into the tumor sites. LIBS allowed to localize the boron into different organs, including the tumor. Promising in vitro results of AB-NCT were obtained and are encouraging for the next experiments of therapy in mice.

Poster # 38

Development of FACS-Based High Throughput RNAi Screening to Identify New Therapeutic Targets in Cancer

Eric SULPICE[1], Sylvain PAUTET[1], Stéphanie COMBE[1], Frédérique MITTLER[1], Nadendla SANDEEP KUMAR[1], Jonathan BRUNIAUX[1], Fabrice NAVARRO[2], Xavier GIDROL[1]

1. Univ. Grenoble Alpes, CEA, INSERM 1038 – BIG-BGE-Biomics, 38000 Grenoble, France
2. CEA-LETI - DTBS - LBAM, 38000 Grenoble, France

Contact: eric.sulpice@cea.fr

Keywords: functional genomics, RNAi, cancer, FACS screening, therapeutic target, next generation sequencing, nanovector

Several recent studies have highlighted the power of large scale RNAi screening approaches to characterize the clinical relevance of specific genes to fight cancer progression. The potential to identify new therapeutic targets in cancer now at reach through advances in high throughput and high content RNAi screens. The RNAi microarrays/microtiter plate we routinely manufacture is certainly one way to perform it, and we have recently demonstrated the potential of these screening tools in prostate cancer. However, this screening methods suffer several limitations. First, with these formats it remains difficult to screen suspensions cells and/or human 3D cell cultures. Second, tracing of transfected cells without any modification of the RNAi compounds remains difficult. Third, these formats are very demanding in automatic image analysis capacities. Fourth, we are unable to recover cells after screening. As consequence, new technological development that would circumvent these limitations would be extremely valuable. We propose to take advantages of the recent progress in next generation sequencing (NGS) and nanoparticles design to develop a new technological platform for large scale functional genomic and new therapeutic target discovery in cancer that will overcome most of the limitations mentioned above.

Our pipeline includes massively parallel transfection using a lipid nanovector named Lipidots® that can mediate simultaneous delivery at the same site, two independent nucleic acid molecules, a siRNA and a specific DNA barcode, along with a fluorescent tagging of the transfected cells. After transfection cell are pooled, labelled in the same tube then sorted by FACS using two parameters, the presence of the fluorophore carried by the nanoparticles, and the phenotype of interest. Putative hits are identified by Lipidots® code deconvolution using NGS of barcode present in sorted cells leading to identification of the siRNA at the origin of the phenotype of interest.

Poster # 39

Use of LC-MS Multiplex mAbs Analysis in Drug Development

Quentin ENJALBERT, Chloé BARDET, Tanguy FORTIN

ANAQUANT
Contact: quentin.enjalbert@anaquant.com

Keywords: mAbs, drug development, LC-MS

Through the different development phase of new Biologics, quantitative analysis of mAbs in biological fluids is mainly conducted with ligand binding assays (LBAs). Ligand-binding-assays (LBAs), such as ELISA, offer a high degree of specificity, sensitivity and throughput. However, for pre-clinical phase, when dozens of putative new biologics are studied, specific and dedicated LBAs suffer from lengthy assay development. They also can be affected by matrix effect and are antibody dependent with poor multiplexing possibility. Over the past 10 years, Liquid chromatography-mass spectrometry coupling in Selected Reaction monitoring mode (LC-MS-SRM assays) have increased capacity and selectivity compared with LBAs. LC-MS-SRM is conducted to support data collection during pharmacokinetic (PK), pharmacodynamics (PD) or toxicokinetic(TK) studies.

Meanwhile, R&D strategies and development phases have to be performed with limited cost and time. Thus, one approach would consist in co-injecting several putative biologics within rodents and then comparing their PK properties in rodent-based triage study, with the objective to limit the number rodent animals used for the study.

In this study, we investigate, as proof of concept, the use of a highly specific method for the multiplexed quantitation of 6 FDA and EMA approved mAbs within a 20 min analysis directly in total serum. We reach sub 1 µg/mL on LOQ for the 6 mAbs.

Environment, Nutrition and Epidemiology

Poster # 40

Prise en charge en activité physique adaptée pendant et après un cancer du sein par l'apport des objets connectés et de l'éducation thérapeutique : étude DISCO

Baptiste FOURNIER[1], Marina TOUILLAUD[1,2], Olivia PEROL[1], Lidia DELRIEU[1,3], Aurélia MAIRE[1], Magali HUREAU[1], Lionel PERRIER[1,4], Marie PREAU[5] et Béatrice FERVERS[1,2]

1. Centre Léon Bérard
2. Centre de Recherche en Cancérologie de Lyon UMR INSERM 1052 CNRS 5286 CLB
3. Université de Lyon-Laboratoire Interuniversitaire de Biologie de la Motricité EA 7424 UFR STAPS
4. Université de Lyon Groupe d'Analyse et de Théorie Economique UMR CNRS 5824
5. Université Lumière Lyon 2 Laboratoire GRePS EA4163 Institut de Psychologie

Contact : baptiste.fournier@lyon.unicancer.fr

Mots clés : Cancer du sein, prévention tertiaire, activité physique, sédentarité, objets connectés, éducation thérapeutique

Contexte et objectifs : Chez les femmes atteintes de cancer du sein, la mise en place d'une activité physique (AP) n'est pas systématique dans le parcours de soins, malgré ses nombreux bénéfices démontrés sur la fatigue, la qualité de vie et possiblement la survie. L'étude DISCO propose de tester l'efficacité d'un dispositif connecté et d'un programme d'éducation thérapeutique du patient (ETP) comme prises en charge en AP pendant 6 mois, dans le but d'atteindre les recommandations internationales en termes d'AP.

Méthodes : Cette étude d'intervention, contrôlée, randomisée, multicentrique sera menée auprès de 432 femmes traitées pour un cancer du sein localisé. Elles seront randomisées dans quatre bras d'effectifs égaux, bénéficiant respectivement d'un dispositif connecté (bracelet, application et site internet permettant grâce à un algorithme de proposer un programme d'AP adaptée à réaliser en autonomie), d'un programme d'ETP, des deux modalités combinées et d'une prise en charge standard (bilan et recommandations d'AP). Des évaluations seront réalisées à l'inclusion, 6 mois puis 12 mois sur le niveau d'AP et des critères physiques, cliniques, psychologiques et biologiques. L'impact médico-économique des programmes par rapport aux bénéfices qu'ils apportent et l'acceptabilité et la perception du bracelet connecté seront également évalués.

Résultats : Une enquête préliminaire réalisée auprès de 102 femmes traitées pour un cancer du sein localisé a montré la bonne acceptabilité de l'étude (66%), du bracelet connecté (73%) et de l'ETP (77%) par les patientes et leur grande motivation pour l'AP (64%). Les résultats de l'étude principale sont attendus dans 3 ans.

Conclusions : Les retombées sont d'identifier de nouvelles modalités pour intégrer l'AP dans la vie quotidienne des patientes pendant et après les traitements du cancer du sein. Les enjeux sont de promouvoir l'intégration systématique de l'AP dans le parcours de soins des patients atteints de cancer en France.

Poster # 41

Les cancers digestifs dans la wilaya d'Annaba - Données du registre du cancer 2014-2015

S BOUZBID[a], N ARABAOUI[b], H MARDACI[b], H DJEDI[c], F YASSI[d]

a) Registre du cancer d'Annaba, Centre de Lutte Contre le Cancer - CHU d'Annaba
b) Service de chirurgie viscérale – CHU Annaba
c) Service d'oncologie médicale, Centre de Lutte Contre le Cancer - CHU d'Annaba
d) Service d'anatomie et de cytologie pathologique , Centre de Lutte Contre le Cancer - CHU d'Annaba

Contact : bouzbidsabiha@gmail.com

Mots clés : cancer- colon- digestif- incidence-Algérie

Objectif : Déterminer l'incidence de cancers digestifs dans la wilayas d'Annaba.
Décrire les caractéristiques démographiques et pathologiques par type de cancer.

Matériel et **Méthode** : Les données ont été extraites du registre du cancer de la wilaya d'Annaba pour la période 2014-2015. Annaba compte plus de 650 000 habitants.
Les localisations retenues étaient selon la CIM-O3 de C15 à C26.

Résultats : Parmi 1743 de nouveaux cas de cancers qui sont survenus pendant la période 2014-2015, 396 des cas étaient des cancers de l'appareil digestif avec les lymphomes inclus, soit une incidence annuelle brute de 29,3 cas pour 100000 habitants.
Le cancer du colon-rectum représente plus de 50% des cancers de l'appareil digestif avec une incidence brute de 15,8 cas pour 100000 habitants et respectivement chez l'homme et chez la femme une incidence de 14,1 cas pour 105 hommes (3ème position) et de 16,3 pour 105 femmes (2 ème position). La moyenne d'âge est de 60 ±14 ans et l'adénocarcinome type intestinal représente 52% des tumeurs.
Le cancer de l'estomac occupe la 2 ème position des cancers de l'appareil digestif avec une proportion de 22,5% et une incidence brute de 6,6 cas pour 105 habitants et respectivement chez l'homme et chez la femme une incidence de 3,5 cas pour 105 hommes et de 3,0 pour 105 femmes. La moyenne d'âge est de 59 ±14 ans.
Le cancer de la vésicule biliaire représente 8,9% de l'ensemble des cancers avec 35 nouveaux cas, le cancer du foie 6% des cas et le pancréas 5% des cas.
Conclusion: Les cancers digestifs sont relativement fréquents en Algérie.

Poster # 42

Survival of Childhood Cancer in a Paediatric Ward

Sabiha BOUZBID[1,2], Zoubaida OUALIA[3], Wided BOUTABIA[2,3], Nadira BOUCHAIR[2,3]

1. Cancer registry of Annaba- University Hospital of Annaba
2. Annaba BADJI Mokhtar University – Faculty of medicine
3. Paediatric ward - University Hospital of Annaba

Contact: bouzbid_sabiha@yahoo.fr

Keywords: child- cancer - survival - Africa

Objective: To determine the survival ofchildhood cancer in a paediatric ward in Algeria.

Material and Methods: All cancer cases admitted in paediatric ward of University Hospital of Annaba, in the period between 2014 and 2017 were included.
The tumors were classified according to the third edition of the International Classification of Childhood Cancer (ICCC-3)
Survival overall and specific rates (according cancer group and age groups) were calculated using Kaplan Meier method.

Results: Among 272 cancer cases included, 56% were boys and 44% were girls.
The main cancer groups were: leukemia (36.8%), lymphoma (14.7%), central nervous system tumors (13.6%), nephroblastoma (11.8%), bone tumors (5.9%), sympathetic nervous system tumors (5.1%), soft-tissue sarcomas (5.1%) and others 6.0 %.
The Median survival of overall cancers was 2.7 ± 0.5 years**.** According the sex, it was 2.7 ± 0.5 years for girls and 2.3 ± 0.6 years for boys ($p > 0.05$).
According age groups: the median survival was better for children aging more 2 years old (3.0 ± 0.5 years) compared to children less than 2 years old (1.4 ± 0.6 years) and $p < 0.05$
The median survival of leukemia was 3.0 ± 0,6 years, of lymphoma was 5.9 ± 0.00 years and 1.8 ± 0.0 years for central nervous system tumors. For nephroblastoma 56.7% of cases were in live until 2 years.

Conclusion: More efforts have to be done for improving the survival rates.

Poster # 43

Nonsteroidal Anti-Inflammatory Drug Use and Breast Cancer Risk in a Prospective Cohort Study

Manon CAIRAT, Agnès FOURNIER, Neil MURPHY, Carine BIESSY, Augustin SCALBERT, Sabina RINALDI, Marc J. GUNTER, Laure DOSSUS, on behalf of EPIC

Nutrition and Metabolism Section, International Agency for Research on Cancer
Contact: cairatm@students.iarc.fr

Keywords: Breast cancer, nonsteroidal anti-inflammatory agents, chemoprevention, cohort studies, postmenopausal hormone replacement therapy

Inverse associations between nonsteroidal anti-inflammatory drugs (NSAIDs) use and breast cancer risk have been reported in most case-control studies, but results from cohort studies are less consistent. Our objective was to assess the association between NSAID use and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC).

EPIC is a prospective cohort study initiated in 1992 in 10 European countries. Self-reported information on NSAID use at baseline has been collected in five EPIC countries. Multivariable Cox regression models were used to estimate hazard ratios (HRs) for the association of NSAID use with breast cancer incidence with adjustment for potential confounders. We also assessed effect modification by breast cancer risk factors and examined the associations within specific breast cancer subtypes.

Among the 140,981 women included in the analysis, 7% were regularly using NSAIDs at baseline. During a median follow-up time period of 13 years, 7,379 incident breast cancer cases were diagnosed (816 in situ and 6,563 invasive). There were no statistically significant associations between NSAID use and breast cancer risk, overall and by subtypes. However, a statistically significant interaction was observed between NSAID use and ever use of menopausal hormonal therapy (MHT) among postmenopausal women for invasive breast cancers [among MHT ever users: HRNSAID use = 0.84 (0.73 – 0.96); among MHT never users: HRNSAID use = 1.08 (0.93 – 1.25); Pinteraction= 0.05].

Our results indicate potential effect modification of MHT use on the association between use of NSAIDs and breast cancer risk which deserves in-depth investigation in studies with accurate data on both NSAID and MHT use, including type, dosage, frequency and duration of use. We are currently exploring this further in a study within the French-EPIC cohort (E3N cohort) including 61,107 women with individual drug-reimbursement data available from years 2004 .

Poster # 44

Development and Performance Evaluation of a GIS-Based Metric to Assess Exposure to Airborne Pollutant Emissions from Industrial Sources

T. COUDON[1,2], A. DANJOU[1], E. FAURE[1], D. PRAUD[1], FR. MANCINI[3], G.SEVERI[3], P. SALIZZONI[4], B. FERVERS[1,2]

1. Département Cancer & Environnement, Centre Léon Bérard, Lyon, 69008, France
2. Université Claude Bernard Lyon 1, Villeurbanne 69100, France
3. Centre de Recherche en Épidémiologie et Santé des Populations (CESP, Inserm U1018), Facultés de Medicine, Université Paris-Saclay, UPS, UVSQ, Gustave Roussy, Villejuif, France.
4. Laboratory of Fluid Mechanics and Acoustics, Ecole Centrale de Lyon, Ecully 69134, France

Contact: thomas.coudon@lyon.unicancer.fr

Keywords: dioxin, cadmium, breast cancer, exposure assessement, GIS, industrial emissions

Few studies have investigated the effect of airborne exposure to dioxins and cadmium on breast cancer risk and overall results are inconclusive. The multiplicity of exposure sources and the latency between exposure and cancer occurrence require to precisely characterize the spatial-temporal variability of exposures over large areas and long time-periods.

This study aimed to develop and assess the performance of an exposure metric based on a Geographic Information System (GIS) through comparison with a dispersion model to estimate historical (1990-2008) dioxin and cadmium exposures.

We carried out a detailed retrospective inventory of dioxin and cadmium emitting sources from 1990 to 2008, and estimated annual dioxin and cadmium emissions. The location of each facility was precisely geocoded and together with the emission estimates used as input data for the GIS based metric.

We identified relevant parameters to be included into the GIS based metric: emissions' intensity and location, subject's residence-to-source distance, wind direction and speed, exhaust smoke velocity and stack height. To identify the most relevant combination of parameters, we compared agreement of categorical dioxin exposure classification of study subjects, between the GIS based metric and a referent dispersion model (SIRANE) in 3 selected areas (rural, urban and urban-costal).

Between 1990 and 2008, we inventoried and estimated emissions of respectively 2620 and 2700 sources of dioxins and cadmium, respectively. The agreement between the final GIS-based metric and the dispersion model for dioxin and cadmium exposure varied from "substantial" to "almost perfect": median $w\kappa$ =0.78 (1st quintile=0.72, 3rd quintile =0.82) and median R^2 =0.82 (1st quintile= 0.71, 3rd quintile=0.87).

This metric was used to estimate historical dioxin and cadmium exposure in an epidemiological study on breast cancer risk and may be able to assess exposure to other air pollutants (i.e. heavy metals, PM10 etc.).

Poster # 45

Anthropometry and Risk of Breast Cancer Among Premenopausal Women in Latin America: Results from the PRECAMA Study

Mathilde HIS[1], Carine BIESSY[1], Gabriela TORRES-MEJIA[2], Gloria Inés SANCHEZ[3], Carolina PORRAS[4], Maria Luisa GARMENDIA[5], Magali OLIVIER[6], Peggy PORTER[7], Isabelle ROMIEU[1], Sabina RINALDI[1], on behalf of the PRECAMA team

1. Section of Nutrition and Metabolism, International Agency for Research on Cancer, Lyon, France
2. Centre for Population Health Research, National Institute of Public Health, Cuernavaca, Mexico
3. Group Infection and Cancer, School of Medicine, University of Antioquia, Medellín, Colombia
4. Agencia Costarricense de Investigaciones Biomédicas (ACIB)-Fundación INCIENSA, Costa Rica
5. Instituto de Nutrición y de Tecnología de los Alimentos, Santiago, Chile
6. Molecular Mechanisms and Biomarkers Group, Section of Mechanisms of Carcinogenesis, International Agency for Research on Cancer, Lyon, France
7. Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, USA

Contact: hism@fellows.iarc.fr

Keywords: Anthropometry, breast cancer, Latin America, premenopausal

Objective: Premenopausal breast cancer risk has been associated with greater height and inversely associated with excess adiposity in many studies conducted among Western populations. However, data are scarce on Hispanic populations, in particular in Latin America. We investigated the associations between excess adiposity and risk of breast cancer among premenopausal Latin American (LA) women from the PRECAMA study.

Methods: PRECAMA is an on-going multicentric population-based case-control study conducted in premenopausal women from four LA countries: Chile, Colombia, Costa Rica, and Mexico. Women aged 20 to 44 years are recruited. Cases are women diagnosed with first primary invasive breast cancer, recruited before any treatment. Population-based controls are matched to cases on age, area of residence and health institution. Anthropometric measurements were performed by medical staff according to standardized protocols, and lifestyle data were collected. Height, weight, BMI, waist and hip circumferences, and their ratios were categorized into tertiles and analyzed using multivariate conditional logistic regression models adjusted for potential confounders.

Results: Preliminary analyses on 283 cases and matched controls showed no difference in height (average of 1.58 m in cases vs 1.57 m in controls). Average BMI was 26.9 kg/m2 in cases and 29.1 kg/m2 in controls. Adjusted odds ratios (OR) showed a linear inverse association between BMI and breast cancer risk (OR T2 vs T1=0.65; 95% confidence interval (CI)=0.39-1.09; OR T3 vs T1=0.38; 95% CI=0.21-0.68; p-trend less than 0.01). No association was reported with height or any other anthropometric index.

Conclusions: In this population of LA women, BMI was the only anthropometric factor inversely associated with risk of premenopausal breast cancer, and no association was observed with height. These results suggest that risk factors for breast cancer may differ from those in other populations.

Poster # 46

Evaluate the Link Between Biomarker of Endogenous Lipogenesis, DNA Methylation Patterns and Breast Cancer in EPIC

Flavie PERRIER[1], Pietro FERRARI[1], Vivian VIALLON[1], Akram GHANTOUS[2], Zdenko HERCEG[2], Isabelle ROMIEU[3] and Véronique CHAJES[3]

1. Nutritional Methodology and Biostatistics group, International Agency for Research on Cancer (IARC)
2. Epigenetics group, IARC
3. Nutritional epidemiology group, IARC

Contact: PerrierF@students.iarc.fr

Keywords: fatty acids, epigenetic, breast cancer, DMRs analysis, EPIC

Background: There is increasing epidemiological evidence showing that increased circulating plasma palmitoleic acid to palmitic acid ratio (DI16), as a marker of endogenous synthesis of monounsaturated fatty acids (MUFA), is associated with increased risk of breast cancer (BC). Among potential mechanisms, increased endogenous synthesis of MUFA may alter the epigenome. In this work the relationship between DI16, DNA methylation patterns and BC risk was assessed in the European Prospective Investigation into Cancer and nutrition (EPIC) study.

Methods: 451 incident invasive BC cases and as many matched controls were analysed as part of a nested case-control study on BC within the EPIC cohort. Genome-wide DNA profiling in white blood cells was measured among cancer free women on about 450,000 CpG sites. DI16 was quantified in prediagnostic plasma phospholipids for a sub-sample of 270 matched pairs. Differentially methylated regions (DMRs) analysis was conducted to identify epigenetics regions modulated by DI16. Principal component analysis (PCA) was applied to summarize DMRs information. Conditional logistic regression was then conducted to assess the impact of first PCA scores on BC risk.

Results: DI16 was significantly associated to changes in methylation levels in 16 DMRs. A third of these regions where localized into a gene body region. The second most significant DMRs was associated with a decrease of methylation levels in 6 CpGs (minimum q-value: 0.0003, maximum coefficient: -0.033). This DMR was associated with the MAP3K6 gene, which may play a crucial role in both angiogenesis and tumorigenesis. The two first PCA components of this DMR explained respectively 80% and 9% of the information. The second component was found significantly associated with a decreased of BC risk (OR=0.96, p-value=0.04).

Conclusion: Our findings suggest that an increased endogenous synthesis of MUFA may be associated with increased risk of BC through changes in methylation of MAP3K6.

Poster # 47

Association Between Serum Phospholipid Fatty Acid Levels and Adiposity in Lebanon

Sahar YAMMINE[1*], Patricia MOGHAMES [2*], Carine BIESSY[1], Farah NAJA[2§], Lara NASREDDINE[2§], Véronique CHAJES[1§]

1. International Agency for Research on Cancer - Nutritional Epidemiology group, Lyon, France
2. American University of Beirut, Lebanon

*,§: Equal co
Contact: yammines@students.iarc.fr

Keywords: nutrition, fatty acids, obesity, epidemiology, low-to-middle income countries.

Objective: Alarming increases in obesity prevalence in Lebanon have been reported the last decades. Fatty acids have been postulated to influence obesity, but few epidemiological studies addressing this hypothesis have been conducted. The aim of this study is to investigate the correlation between serum phospholipid fatty acid levels and indicators of obesity in Lebanese adults in Greater Beirut area.

Methods: A cross sectional study was designed within a cohort of 501 Lebanese adults. A total of 395 available serum samples (129 men, 266 women) were profiled for phospholipid fatty acid composition using a state-of-the-art lipidomic platform at the international Agency for Research on Cancer. Fatty acids were expressed as percent of total fatty acids. Spearman correlation coefficients adjusted for relevant confounders and corrected for multiple testing were calculated to determine the strength of the association between serum fatty acids, desaturation indices (DI as biomarkers of endogenous lipogenesis) and indicators of adiposity (Body Mass Index, and waist). Analyses were performed separately in men and women.

Results: BMI was significantly positively correlated with total saturated fatty acids in both men ($r=0.40$, $p=6.78\times10^{-6}$, $q=2.00\times10^{-4}$) and women ($r=0.33$, $p=4.37\times10^{-8}$, $q=1.3\times10^{-6}$). BMI was significantly positively correlated with monounsaturated fatty acid palmitoleic acid ($r= 0.15$, $p=0.01$, $q=0.03$) as well as with the ratio of palmitoleic to palmitic acid or DI16 ($r=0.13$, $p=0.03$, $q= 0.07$) in women only. No significant correlation was found with polyunsaturated fatty acids.

Conclusion: This study suggests that a high intake of dietary saturated fatty acids, as well as increased endogenous synthesis of palmitoleic acid, may increase adiposity in the study population. These data need to be replicated in epidemiological settings, and the causality of these associations needs to be explored in experimental settings.

Poster # 48

A GIS-Based Method to Define Geographical Determinants of Environmental Exposure to Agricultural Pesticides in France

E FAURE[1], R BERANGER[2], J BLAIN[1], J CHUZ[3], B FERVERS[1]

1. Cancer and Environment Department, Centre Léon Bérard, Lyon, France
2. INSERM UMR S1085, Team 9, Rennes France
3. Environment and Radiation Unit, IARC, Lyon, France

Contact: elodie.faure@lyon.unicancer.fr

Keywords: GIS, Epidemiology, Exposure assessment

Exposure to pesticides has been suggested as a risk factor for several diseases. The use of Geographic Information Systems (GIS) in epidemiological studies to assess environmental exposure to agricultural pesticides (EEAP) is growing. US studies have reported a positive correlation between crop acreage and contamination of indoor dust by agricultural pesticides. Residential proximity is used as a surrogate of EEAP. In France, by using public data allows to describe the relationship between the proximity of agricultural areas and EEAP. We aimed to assess geographical determinants of the indoor dust contamination by agricultural pesticides (SIGEXPO).

A GIS was developed for 239 residences, from 3 different agricultural areas. For each household, GIS consider the agricultural land use, proximity of household to agricultural crops and 2 new dimensions that influence presticide drift : winds direction and obstacles (vegetal, structural or topographic barriers) for 5 buffer sizes. In parallel, both recent (6 months) indoor dust samples were collected and analyzed. Redundancy analyzes were conducted to define the geographical determinants that best explain the indoor dust concentrations of the 27 agricultural pesticides detected in more than 10% of study households.

Overall, main determinants of agricultural pesticides contamination in indoor dust were crop acreage within 500m (orchards) or 1000m buffer size (vineyards and cereals), as well as prevailing winds, and the presence of vegetative barriers. Our different models explained up to 18.3% of the variability of the pesticide contamination in indoor dust.

While the explained variability remains modes overall, it was above or comparable to previous studies. The determinants identified should be taken into account in future GIS-based approache aiming to assess EEAP in the French context. The approach developed to assess the impact of wind and barriers need to be validated on additional datasets.

Poster # 49

Development of a Software Based on Automatic Multi-Temporal Aerial Images Classification to Assess Retrospective Environmental Exposures to Pesticides in Epidemiological Studies

E FAURE[1], R RATAJCZAK[1,2], C CRISPIM-JUNIOR[2], O PEROL[1], L TOUGNE[2] and B FERVERS[1]

1. Cancer and Environment Department, Centre Léon Bérard, Lyon, France
2. LIRIS,UMR CNRS 5205 - University Lyon 2, Bron France

Contact: elodie.faure@lyon.unicancer.fr

Keywords: GIS, Computer vision, epidemiology, exposure assessment

Environmental exposure to agricultural pesticides (EEAP) resulting from the drift of agricultural pesticides applied on fields and is suspected to be a risk factor for several diseases. Geographic Information System (GIS) are increasingly used in environmental epidemiological studies to assess EEAP. Crop acreage proximate to subjects residences has been suggested as a surrogate for EEAP. Retrospective characterization of EEAP is essential due to long latency. Earlier data are lacking and limiting the capacity to capture the life-course effects of exposure. We aimed to develop an innovative software to analyze the historical monochromatic aerial images to reconstruct land use to characterize EEAP retrospectively.

Three phases were adopted: firstly, we have collected a new multi-scale multi-date dataset (HistAerial) composed of 4.9 million non-overlapping patches of the French territory (1970-1990). Secondly, an extensive comparison study of computer vision methods has carried out. Using 6000 randomly sampled patches per class of the HistAerial dataset, we compared the performance of 59 computer vision methods for automatic land use identification. An ergonomic software has been designed to generate a land use with the most efficient algorithms.

The handcrafted filters have performed similarly to the learned DCNNs around 90%. The best classification rate for land use with the three different sizes of patches and with the different handcraft filter methods varied from 45% to 89%. The most accurate method was a combination of handcrafted filters (89,3%) on 100-pixel patch size. The resulting software has been applied on aerial images representing 1.5 km^2 areas.

This study has developed a software to generate retrospective land use that will be integrated into a GIS to assess EEAP. It was able to produce realistic historical land use in 5 minutes. The availability of an accurate retrospective land use dataset is a requirement to assess EEAP in epidemiological studies.

Poster # 50

Development of a Sensitive Analytical Method for the Measurement of Sex Steroids in Plasma/Serum Samples from Large-Scale Epidemiological Studies

Agneta KISS, Anne-Sophie NAVIONIS, Augustin SCALBERT, Sabina RINALDI, Pekka KESKI-RAHKONEN

International Agency for Research on Cancer (IARC), Biomarkers Group, Nutrition and Metabolism Section, Lyon, France
Contact: kissa@fellows.iarc.fr

Keywords: analytical methodologies, sex steroids, mass spectrometry

Sex steroids have been associated with the risk of several cancers such as breast and endometrium. However, little is known about their associations with other cancer sites, as thyroid, colorectal, kidney, and pancreatic cancers. So far, measurements of steroids in serum/plasma samples from large-scale epidemiological studies have been mainly performed by direct immunoassays, because of their suitability to large series of samples. However, these assays may suffer from matrix effects and lack of standardization. As an alternative to commercially available immunoassays, highly sensitive liquid chromatography mass spectrometry (LC-MS) methods have now been developed, but those set up so far often include small number of analytes, and lack sensitivity for application to samples from children or post-menopausal women not using exogenous hormones, where oestrogens levels are very low.

We developed and validated a highly-sensitive, targeted LC-HRMS method for the quantification of endogenous concentrations of androstenedione, testosterone, dehydroepiandrosterone, estrone, oestradiol and progesterone. The sample preparation consists in liquid-liquid extraction and derivatization with 1,2-dimethylimidazole-5-sulfonyl chloride. Samples are then injected into the LC-HRMS system consisting of an UltiMate 3000 UHPLC and a Q-Exactive mass spectrometer (Thermo Scientific) acquiring in MS2 mode (R=35000).

This method allows a simple, fast and reproducible sample preparation, warrantying at the same time the required resolution and selectivity to unequivocally distinguish the different hormones. Its high sensitivity allows the measurements of these steroids in small plasma/serum volumes even when present at very low concentrations (few pg/ml). This method has been successfully applied to a case-control study nested within the European Prospective Investigation into Cancer and Nutrition cohort, to study the etiology of thyroid cancer. Preliminary results will be presented.

Poster # 51

Prolymphome: A Multicenter Study to Assess the Feasibility of a Systematic Screening for Occupational Exposures in Hematologic Malignancies

Olivia PEROL[1], Barbara CHARBOTEL[2,3], Amine BELHABRI[4], Elodie BELLADAME[1], Jean-Claude NORMAND[3], Gilles SALLES[5] and Beatrice FERVERS[1,6]

1. Centre Léon Bérard, Département Cancer et Environnement
2. Université Lyon 1, UMRESTTE
3. Centre Hospitalier Lyon Sud, Service des Maladies Professionnelles
4. Centre Léon Bérard, Département d'Oncologie Médicale
5. Centre Hospitalier Lyon Sud, Service d'Hématologie clinique
6. Centre de Recherche en Cancérologie de Lyon, UMR INSERM 1052-CNRS 5286

Contact: olivia.perol@lyon.unicancer.fr

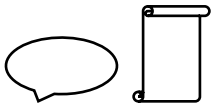
Keywords: hematologic malignancies, occupational exposures, systematic screening

Introduction: Occupational exposures in hematologic malignancies (HM) are under-reported. In 2015, a French decree established a new Table for non-Hodgkin lymphoma caused by pesticides to be covered by occupational disease compensation. A systematic screening -combining a self-administered questionnaire (SAQ) and an occupational consultation- has been previously shown efficient to improve report and compensation of occupational lung cancer. We assessed this systematic screening in HM.

Methods: Patients identified through the multidisciplinary HM board, received a SAQ to collect their job history and potential carcinogen exposures. At reception, a physician assessed the SAQ and recommended an occupational consultation if necessary. During the consultation, a physician assessed if the cancer was work-related and if it was, delivered a medical certificate to claim for compensation.

Results: Over one year, 753 patients in 3 hospitals received the SAQ: 355 (47%) completed the questionnaire in 41 days on average. In the SAQ, 64 patients (18%) mentioned occupational exposure to trichloroethylene (TCE) and 53 (15%) to pesticides. A consultation was proposed to 120 patients, 88 attended. Twelve patients were considered to have work-related cancer with a possible compensation (7 exposed to pesticides and 5 to TCE) and received a medical certificate. For 24 other patients, the disease was judged work-related but unlikely to be compensated. For the 52 remaining patients, the HM was not considered work-related. Two patients received compensation, other claims are under assessment.

Discussion: Our study showed a systematic SAQ can identify patients with HM potentially exposed to carcinogens in different structures. As HM gather different diseases and numerous histological subtypes and as compensation is currently only possible for specific occupational exposures (TCE, pesticides), a more targeted screening may be considered.



Poster # 52

PROPOUMON: Systematic Screening For Occupational Exposures In Lung Cancer Patients: A Prospective French Cohort

Olivia PEROL, Barbara CHARBOTEL, Lionel PERRIER, Elodie BELLADAME, Virginie AVRILLON, Maurice PEROL and Beatrice FERVERS

Centre Léon Bérard, Département Cancer et Environnement
Contact: olivia.perol@lyon.unicancer.fr

Keywords: lung cancer, occupation, social deprivation, systematic screening

Occupational lung cancers remain under-reported and under-compensated worldwide. We assessed systematic screening for occupational exposures to carcinogens combining a self-administered questionnaire and a consultation to improve the detection of occupational lung cancers and their compensation. Social deprivation and the costs of this investigation were estimated.

Patients were identified through the multidisciplinary lung cancer board; they received a self-administered questionnaire to collect their job history, potential exposure to carcinogens and deprivation (EPICES). At reception, a physician assessed the questionnaire and recommended a consultation if necessary. During the consultation, a physician assessed if the cancer was work-related and if it was, delivered a medical certificate to claim for compensation.

During 18 months, 440 patients received the self-administered questionnaire: 234 returned it. Among the 206 patients who did not complete the questionnaire, 84 did not feel concerned. Of the 120 patients invited to the consultation, 97 attended: 59 were considered to have occupational-related cancer. A claim for compensation was judged possible for 41 patients and the certificate was delivered to 35 patients (5 did not want to claim and 1 had already filed a claim). Compensation was awarded to 19 patients, 5 claims were rejected, 3 are under assessment and 8 did not submit a claim.
The mean EPICES score was 28.7. Patients classified as deprived took longer to return the questionnaire.
The mean cost of this systematic screening was €62.65 per patient.

Our study confirms the frequency of occupational exposures in lung cancer patients. Our results showed a systematic questionnaire can be used to identify patients potentially exposed to carcinogens. In France, only 2.3% of lung cancers have been compensated in 2014; this percentage has doubled with our screening which shows its capacity to improve the compensation of occupational lung cancers.

Poster # 53

Predicting Clinical Benefits of Combined Bevacizumab and Paclitaxel Therapy for HER-2 Negative Metastatic Breast Cancer: A Serum NMR Metabolomics Investigation

Elodie JOBARD[1], 2,Bénédicte ELENA-HERRMANN[1] and Olivier TREDAN[2]

1. Université de Lyon, Centre de RMN à très hauts champs, Institut des Sciences Analytiques, UMR 5280, CNRS, Université Lyon 1, ENS Lyon - 5, rue de la Doua, F-69100 Villeurbanne, France
2. Département d'Oncologie Médicale, Université de Lyon, Centre Léon Bérard, 28 rue Laënnec, 69008 Lyon, France

Contact: ejobard@gmail.com

Keywords: Serum, Metabolomics, NMR, metastatic breast cancer, Bevacizumab, Paclitaxel

Bevacizumab combined with chemotherapy improves the response rate and prolongs progression-free survival when used as first- or second-line treatment for advanced-stage breast cancer. A major challenge is the early identification of subgroups of patients that will benefit most from this treatment in order to provide a more specific administration of bevacizumab and allow potential non-responder patients to benefit from alternative therapeutic strategies. We present a longitudinal metabolomic investigation of serum samples from patients with HER-2- metastatic breast cancer, and identify metabolic signatures of the response to association of bevacizumab and paclitaxel treatments.

Pre-treatment and on-treatment serum samples were available for 312 patients with HER-2- metastatic breast cancer from the French multicenter clinical trial COMET. Patients received paclitaxel associated with bevacizumab in the first line of cancer treatment and were not previously treated with chemotherapy for metastatic disease. A series of venous blood samples were collected under fasting conditions for each patient: at baseline, day 8 of cycle 1, and day 1 of cycle 2 of chemotherapy, and corresponding metabolic profiles were obtained using proton high-field NMR. After outliers' identification in the COMET dataset, multivariate statistical modelling of the data discriminates metabolic profiles before and after several days/weeks of treatment that reflect global changes in the metabolism of patients in response to chemotherapy. This therapeutic association causes fast modifications of the host metabolism, detected after only one week of treatment. Furthermore, stratified analysis shows that significant metabolic signatures associated with clinical benefit can be distinguished at baseline and after only 8 days of treatment for patients with negative hormone receptors status. These results open up promising routes for application of metabolomics strategies to patients' management in oncology.

Poster # 54

Mammary Myoepithelial Cells: Key Actors in Breast Cancer Associated with Obesity?

Laetitia DELORT[1], Marion BERNARD-VERMERIE[1], Valentin MONTAGNON[1], Caroline DECOMBAT[1], Ali MOJALLAL[2], Céline AUXENFANS[3], Florence CALDEFIE-CHEZET[1]

1. Clermont Auvergne University, INRA, UNH, Human Nutrition Unit, CRNH-Auvergne, F-63000 Clermont-Ferrand
2. Plastic, Reconstructive and Aesthetic Surgery Service, Edouard-Herriot Hospital, F-69000 Lyon
3. Tissue and cell bank, Edouard-Herriot Hospital, F-69000 Lyon ; FRANCE

Contact: laetitia.delort@uca.fr

Keywords: Breast cancer, obesity, microenvironment, myoepithelial cells

Obesity is a recognized breast cancer risk factor in postmenopausal women, and is also responsible for higher rates of recurrence and mortality. Among all the cell types present in the breast, myoepithelial cells (MyoEpCs) are considered as "tumor suppressors" since they could inhibit tumor growth, invasion and angiogenesis. During the transition from *in situ* to invasive ductal carcinoma, a disorganization of MyoEpCs is observed which favors the migration capacity of cancer cells. As adipose microenvironment could promote breast carcinogenesis, we would like to characterize its role on the functionality of MyoEpCs in a context of obesity.

MyoEpCs (Hs 578Bst) were co-cultured with adipose stem cells (hASC) using a human cell line (hMAD) or with hASCs obtained from thin or obese patients (hASC20, hASC30) and differentiated into mature adipocytes (MA20, MA30). The proliferation (resazurine, Fluoroskan Ascent FL®) and apoptosis (annexin V-FITC/PI, K2 Image cytometer, Nexcelom) of MyoEpCs were evaluated.

In the presence of hASC, the proliferation of MyoEpCs was decreased (-22%/-15% with hMAD/hASC respectively; n=6, $p<0.05$) associated with a slight increase of apoptosis. The same modifications were obtained with hASC20 and hASC30. The secretome of hASC alone reduced the proliferation of MyoEpCs (-14%, n=6, p=0.01), this effect was mainly due to the secretions of hASC30 (-22%, n=3, $p<0.05$). MA differentiated from hMAD appeared to decrease the proliferation of MyoEpCs (-11%, n=6, p=0.01) but no effect of obesity was observed.

These preliminary results confirmed that adipose cells and their secretome could influence the behavior of MyoEpCs, so favoring the development and progression of breast cancer. A 3Dmodel of spheroids is currently developed to evaluate the influence of adipose secretome on the structure and functionality of MyoEpCs and will help to identify new preventive and therapeutic targets for breast cancer.

Project funded by ARC Foundation for cancer research

Poster # 55

Use of Dietary Supplements in Soy Isoflavones and Risk of Breast Cancer Among Women Aged Over 50 Years: Results From The E3N Prospective Cohort

Marina TOUILLAUD[1], Amandine GELOT[2], Sylvie MESRINE[2], Françoise CLAVEL-CHAPELON[2], Fabrice BONNET[2], Catherine BENNETAU-PELISSERO[3], Marie-Christine BOUTRON-RUAULT[2], Agnès FOURNIER[2]

1. Léon Bérard Cancer Centre, Lyon, France; Cancer Research Centre of Lyon, UMR Inserm 1052 CNRS 5286 CLB, Lyon, France
2. CESP "Health across Generations", INSERM, Univ Paris-Sud, UVSQ, Univ Paris-Saclay, Villejuif, France
3. Univ Bordeaux, Physiopathologie de la plasticité neuronale, U1215 INSERM, Neurocentre Magendie, Bordeaux, France

Contact: marina.touillaud@lyon.unicancer.fr

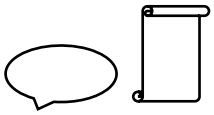
Keywords: breast cancer, cohort, dietary supplements, soy, isoflavones

Background: Soy-based dietary supplements have been proposed as alternatives to menopausal hormone therapy, but their effect towards breast cancer risk is controversial and has little been evaluated.

Methods: To investigate the association between soy-based supplements and breast cancer risk, 76 442 women from the E3N cohort, born 1925-1950, were followed between 2000 and 2011 (11.2 years on average; 3608 incident breast cancers), with dietary supplement use assessed every 2-3 years. Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using multivariable Cox models.

Results: HRs associated with current use of soy-based dietary supplements were 0.92 (95% CI=0.76–1.11) for all, 0.78 (95% CI=0.60–0.99) for ER-positive, and 2.01 (95% CI=1.41–2.86) for ER-negative breast cancers, compared to never use. No associations were observed for past use. We found effect modification by family history of breast cancer (p=.03) and menopausal status (p=.04): HRs for current use were 1.36 (95% CI=0.95-1.93) and 0.82 (95% CI=0.65–1.02) among women with and without family history of breast cancer, respectively, and 1.06 (95% CI=0.87–1.30) over 5 years after menopause and 0.50 (95% CI=0.31–0.81) in perimenopause or within 5 years after menopause onset.

Conclusion: Our results show opposite associations of soy-based dietary supplements with ER-positive and ER-negative breast cancer risks. They prompt special caution in their use among women with a family history of breast cancer. Whether their risk profile may be more favorable among premenopausal/recently postmenopausal women deserves further investigation.



Poster # 56

Seasonal Variations of Exposure to Agricultural Pesticides in Residents Proximate to Vineyards: SIGEXPOSOME Study

Nicole FALETTE[1], Agneta KISS[2], Liacine BOUAOUN[3], Marie-Laure BAYLE[4], Séverine CROZE[5], Elodie FAURE[1], Joël LACHUER[5], Bruno COMBOURIEU[3], Joachim SCHUZ[4], Augustin SCALBERT[2], Béatrice FERVERS[1,6,7]

1. Centre Léon Bérard, Département Cancer Environnement, Lyon, France
2. International Agency for Research on Cancer (IARC), Biomarkers Group, Nutrition and Metabolism Section, Lyon, France
3. International Agency for Research on Cancer (IARC), Environment & radiation (ENV)
4. Rovaltain Research Company, 26300, Alixan, France
5. Centre de Recherche en Cancérologie de Lyon – Plateforme génomique ProfileXpert
6. Université Claude Bernard Lyon 1, 43 Boulevard du 11 Novembre 1918, 69100 Villeurbanne, France
7. Centre de Recherche en Cancérologie de Lyon UMR INSERM 1052-CNRS 5286 Equipe « Signalisation des hormones stéroïdes et cancer du sein »

Contact: katia.nardot@lyon.unicancer.fr

Keywords: SIGEXPOSOME

Environmental exposure to pesticides is a major public health concern. Residential proximity to treated farmland has been associated with increased pesticides concentrations in residential dust and urine samples. The project investigates seasonal variations of exposure to agricultural pesticides of residents close to vineyards and of pesticide applicators (Beaujolais area, Auvergne-Rhône-Alpes Region), in a longitudinal study with repeated sampling of house dust, urine, blood and hair. We report pilot data for 19 residents (non-smoking men, aged 18-65).

Methods: We sampled morning urine and house dust in July and October 2015. House dust: Efficiency and repeatability analyses of analytical methods (GC–MS, LC–MS/MS) allowed to retain 53 out of 62 preselected pesticides for analyses (recovery rate 70 -120%; RSD < 20%; LOQ 20-1000 ng/g dust). Urine samples: To screen presence of pesticides and their metabolites, a database containing 59 pesticides and 519 associated metabolites with their exact monoisotopic mass was set up. After solid phase extraction, the concentrated extracts of urine samples were analyzed in full scan mode by LC-HRMS.

Results: 40 pesticides were quantified in dust, including 11 compounds of high public health priority. Among compounds with a prevalence >70% for one of the 2 sampling periods, significant seasonal variations in pesticide prevalence (n=10) and concentrations (n=14) was found with average concentrations higher in July than in October. 2 of the 3 pesticides metabolites detected in urine, specific to chlorpyrifos & chlorpyrifos-methyl and tebuconazole (both present in house dust), were confirmed by comparison with authentic standards.

Conclusion: Our study showed seasonal variations of agricultural pesticides in housedust of residents close to vineyards. Correlation between residential dust and urine contamination and proximity to treated vineyards will be further explored.

Funding: Auvergne-Rhône-Alpes Region; Métropole de Lyon.

Progression and Tumor Resistance, Innovative Therapies

Poster # 57

Nucleotide Metabolism and Cancer Cell Aggressiveness

Octavia CADASSOU, Muhammad ZAWWAD RAZA, Emeline CROS-PERRIAL, Célia ARMANET, Laura GUDEFIN, Kamel CHETTAB, Charles DUMONTET, Lars Petter JORDHEIM

Anticancer Antibodies team- CRCL
Université Claude Bernard Lyon 1
Contact : octavia.cadassou@univ-lyon1.fr

Mots clés : nucleotide metabolism, adenosine, migration, cN-II, CD73

En plus de jouer un rôle majeur dans la réplication d'ADN, les nucléotides sont impliqués dans divers processus comme la signalisation, la migration et la régulation de la balance énergétique. L'instabilité génétique, les dérégulations de l'homéostasie énergétique et les signaux pro-prolifératifs sont des éléments classés dans les caractéristiques du cancer, telles qu'Hanahan et Weinberg les définissent. Comme précédemment démontré, ces paramètres dépendent aussi du métabolisme des nucléotides. Ainsi, ce processus complexe est devenu une cible pour les nouvelles thérapies anti-cancéreuses. Cependant, dans cette dynamique, la connaissance et la compréhension du métabolisme nucléotidique doivent être approfondies.

Le métabolisme des purines implique plusieurs enzymes intra- et extracellulaires, dont cN-II et CD73, deux 5'nucléotidase capables de convertir les nucléotides monophosphates en nucléosides correspondants. En prenant en compte le rôle des nucléotides/nucléosides puriques, il est possible que cN-II et CD73 soient impliquées dans des phénomènes qui modulent l'agressivité de la cellule cancéreuse.

Nous avons donc évalué leur impact sur la prolifération cellulaire et la migration. En utilisant la technique du CRISP/Cas9 sur des MDA-MB-231 (lignée de cancer du sein triple négatif), des modèles déficients ou non pour cN-II et/ou CD73 ont été générés. Nous avons tout d'abord démontré que ces 5'-nucléotidases n'impactent pas la prolifération ou la survie cellulaires, bien que ces paramètres soient sensibles aux pools de purines extracellulaires. Puis nous avons entrepris de comprendre l'implication de ces facteurs dans des modulations de la migration cellulaire, grâce à un test de cicatrisation sur l'Incucyte et l'étude de facteurs décrits comme régulateurs de ce processus.

Les résultats qui seront présentés confirment la pertinence des efforts fournis pour mieux comprendre l'implication du métabolisme nucléotidique dans l'agressivité de la cellule cancéreuse.

Poster # 58

Paired Cell for Deciphering Lung Tumorigenesis and Preclinical Drugs Evaluation

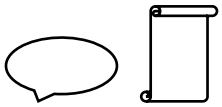
Cédric DURET, Joëlle FAUVRE, Carole FERARO-PEYRET, Cédric CHAVEROUX, Serge MANIE

CRCL, INSERM U1052, Lyon
Contact: cedric.duret@inserm.fr

Keywords: cellular models in oncology, lung cancer models, non-tumoral lung cell lines generation, association of tumoral and non-tumoral paired cells

Our laboratory studies the metabolic mechanisms allowing adaptation of tumor cells facing microenvironmental stresses and therapies. We are developing a cellular engineering project that aims at modeling in vitro pulmonary cell transformation and lung tumor microenvironment by using fresh human tissues. To this end, we have already optimized the separation process of healthy cells from distal tissue of lung cancer biopsies. By immortalizing these cells, we aim at the creation of a large panel of non-tumoral cell lines for anticipating potential side effects of treatments (most of cell lines commercially available are tumor cells). We also plan to immortalize the cancerous epithelial cells from the same biopsies and therefore generate the first paired-cell models in lung oncology associating non-cancerous epithelial cells and tumor cells from the same patient sample. This allows the comparative studies of mutations outcome involved in therapies resistance with the healthy counterparts; the possibility to genetically modify normal cells to study oncogene-related transformation process; and the possibility to co-culture the cells to model tumor microenvironment and study cells communication.

We believe that non-cancerous cell lines for preclinical studies offer a novel and relevant tool for first evaluation of therapies. This cellular system represents an alternative model for the first-line evaluation of toxic effects of a candidate drug on paired non-tumoral and tumoral cells. It also permits to anticipate its effects on epithelial cells from patients with pneumopathologies. Finally, estimation of drug toxicity on these paired-models could help in the decision to proceed to animal testing, saving time, money and being more ethical in the drug development process.



Poster # 59

Epithelial Cells in Hypoxic Environnement: The Race to Oxygen! Is This Mechanism Relevant for Metastasis?

Philippe GONZALO[1], Ivan MIKAELIAN[1], Mathieu DEYGAS[1], Rudy GADET[1], Michel PEOC'H[2], Céline CHAULEUR[3]

1. Centre de Recherche en Cancérologie de Lyon UMR INSERM 1052 - CNRS 5286 - Université de Lyon
2. Laboratoire d'Anatomo-Cytologie-Pathologique/ Centre de Ressource Biologique CRB-42 Tumorothèque, CHU de Saint-Etienne Faculté de Médecine Jacques Lisfranc, Université de Saint-Etienne
3. Service de chirurgie gynécologique et obstétricale, CHU de Saint-Etienne - Faculté de Médecine Jacques Lisfranc, Université de Saint-Etienne

Contact: philippe.gonzalo@lyon.unicancer.fr

Keywords: cell plastcity - metastasis- breast cancer

We have shown that mammalian cells in profound hypoxia have the capacity to move towards oxygen (Deygas et al., under review in Nature Communication). This process called aerotaxis described in bacteria for more than 130 years has been demonstrated in the laboratory for epithelial cells. This process could play a critical role in tumor progression by orienting the migration and invasion of cells from the primary hypoxic tumor to the nearest blood capillaries, thus promoting metastatic spread. The objective of this new research project is to test the aerotactic capacities of mammary tumor cells of a series of fresh tumors and to validate the hypothesis of a role of aerotaxis in tumor progression. Validating the ability to detect an "aerotactic" signature will eventually signal tumors with greater metastatic potential. The effort to identify aerotactic signal transduction pathways that we will carry out in parallel will open up therapeutic opportunities against the metastatic progression of mammary tumors.

Poster # 60

In Vivo Activity of Combinations of Cytotoxic Regimens with Anti-PD1 and Anti-Pdl1 in Various Syngeneic Cancer Models

Chloé GRASSELLY[1,2], Morgane DENIS[1,2], Aurore BOURGUIGNON[1,2], Nolan TALHI[2], Doriane MATHE[2], Anne TOURETTE[2], Laurent SERRE[3], Lars Petter JORDHEIM[1], Charles DUMONTET[1,4]

1. Anticancer Antibodies, CRCL, INSERM U1052, CNRS UMR 5286, CLB, UCBL, Lyon, France
2. ANTINEO, Lyon, France
3. Univ Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Centre Léon Bérard, Cancer Research Center of Lyon, Lyon, France
4. Hospices Civils de Lyon, Lyon, France

Contact: chloe.grasselly@antineo.fr

Keywords: immune checkpoint inhibitor, oncology, immuno-oncology, combinaison therapy

In spite of impressive response rate in multiple cancer types, immune checkpoint inhibitors (ICIs) are active in only a minority of patients.

Alternative strategies currently aim to combine immunotherapies with conventional agents such as cytotoxic chemotherapies. Here, we performed a study of PD-1 or PDL-1 blockade in combination with reference chemotherapies in four fully immunocompetent mouse models of cancer. We analyzed both the in vivo antitumor response, and the tumor immune infiltrate four days after the first treatment. In vivo tumor growth experiments revealed variable responsiveness to ICIs between models. We observed enhanced antitumor effects of the combination of immunotherapy with chemotherapy in the MC38 colon and MB49 bladder models, a lack of response in the 4T1 breast model, and an inhibition of ICIs activity in the MBT-2 bladder model. Flow cytometry analysis of tumor samples showed significant differences in all models between untreated and treated mice. At baseline, all the tumor models studied were predominantly infiltrated with cells harboring an immunosuppressive phenotype. We found that the balance between effector cells and immunosuppressive cells in the tumor microenvironment could be altered with some treatment combinations, but this effect was not always correlated with an impact on in vivo tumor growth.These results show that the combination of cytotoxic chemotherapy with ICIs may result in enhanced, similar or reduced antitumor activity, in a model- and regimen-dependent fashion.

Early alterations of the tumor immune infiltrate were found to be highly variable. The present investigations should help to select appropriate combination regimens for ICIs.

Poster # 61

Identifying and Characterizing Epigenetic Modifier Genes ('Epidrivers') in Tumour Development and their Link to Environmental Carcinogens

A HALABURKOVA[1], C CUENIN[1], S AMBATIPUDI[1], N FERNANDEZ JIMENEZ[1], D DEGLI ESPOSTI[1], M KORENJAK[2], J ZAVADIL[2], A GHANTOUS[1] AND Z HERCEG[1]

1. Epigenetics Group (EGE)
2. Molecular Mechanisms and Biomarkers Group (MMB), Section of Mechanisms of Carcinogenesis (MCA), International Agency for Research on Cancer, Lyon, France

Contact: halaburkovaa@fellows.iarc.fr

Keywords: epidrivers, carcinogenesis, tumor plasticity

One of the most remarkable and consistent findings of the major international high-resolution cancer genome sequencing efforts is the high frequency of mutations in genes encoding epigenetic regulators in virtually all types of human malignancies. Deregulation of these epigenetic regulators (known as "epidrivers) has the potential to disrupt the epigenome thus placing epidriver deregulation at the leadership of oncogenic transformation and cancer biology. We aimed to test the hypothesis that deregulation of these epidrivers, through either mutational or non-genetic events, has the potential for genome-scale disruption of the epigenome and that this process is at the very heart of carcinogenesis. In silico approach, we defined the list of over 400 important epigenetic candidate genes that are subjected to genome editing CRISPR-Cas9 library screen to study their function in oncogenic transformation and tumour plasticity. To this end, lentiviral-based CRISPR-Cas9-mediated screen is used on different non-tumorigenic cell lines. The impact of epidrivers mutation on the epigenome reconfiguration and transcriptional reprogramming as well as multiparametric phenotyping is investigated. Clones that pass this primary screen by exhibiting molecular and phenotypic markers of cell transformation are further expanded and analyzed by a second-stage screen that show cancer hallmarks, including migration/invasion assays, EMT and tumorogenicity in nude mice. This project is expected to improve the knowledge of epigenetic mechanisms involved in the development of cancer cells and tumour plasticity, which should provide important information for the development of novel strategies for cancer prevention and treatment as well as carcinogen evaluation.

Poster # 62

Hétérogénéité tumorale et échappement métastatique des carcinomes mammaires triples négatifs

Noura KHALED, Nina RADOSEVIC-ROBIN, Yannick BIDET

IMoST - UMR 1240 Inserm / UCA, BP 184, 58, Rue Montalembert, 63005 CLERMONT-FERRAND / Centre Jean Perrin, 58, Rue Montalembert, 63011 CLERMONT-FERRAND

Contact : Noura.KHALED@uca.fr

Mots clés : cancer de sein triple négatif, métastase, hétérogénéité tumorale, microenvironnement immunitaire, transcriptomique, génétique, immunohistochimie, signature tumorale, signature immunitaire, signature pronostique

Avec environ 54000 nouveaux cas par an en France et 1 million dans le monde, le cancer de sein est considéré comme la première cause de mortalité féminine. Bien que la prise en charge des cancers du sein n'ait cessé de progresser sur tous les fronts, les cancers du sein triple négatifs (CSTN) restent sans thérapie ciblée. Très agressifs et de mauvais pronostic, ces tumeurs qui représentent 15% de l'ensemble des cancers mammaires. Initialement sensibles à la chimiothérapie, elles développent dans 40% des cas un mécanisme d'échappement métastatique, principalement vers les poumons. L'origine de cet échappement réside dans la grande hétérogénéité des populations cellulaires tumorales et immunitaires.

Notre projet de thèse vise donc à déterminer les caractéristiques des clones tumoraux responsables des métastases observées à distance et l'impact du microenvironnement immunitaire sur la dissémination métastatique.

2 types d'analyses seront menées sur 2 types cellulaires appartenant à 3 types d'échantillons différents : une analyse transcriptomique fine par RNA Seq et une analyse génétique par séquençage d'un panel de points chauds de mutations seront conduites à la fois sur des sous-populations de cellules tumorales et de cellules immunitaires. Ces sous-populations seront issues de 3 types de blocs tumoraux : triple négatif sans métastase, triple négatif métastasé et métastase pulmonaire appariée.

L'ensemble de ces données permettra de dégager des signatures moléculaires tumorales et immunitaires dont la combinaison aura une valeur pronostique. Cette signature globale sera validée au niveau protéique par immunohistochimie sur une seconde cohorte tumorale mammaire.

Nous tenterons enfin d'élargir cette signature pronostique globale en la confrontant aux résultats en cours sur 2 autres types d'adénocarcinomes afin d'identifier de nouveaux facteurs pronostiques, voies métaboliques et mécanismes moléculaires pouvant conduire à de nouvelles cibles thérapeutiques.

Poster # 63

Functional Relationship Between the Estrogen Receptor Splice Variant Erα36 qnd PR in Breast Cancer

Henri-Philippe KONAN[1,2], Soleilmane OMARJEE[1,3], Julien JACQUEMETTON[2], Loay KASSEM[4], Laura CORBO[2], Olivier TREDAN[5], Isabelle TREILLEUX[6], Muriel LE ROMANCER[2]

1. Université Lyon 1, Lyon, France
2. CNRS 5286/INSERM 1052, Centre de Recherche en cancérologie de Lyon, Lyon, France
3. Cambridge cancer research UK, Cambridge, UK
4. Cairo oncology centre, Cairo, Egypt
5. Centre Léon Bérard, Lyon, France
6. Centre Léon Bérard, Pathology Department, Lyon, France

Contact: henriphilippe.konan@lyon.unicancer.fr

Keywords: breast cancer, estrogen and progesterone receptors, cancer progression

Estrogen and progesterone are known to promote proliferation and cell growth of breast cancer cells via the binding to their receptors, ERα and PR respectively. Upon hormone stimulation, both receptors induce the activation of genes through two pathways: the genomic pathway in which the nuclear receptors act as transcription factors and the non-genomic pathway which involves the rapid activation of protein-kinases, such as ERK. A few years ago, ERα36, a new ERα spliced variant was identified (Wang et al, 2005). Unlike ERα, this variant has a main cytoplasmic and plasma membrane localization, triggering non-genomic signaling through activation of the ERK pathway. Interestingly, ERα-36 expression has been shown to be involved in hormonotherapy and chemotherapy resistance in breast cancer. Recently, we studied ERα-36 expression in 2 cohorts of breast tumors and found that ERα-36 expression was correlated with poor patient survival. Moreover, ERα-36 bad outcome was restricted to PR-positive breast tumors suggesting that it could interfere with progesterone signaling.

By several approaches, we have established a functional link between ERα36 and PR. First, we demonstrated that ERα36 interacts with PR in the nucleus and ERα36 decreases PR phosphorylation, reducing PR transcriptional activity on target genes. We are currently investigating by which mechanisms and the large scale binding of PR on chromatin by Chip-seq experiments.

We also plan to study ERα36 expression in a new cohort of breast tumor samples to confirm whether ERα36 can constitute a new prognosis marker for a subset of PR positive tumors. Moreover, the engineering of an antibody drug conjugate targeting ERα36 will constitute a new therapeutic target.

Poster # 64

Comparaison du profil d'expression génique de biopsies et de cellules tumorales circulantes dans le suivi thérapeutique des cancers des VADS

Alexandra LAURET[1], Pierre PHILOUZE[2], Céline MALESYS[1], Philippe CERUSE[2], Jonathan LOPEZ[3], Gersende ALPHONSE[1,3], Claire RODRIGUEZ-LAFRASSE[1,3]

1. Univ Lyon, Faculté de Médecine Lyon-Sud, Laboratoire de Radiobiologie Cellulaire et Moléculaire, CNRS UMR5822, 69921 Oullins, France
2. Hospices Civils de Lyon, Centre Hospitalier de la Croix-Rousse, 69317 Lyon, France
3. Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, 69495 Pierre-Bénite, France

Contact : alexandra.lauret@univ-lyon1.fr

Mots clés : HNSCC,CTCs, biopsie liquide, nanostring

Introduction : La survie à 5 ans des patients ayant un cancer des VADS n'excède pas 40% en raison d'un taux élevé de récidives loco-régionales et à distance. Le phénomène métastatique est gouverné par une série complexe d'évènements incluant la migration des cellules tumorales à partir du site primaire, leur passage dans la circulation sanguine et l'invasion du tissu cible. Les cellules, appelées cellules tumorales circulantes (CTCs), sont le reflet de l'agressivité et de la progression tumorale. Ce travail s'intéresse à la numération et caractérisation des CTCs chez des patients atteints de cancer des VADS en regard de l'analyse de biopsies tumorales.

Méthodes : Des prélèvements sanguins et biopsiques sont réalisés avant et pendant le traitement (chimiothérapie/radiothérapie) et en cas de récidive. Les CTCs sont isolées à partir du sang (Rosette et ISET). Un marquage immunohistochimique de protéines spécifiques de cellules souches cancéreuses et de la transition épithélio-mésenchymateuse est ensuite réalisé afin de les compter et les caractériser. L'analyse transcriptomique des voies de progression tumorale et des systèmes de réparation des lésions de l'ADN est réalisée par la technologie Nanostring sur les biopsies tumorales et les CTCs (après amplification).

Résultats : Dix-huit patients ont été inclus dans l'étude à ce jour. Les premiers résultats de comptage montrent une grande hétérogénéité au niveau du nombre de CTCs. Différents phénotypes (mésenchymateux ou épithéliaux) de CTCs sont mis en évidence selon les patients. L'analyse transcriptomique des biopsies et CTCs est en cours.

Conclusion : La numération et la caractérisation (phénotype et profil transcriptomique) des CTCs et leur comparaison aux données des biopsies devraient permettre de définir des paramètres biologiques prédictifs de la réponse thérapeutique des cancers des VADS.

Soutenu par le Cancéropôle CLARA, Grenoble-Alpes Métropole, Conseil Régional Rhône-Alpes, Conseil Général du Rhône et LabEx PRIMES

Poster # 65

Evaluation prédictive de l'efficacité thérapeutique de la molécule EI-52 en utilisant une plateforme Ex-Vivo chez des patients atteints de carcinomes épidermoïdes de la tête et cou

Sophie LEON[1], Sophie DENEUVE[2], Stéphane GIRAUD[3], Julie VALANTIN[5,7], Nicolas GADOT[5],Antonin TORTEREAU[6], Mélanie BONNET[4], Léa MAGADOUX[4],François VIRARD[4 8],Isabelle COSTE[4], Séverine TABONE-EGLINGER[3] ,Toufic RENNO[4]

1. Plateforme Ex-Vivo, Département de Recherche Translationnelle et d'Innovation, Centre Léon Bérard, Lyon, France
2. Département de Chirurgie Centre Léon Bérard, Lyon, France
3. Plateforme C3D, Département de Recherche Translationnelle et d'innovation, Synergie Lyon Cancer, Centre Léon Bérard, Centre de Recherche en Cancérologie de Lyon, France
4. Centre de Recherche en Cancérologie de Lyon, France
5. Plateforme Anatomopathologie-Recherche Département de Recherche Translationnelle et d'Innovation, Centre Léon Bérard, Lyon, France
6. Université de Lyon, VetAgro Sup, UPSP 2011-03-101, ICE, Marcy-l'Étoile, France
7. Université Claude Bernard Lyon, France
8. Hospices Civils de Lyon, France

Contact : sophie.leon@lyon.unicancer.fr

Mots clés : ex-vivo, tests prédictifs, cancers ORL, agent thérapeutique

Introduction : Les carcinomes épidermoïdes des voies aérodigestives supérieures représentent le 6eme cancer dans le monde et le 4eme cancer en France. Malgré les progrès de la chirurgie, de la radiothérapie, et l'avènement des thérapies ciblées, ces cancers restent associés à un taux de mortalité élevé avec une survie à 5 ans entre 35 et 50%, et de fréquentes récidives locorégionales. La prédiction de la réponse au traitement dans les cancers ORL reste problématique. La plateforme Ex-Vivo, développée sur le Centre Léon Bérard, a mis en place une technique innovante sur coupes de tumeurs fraiches de patients, qui permet d'évaluer la sensibilité des cellules tumorales vis-à-vis d'un traitement donné.
Dans le cadre d'un projet sur les cancers ORL, cette technique va permettre d'évaluer la sensibilité de la tumeur à un nouvel agent thérapeutique (EI-52) agissant sur l'inhibition des interactions de Erk.
Méthodes : Des échantillons de tumeurs issus de résections chirurgicales d'une taille d'environ 200 mm 3 sont coupés en tranches de 250 µm au moyen d'un vibratome. Dix échantillons de HNSCC (Head and Neck Squamous Cell Carcinoma) ont ainsi été cultivés extemporanément en milieu de culture spécifique sur 24h à 37°C en présence ou non de la molécule d'intérêt et des chimiothérapies de référence. A l'issue des 24h, les tranches sont ensuite fixées et incluses en paraffine. Une analyse morphologique des tissus ainsi que des marquages immuohistochimiques sont réalisés afin d'évaluer l'indice de prolifération cellulaire (KI67) et le taux d'apoptose (PARP Clivée). La comparaison des résultats des coupes ayant reçu des traitements par rapport aux conditions contrôles permet de classer les tumeurs comme répondant ou non au traitement. Des prélèvements peuvent être exclus de l'analyse pour cause de trop faible quantité de matériel tumoral.
Résultats : Une première analyse qualitative a validé la technique montrant des résultats immunohistochimiques (KI67, PARP clivée) interprétables. Les résultats obtenus avec la molécule EI-52 montrent une apoptose spécifique des cellules cancéreuses tout en épargnant les cellules stromales normales.
Conclusion : Ce nouveau concept de tests prédictifs ex-vivo semble être adapté pour évaluer l'efficacité d'une molécule thérapeutique dans les cancers ORL. Ceci pourrait former la base d'un test prédictif de réponse aux différents traitements.

Poster # 66

Progesterone Signaling in Breast Cancer: Novel Insights

Lucie MALBETEAU[1,2,3], Muriel LE ROMANCER[2,3], Laura CORBO[2,3]

1. Université Claude Bernard Lyon 1 (UCBL), France
2. Inserm U1052, Centre de Recherche en Cancérologie de Lyon, France
3. CNRS UMR 5286, Centre de Recherche en Cancérologie de Lyon, France

Contact: lucie.malbeteau@lyon.unicancer.fr

Keywords: breast cancer, progesterone receptor, post-translational modification, arginine methylation, transcriptional regulation

Breast cancer progression is mainly driven by oestrogen and progesterone signaling and therapies modulating oestrogen's action have improved the survival of oestrogen receptor (ERα)-positive cancer patients. As progesterone receptor (PR) is an ERα target gene, its expression in breast cancer is considered as a predictive marker of ERα activity. However, recent studies are converging on the concept that PR can directly affect ERα functions in breast cancer cells, leading to a potential improvement of the tumour response to anti-oestrogen therapies.

In considering the differential effects of progesterone in breast cancer, it is important to define variables that might influence its pathway. Recently, Beato and al. reported that the unactivated form of PR bind to genomic sites and target a repressive complex containing enzyme-modifying chromatin. This action leads to the transcription inhibition of PR-target genes in absence of progesterone. In addition, PR-post-translational modifications may affect progesterone-induced cellular responses. Indeed, we have previously shown that PR is methylated by the arginine methyltransferase PRMT1 on several arginine residues.

By in vitro and in vivo approaches, we are studying the impact of PRMT1 on PR signaling pathways. In T47D breast cancer cells, we demonstrated that PR interact with PRMT1, mainly in the nucleus and of interest also in absence of hormonal stimulation. PRMT1 appears as a new member of the repressive complex on a subset of progesterone inducible genes. Our results also indicate that PRMT1 expression affects PR transcriptional activity. Moreover, we produced an antibody directed against the methylated form of PR to precise the impact of PRMT1-dependant methylation on the regulation of progesterone signaling.

Our data highlight the impact of PRMT1 expression on PR signaling, which is essential in breast cancer progression.

Poster # 67

Intérêt d'une approche thérapeutique ciblant la matrice extra-cellulaire et l'hypoxie pour la prise en charge du chondrosarcome

Elise MAUBERT, Aurélien VOISSIERE, Flora PONELLE CHACHUAT, Yannick BIDET, Sandrine VIALA, Caroline PEYRODE, Valérie WEBER, Yvain GERARD, Jean-Michel CHEZAL, Françoise DEGOUL[1], Elisabeth MIOT-NOIRAULT

UMR 1240 Inserm, IMoST/Université Clermont Auvergne, 63005 Clermont-Ferrand, France
Contact : elise.maubert@inserm.fr

Mots clés : chondrosarcome, protéoglycane, hypoxie, prodrogue activable en hypoxie, vectorisation, RNAseq, culture cellulaire en 3D

Le chondrosarcome, ou tumeur maligne du cartilage, est une tumeur chimio- et radio-résistante. A l'heure actuelle, le seul traitement reste la chirurgie, particulièrement invalidante et possédant un taux de survie inférieur à 21% en cas de rechute et dans les formes les plus graves. Fort de ce constat, l'UMR 1240 Inserm/IMoST UCA développe des prodrogues exploitant le microenvironnement du tissu tumoral. En effet, le chondrosarcome se caractérise par une matrice extracellulaire chondrogénique, riche en protéoglycanes, et est également une tumeur très hypoxique. L'équipe de chimiste de l'unité a donc développé des prodrogues vectorisées vers les protéoglycanes et activables en hypoxie (Hypoxia activable prodrug ou HAP). La molécule 8QA a démontrée son efficacité dans de nombreuses études in vitro mais également in vivo sur un modèle de chondrosarcome humain extra-myxoïde squelettique.

L'objectif de cette étude était de caractériser, au niveau du transcriptome (RNAseq haut débit) les mécanismes à l'origine de l'activité antitumorale de la molécule 8QA, mais également d'optimiser les modèles expérimentaux in vitro. Pour cela, des modèles de culture en 3 dimensions (sphéroïdes) de deux lignées de chondrosarcome humain (JJ012, SW1353) ont été caractérisés, en termes de prolifération cellulaire (marquage ki-67), d'apoptose (TUNEL), et de microenvironnement tumoral (protéoglycanes et hypoxie).

En conclusion, les différents modèles mis au point sont représentatifs de la pathologie étudiée et la stratégie thérapeutique (ciblant les protéoglycanes et l'hypoxie) est prometteuse pour la prise en charge thérapeutique du chondrosarcome.

Soutiens : Ligue Auvergne-Rhône Alpes contre le cancer, Projet PRTK InCa/DGOS,
Remerciements : Christelle Soubeyrand-Damon (ANIPATH, GReD), Christelle Blavignac (CICS).

Poster # 68

ALK Fusion Variants Detection by Targeted RNA-Next Generation Sequencing and Clinical Responses to Crizotinib in ALK-Positive Non-Small Cell Lung Cancer

Anne McLEER-FLORIN[a,b,f,h], Michael DURUISSEAUX[c,f], Julian PINSOLLE[c,f], Sylvian DUBOURG[b], Julie MONDET[a,b,g,h], Mathilde PHILLIPS HOULBRACQ[c,f], Nelly MAGNAT[b], Julien FAURÉ[d,h], Amandine CHATAGNON[d], Florence de FRAIPONT[b,f], Matteo GIAJ LEVRA[c,f], Anne-Claire TOFFART[c,f,h], Gilbert FERRETTI[e,f,h], Pierre HAINAUT[b,f,h], Elisabeth BRAMBILLA[f,h], Denis MORO-SIBILO[c,f,h], Sylvie LANTUEJOUL[f,h,i]

a) Département d'Anatomie et Cytologie Pathologiques, Pôle de Biologie et Pathologie, CHU Grenoble Alpes, Grenoble
b) Plateforme de Génétique Moléculaire des Cancers, Pôle de Biologie et Pathologie, CHU Grenoble Alpes, Grenoble
c) Clinique de Pneumologie, Unité d'Oncologie Thoracique, Pôle Thorax et Vaisseaux, CHU Grenoble Alpes, Grenoble
d) Plateforme de Biologie Moléculaire, Pôle de Biologie et Pathologie, CHU Grenoble Alpes, Grenoble
e) Clinique Universitaire de Radiologie et Imagerie, CHU Grenoble Alpes, Grenoble,
f) UGA/INSERM U1209/CNRS 5309-Institute for Advanced Biosciences - Université Grenoble Alpes, Grenoble
g) TheRex TIMC-IMAG CNRS UMR 5525, Grenoble
h) Université Grenoble Alpes, Grenoble
i) Département de biopathologie – MESOPATH, Centre de Lutte Contre le Cancer Léon Bérard, Lyon FRANCE

Contact: amcleer@chu-grenoble.fr

Keywords: lung; ALK; FISH; IHC; NGS; RNA-seq; crizotinib; borderline-positive FISH

Objectives: The aim of the present study was firstly to assess in a clinical setting the yields of an amplicon-based parallel RNA sequencing (RNA-seq) assay for ALK fusion transcript variants detection in comparison with immunohistochemistry (IHC) and fluorescent in-situ hybridization (FISH) in a selected population of ALK-positive and ALK-negative non-small cell lung cancer (NSCLC) cases, and secondly to evaluate the impact of the ALK variant on crizotinib efficacy.

Materials and methods: The cohort used for the assessment of the RNA-seq assay comprised 53 samples initially diagnosed as being ALK-positive based on the results obtained by IHC and/or FISH, and 23 ALK-negative samples. A distinction was made between 'truly' IHC/FISH positive or 'truly' IHC/FISH negative samples, and those for which the IHC and/or FISH were equivocal (IHC) or borderline-positive (FISH).

Results: On the overall population, RNA-seq sensitivity (Se) and specificity (Spe) were of 80% and 100%, respectively when IHC and FISH were combined. For the 31 'truly positive' samples, Se and Spe of 100% were reached. An ALK status could be assigned by RNA-seq in 10/10 of the equivocal and/or borderline-positive IHC/FISH cases, 2/7 IHC/FISH discordant cases. When crizotinib efficacy was evaluated according to the type of ALK variant, better clinical outcomes were observed in crizotinib-treated patients with EML4-ALK v1/v2/others variants compared to v3a/b variants.

Poster # 69

Development of Preclinical Models to Accelerate the Identification of Next Generation Treatments for Patients with Acquired Resistance to Targeted Therapies

Philippe MICHON[1], Guillaume LANG[1], Ludovic BIGOT[2], Olivier DEAS[1], Luc FRIBOULET[2], Yohann LORIOT[2], Fabrice ANDRE[2], Jean-Charles SORIA[2], Stefano CARO[1], Marie TAVERNIER[1], Katell MEVEL[1], Enora LE VEN[1], Jean-Gabriel JUDDE[1], Benjamin BESSE[2]

1. XenTech, Evry, France
2. Institut Gustave Roussy, Villejuif, France

Contact: philippe.michon@xentech.eu

Keywords: EGFR TKi, FGFR, cancer therapy, PDX, acquired resistance

The last 20 years have witnessed the identification of an increasing number of druggable oncogenic drivers and the development and clinical use of specific inhibitors against these targets. Unfortunately, patients treated with targeted therapies consistently develop resistance and progression under treatment. Hence, important scientific, pharmaceutical and medical research efforts are directed towards understanding the mechanisms of acquired resistance to explore new therapeutic pathways.

The MATCH-R clinical trial enrolls patients with oncogene-driven cancer who have had previous clinical response to targeted therapy and subsequently experienced disease progression. In the framework of this project, Gustave Roussy and XenTech are joining forces to develop a panel of patient-derived xenografts (PDXs) derived from biopsies collected from these patients at the stage of acquired resistance. These PDX models will be used to improve knowledge on the mechanisms underlying resistance to treatment and to evaluate response to new treatments.

In this perspective, the development of 75 PDX-AR (Active Resistance) models is planned over 3 years. All the models are maintained under the same therapeutic pressure the parental tumor was submitted to at the time of biopsy, and will be subjected to extensive phenotypic and genotypic characterization.

Poster # 70

Variation of Ribosome Composition and Translational Reprogramming during Human Mammary Epithelial-To-Mesenchymal Transition

Flora NGUYEN VAN LONG[1], Nathalie PION[1], Yohann COUTE[2], Anne-Pierre MOREL[3], Virginie MARCHAND[4], Yuri MOTORIN[4], Oliver NAMY[5], Alain PUISIEUX[3], Jean-Jacques DIAZ[1] and Virginie MARCEL[1]

1. Cancer Research Center of Lyon, UMR INSERM 1052 CNRS 5286, Centre Léon Bérard, Université Lyon 1, Nuclear domains and pathologies team, Lyon, France
2. Large scale laboratory of biology, UMR_S 1038 Inserm/CEA/Université de Grenoble Alpes, EDyP Laboratory, Grenoble, France
3. Cancer Research Center of Lyon, UMR INSERM 1052 CNRS 5286, Centre Léon Bérard, Université Lyon 1, EMT and cancer cell plasticity team, Lyon, France
4. NGS platform, Bioingénérie Moléculaire Cellulaire et Thérapeutique, Université de Lorraine, Vandoeuvre-les-Nancy, France
5. Institut de Biologie Intégrative de la Cellule, Université Paris-Sud, Paris, France

Contact: Flora.NGUYENVANLONG@lyon.unicancer.fr

Keywords: ribosome, translation, EMT, breast cancer

It has been thought for a long time that ribosome, the machinery translating mRNAs into proteins, displays invariable intrinsic translational activity. However, it emerges that ribosome can act as a direct regulator of translation. Ribosome can indeed exhibit distinct composition that affects its three-dimensional structure on which relies its intrinsic activity. Change in composition occurs both at protein and RNA levels. Our team showed that ribosomes with alteration of rRNA 2'-O-ribose methylation patterns display distinct translational activities (Belin et al, Plos OnE 2009; Marcel et al, Cancer Cell 2013; Erales et al, PNAS 2017). In particular, alterations of rRNA methylation patterns directly favour the Internal Ribosomal Entry Sites (IRES)-dependent translation of a subset of oncogenes promoting tumorigenesis.

It has been pointed out recently that increased IRES-dependent translation of Epithelial-to-Mesenchymal Transition transcription factors (EMT-TFs) contributes to EMT establishment. EMT corresponds to the transdifferentiation of epithelial cells to mesenchymal ones and promotes mammary tumorigenesis that results in one of the most aggressive type of breast cancers, the Claudin-Low subtype. While transcription and epigenetic reprogramming have been largely explored in EMT, little is known about the contribution of translational reprogramming and in particular of the ribosome-induced translational reprogramming.

In this study, we analysed the variations of ribosome composition and translational regulation using original and innovative RNA- and protein-based genome-wide approaches between epithelial and mesenchymal cells. We observed specific ribosome compositions and translatome signatures associated with EMT. Altogether, these data show for the first time the particular composition of EMT-derived ribosome that could become innovative biomarker and therapeutic target for the Claudin-Low tumors.

Poster # 71

Quality Assessment by Proteomics of Exosomes From Cultured Cancer Cells Prepared by Various Centrifugation-Based Protocols

Delphine PFLIEGER[1], Sylvie JAQUINOD-KIEFFER[1], Josiane DENIS[2], Nadia CHERRADI[2]

1. INSERM-CEA-UGA UMR-1038, BGE, BIG, CEA, Grenoble, France
2. INSERM-CEA-UGA UMR-1036, BCI, BIG, CEA, Grenoble, France

Contact: delphine.pflieger@cea.fr

Keywords: cultured cancer cells, small extracellular vesicles, proteomics

Exosomes are extracellular vesicles (EVs) which have been the focus of intensive studies over the last decade to decipher their biogenesis mechanism, their content in various types of biomolecules (namely DNA, mRNAs, microRNAs, proteins) and their impact on recipient cells. However, various preparation protocols were carried out in the diverse studies, which likely led to the more or less selective purification of the desired vesicles, and thus to a variable level of contamination by microvesicles of neighboring size (100-1000 nm compared to 50-130 nm for exosomes). We are interested in analyzing exosomes produced by cultured NCI-H295R cells, a human cell line derived from an aggressive adrenocortical carcinoma. To establish a protocol for exosome collection, we favored options based on iterative steps of centrifugation at increasing speed due to its ease of implementation and time-efficiency. To estimate the enrichment in exosomes of the sample finally obtained by ultracentrifugation, we analyzed serially collected fractions by proteomics. We then referred to the protein markers recently described by Clothilde Théry and co-workers (Kowal J. et al, PNAS 2016) as being specific for tetraspanin-enriched exosomes (TSG101, syntenin-1), for small EVs in general (e.g. ADAM10, EHD4) or specific of medium or large EVs (e.g. actinin-4). Relative quantification of these protein markers allowed estimating the purity level of the exosomes yielded by the tested protocols. We thus here provide a proteomics-based evaluation of protocols using ultracentrifugation to assess the enrichment level in bona fide exosomes and small EVs from cultured NCI-H295R cells. In addition, we show the possibility to identify phosphoproteins from as little as 5 µg of sEV protein material. The first obtained results indicate that a phosphoproteomic analysis of small EVs may allow identifying key proteins involved in signaling pathways that may be perturbed in the studied cancer.

Poster # 72

The Opposite Roles of the NLRP7inflammasome in the Control of Normal and Tumor Placental Development

Déborah REYNAUD[1,2], R ABI NAHED[1,3], PA BOLZE[4], W TRABOULSI[1,2], T ABOUSSAOUIRA[6], H BOUFETTAL[6], M. BENHAROUGA[2,5] and N ALFAIDY[1,3]

1. Biology of cancer and infection Laboratory, BIG, CEA-Grenoble, Grenoble, France
2. Grenoble-Alpes university, Grenoble, France
3. French Health and Biomedical Research Institute (INSERM), Paris, France
4. Gynecology Obstetrical department, Lyon-Sud Hospital, France
5. Biology and Chemistry of metals Laboratory, BIG, CEA Grenoble, Grenoble, France
6. Casablanca Ibn Rochd hospital, Faculty of Medicine and Pharmacy of Casablanca

Contact: deborah.reynaud@cea.fr

Keywords: cancer, placenta, choriocarcinoma, NLRP7 inflammasome , hydatidiforme moles

Placental choriocarcinoma (CC) is a veritable cancer that develops upon abnormal pregnancies, such as Hydatidiform moles (HMs). CC is a very invasive cancer that metastasizes in multiple maternal organs. Recent studies established an association between recurrent HMs and mutations in a gene called Nlrp7. NLRP7 is member of a new family of proteins involved in intracellular inflammatory processes. Nevertheless, the role of NLRP7 remained to be elucidated in normal and tumor human placentation.

2D normal trophoblast (HTR) and choriocarcinoma cells (JEG3) and 3D (first trimester placental explants) culture systems were used to characterize NLRP7 expression, regulation and role in human placental development. A distinctive cohort of sera and placental tissue collected from HM, CC patients and controls was also used.
In the physiological context, we demonstrated that NLRP7 is more expressed during the hypoxic period of placental development compared to its normoxic period. NLRP7 knockdown in HTR cells decreased their proliferation, but promoted their migration and invasion. These results were confirmed in the 3D culture system.
At the clinical level, we demonstrated a differential localizations of NLRP7 between CTL and HM placentas and increased expression of NLRP7 in HM and CC tissues along with an increase in its mRNA levels.
These finding were confirmed by demonstrating that JEG3 expressed higher levels of NLRP7 compared to HTR cells. NLRP7 knockdown in JEG3 decreased their proliferation, migration and invasion. We also demonstrated that JEG3 do not express Caspase 1 and IL-1b, two major effectors of the inflammasome pathway.

Altogether our results demonstrate that NLRP7 controls key parameters of normal and tumor placental development. Its differential control of trophoblast migration and invasion in normal vs tumor trophoblasts strongly suggests its involvement in choriocarcinoma progression through an inflammasome independent pathway.

Poster # 73

L'implication de l'Histone Déacétylase SIRT1 dans le cancer sporadique du sein : un biomarqueur pronostique potentiel ?

Khaldoun RIFAÏ[1,2], Mouhamed IDRISSOU[1,2], Marine DAURES[1,2], Yves-Jean BIGNON[1,2], Frédérique PENAULT-LLORCA[2,3], Dominique BERNARD-GALLON[1,2]

1. Departement d'oncogénétiques du Centre Jean Perrin, CBRV, 28 place Henri-Dunant, 63001, Clermont- Ferrand, France.
2. INSERM U1240 - IMoST, 58 Rue Montalembert, 63005 Clermont-Ferrand, France.
3. Departement de Biopathologie du Centre Jean Perrin, 58 Rue Montalembert, 63011 Clermont-Ferrand, France

Contact : K.rifaii@live.com

Mots clés : cancer du sein, classification moléculaire, SIRT1, déacétylation, analyse statistique

Le cancer du sein est la cause principale de décès par cancer chez les femmes dans le monde. La complexité de la cancérogenèse implique des modifications épigénétiques qui peuvent aboutir à la transformation maligne des cellules. Ces altérations épigénétiques comportent entre autres, les modifications post-traductionnelles des histones. SIRT1 est une histone déacétylase de classe III impliquée dans la tumorigenèse, la réparation de l'ADN, la régulation de l'apoptose, le remodelage de la chromatine et la régulation de l'expression des gènes. Son rôle dans le cancer du sein reste toujours controversé à cause de ses fonctions suppressives de tumeur, ainsi que promotrices de tumeur qui ont été rapportées. En outre, il existe très peu de rapports disponibles où l'expression de SIRT1 est analysée de manière exhaustive dans les tumeurs mammaires humaines classées par sous-type moléculaire. Sur une cohorte de 135 tumeurs de sein et leurs tissus sains correspondants, on a montré pour la première fois un double profil d'expression de SIRT1 dans les carcinomes mammaires humains, suggérant son rôle hétérogène dans les 5 sous-types moléculaires de la classification St Gallen du cancer du sein. On a aussi identifié une nouvelle cible de SIRT1, la marque H3k4ac, en mettant en évidence leur colocalisation et interaction sur les promoteurs de 6 gènes fortement impliqués dans le cancer sporadique du sein {ESR1, ESR2, EZH2, BRCA1, AR et P300}. Cette étude vise donc, à nous donner une idée quant au rôle de SIRT1 dans le cancer du sein, qui semble être largement dépendant de ses taux d'expression dans les différents sous-types moléculaires, ainsi d'investiguer son rôle dans la régulation de ces 6 gènes dérégulés.

Poster # 74

Regulation of Metabolic Enzymes by Lysine Deacetylase Inhibitors in A549 Non-Small Cell Lung Cancer Cells

M SEVE [1,2,3], A MARTIN-BERNABE [1,2,3,4], J TARRAGO-CELADA [4], V CUNIN [1,2,3], S MICHELLAND [1,2,3], R CORTES [4], M CASCANTE [4], S BOURGOIN-VOILLARD [1,2,3]

1. Univ. Grenoble Alpes, LBFA et BEeSy, PROMETHEE Proteomic Platform, Grenoble, France
2. Inserm, U1055, PROMETHEE Proteomic Platform, Grenoble, France
3. CHU de Grenoble, Institut de Biologie et de Pathologie, PROMETHEE Proteomic Platform, Grenoble, France
4. Department of Biochemistry and Molecular Biology, IBUB, Faculty of Biology, Universitat de Barcelona and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Michel.Seve@univ-grenoble-alpes.fr

Keywords: non-small cell lung cancer, metabolic reprogramming, inhibitors of lysine deacetylases, quantitative proteomics

Metabolic reprogramming is nowadays known as a hallmark of cancer. It enables cancer cells to adapt their cellular metabolism to new environmental conditions of limited nutrient and oxygen supply that are characteristic in the tumor microenvironment. Protein lysine acetylation has also emerged recently as a metabolism-coordinating mechanism and growing evidence has shown that acetylation regulation of metabolic enzymes plays an essential role in cancer. Consequently, inhibitors of lysine deacetylases (KDACis) have drawn attention as promising strategies for therapeutic intervention. According this statement, this study aimed to analyse the changes in the proteome of A549 non-small cell lung cancer (NSCLC) in response to hypoxia and KDACi treatments with a special focus on the proteins associated with metabolism. The quantitative proteomics approach was carried out by using the FASP (Filter Aided Sample Preparation) method combined with a dual protease digestion (Lys-C/ trypsin) before labelling the resulting peptides with iTRAQ 8-plex reagents. Then, the labelled peptides were fractionated in two dimensions (OFFGEL/RP nanoLC) prior MALDI-TOF/TOF mass spectrometry analysis. MS and MS/MS data were analysed by Protein Pilot software and quantitation was validated by the R package IsobarPTM. This proteomic approach led to the identification and quantitation of 834 proteins and evidenced the capacity of KDACis to reverse the tumor metabolic phenotype, an effect enhanced under hypoxia conditions, by changing metabolic enzyme expression profiles, especially in glycolysis and Krebs cycle. These enzyme expression changes were validated by Western Blot analysis. Moreover, glucose uptakes, production of lactate analysis and enzyme activity determination corroborated the implication of these enzymes in the reversion of the A549 NSCLC metabolic phenotype. Together, these results allow us to better understand how KDAC inhibitors control metabolic pathways under hypoxia in NSCLC.

Poster # 75

Coordinated Regulation of Focal Adhesion and Actin Dynamic During Cell Migration

Christelle FORCET-VAUCHEL, Violaine TRIBOLLET, Catherine CERUTTI, Jean-Marc VANACKER

Physiopathology of Orphan nuclear receptors, Institut de Génomique Fonctionnelle de Lyon, UMR5242 CNRS/INRA/UCBL/ENS, 32-34 Avenue Tony Garnier, 69364 Lyon cedex 07
Contact: christelle.forcet@ens-lyon.fr

Keywords: adhesion, actin, ERR, cancer

Cell migration is essential for embryonic development, tissue repair and immune response. Its misregulation can lead to several pathologies including tumor formation and cancer metastasis. Cell migration requires reorganization of the actin cytoskeleton and adhesion to the extracellular matrix, two dynamic processes that must be tightly coordinated.

High expression of the ERRα orphan nuclear receptor in tumors is correlated with a poor prognosis. Notably ERRα contributes to cancer progression by regulating cell migration and invasion. In this respect, our recent results show that inactivation of ERRα leads to defects in both actin polymerisation and focal adhesion formation in breast cancer cells. By exploring the molecular mechanisms involved in regulation of these processes, we show that ERRα regulates the p38 signaling pathway which plays a crucial role in control of actin dynamics. Furthermore ERRα modulates the expression of MAP4K4, a protein involved in regulation of focal adhesion disassembly. These results demonstrate that ERRα seems to be a major actor involved in tumoral cell migration through coordinated regulation of actin organization and cell adhesion.

Poster # 76

Developing Humanized Patient-Derived Xenograft (PDX) Models Using the IPS Cells Technology

Pauline WAJDA[1,2,3,4], Isabelle GODDARD[3,4], Aurélia HUYGHE[1], Coline COUILLAULT[2], Séverine TABONE-EGLINGER[4,5], Olivier TREDAN[6], Isabelle RAY-COQUARD[6], Olivier DUCHAMP[7], Caroline MIGNARD[7], Christophe CAUX[2]*, Bertrand DUBOIS[2]* and Fabrice LAVIAL[1]*

1. Cellular Reprogramming and Oncogenesis Laboratory - Cancer Research Center of Lyon, INSERM U1052-CNRS UMR5286, Université de Lyon, France.
2. Lab "Targeting of the tumor and its immune environment" - Cancer Research Center of Lyon, INSERM U1052-CNRS UMR5286, Université de Lyon, France.
3. Laboratoire des modèles tumoraux- Cancer Research Center of Lyon, INSERM U1052-CNRS UMR5286, Université de Lyon, France.
4. Fondation Synergie Lyon Cancer – Centre Léon Bérard, Lyon, France.
5. Department of Translational Research and Innovation, Centre Léon Bérard, Lyon France
6. Medical Oncology, Centre Léon Bérard, Lyon France.
7. Oncodesign, 20 rue Jean Mazen, BP 27627, 21076 Dijon

And the other members of IMODI consortium http://www.imodi-cancer.org/
Contact: pauline.wajda@lyon.unicancer.fr

Keywords: iPS cells, hematopoietic stem cells, humanized mice

Patient-derived xenografts (PDX) maintain molecular profiling and enable to monitor patient tumor growth in a complex microenvironment. However, the use of immunodeficient recipient mice prevents to investigate the interactions between the tumor and the immune system, which now emerge as critical regulators of oncogenesis and as promising therapeutic targets. Although PDX models can be humanized with CD34+ hematopoietic stem cells (HSC), the heterologous origins of the tumor and immune cells may cause artefacts due to alloreactivity.

In this context, the development of PDX models with an autologous immune system would represent a real breakthough, especially to assess the efficacy of novel immunotherapies. As HSC can usually not be obtained from cancer patients, our project aims to take advantage of the human induced pluripotent stem (hiPS) cell technology to generate patient-specific HSC.

In context of the IMODI project, PDX models were established from patients diagnosed with breast or ovarian cancers and peripheral blood cells were collected, from which we generated several hiPS cells (using OSKM Sendai viruses) in parallel. After an in depth molecular characterization based on pluripotency status and in vitro differentiation potential, several hiPS lines were selected and injected by various routes together with OP9 stromal cells into NSG mice to obtain teratomas. Optimal teratoma formation was obtained 6-8 weeks after testis injection and iPS-derived CD34+ cells could be identified. They were found to express typical HSC markers such as CD90 and CD166, can be enriched to a high purity and are currently tested for their capacity to reconstitute an immune system in NSG mice. The next step will be to engraft them with the corresponding PDX.

Such humanized PDX models should allow the research community to address in depth the role of the immune system during cancer progression and to identify new strategies to harness immune cells to control tumor growth.

Poster # 77

La distribution spatiale des radicaux libres oxygénés permet d'expliquer la différence d'activation des processus d'invasion/migration des cellules souches cancéreuses en réponse aux photons et aux ions carbone

Anne-Sophie WOZNY[1,2], Gersende ALPHONSE[1,2], Guillaume VARES[3,4], Caterina MONINI[5], Jean-Baptiste GUY[1,6], Akira FUJIMORI[7], Jean-Claude MONBOISSE[8], Nicolas MAGNE[1,6], Michael BEUVE[4], Tetsuo NAKAJIMA[4] and Claire RODRIGUEZ-LAFRASSE[1,2]

1. Univ Lyon, Faculté Médecine Lyon-Sud, Laboratoire de Radiobiologie Cellulaire et Moléculaire, CNRS UMR5822, 69921 Oullins, France
2. Hospices Civils de Lyon, Centre Hospitalier Lyon-Sud, 69495 Pierre-Bénite, France
3. Advanced Medical Instrumentation Unit, Okinawa Institute of Science and Technology Graduate University, Okinawa, 904-0495, Japan
4. Department of Radiation Effects Research, National Institute of Radiological Sciences, National Institute for Quantum and Radiological Science and Technology, Inage-ku, Chiba, 263-8555, Japan
5. Univ Lyon, Université Lyon 1, UMR CNRS5822 /IN2P3, IPNL, PRISME, PHABIO, 69322 Villeurbanne, France
6. Département de Radiothérapie, Institut de Cancérologie de la Lucien Neuwirth, St Priest en Jarez, France
7. Department of Basic Medical Sciences for Radiation Damages, National Institute of Radiological Sciences, Inage-ku, Chiba, 263-8555, Japan
8. CNRS UMR 6237, Université de Reims Champagne-Ardenne, CHU de Reims, 51100 Reims, France

Contact : anne-sophie.wozny@univ-lyon1.fr

Mots clés : cellules souches cancéreuses, Hypoxie, transition épithélio-mésenchymateuse, ROS, irradiation photonique, ions carbone

Objectifs : La transition épithélio-mésenchymateuse (EMT) est le mécanisme qui permet l'échappement des cellules cancéreuses de la tumeur pour former des métastases. Alors que la radiothérapie conventionnelle favorise l'invasion/migration des cellules souches cancéreuses (CSCs), les ions carbone diminuent ces processus. Cependant, les CSCs, radio/chimiorésistantes sont localisées dans des niches hypoxiques tumorales où l'hypoxie amplifie les effets biologiques liés à la radioresistance. Ainsi, la compréhension des mécanismes différentiels impliqués dans la réponse aux photons et aux ions carbone, particulièrement en hypoxie, permettrait de mieux comprendre le processus d'échappement tumoral.
Méthodes : Les processus de motilité, d'invasion/migration et les voies de signalisation de l'EMT ont été étudiés en réponse à une irradiation par photons et ions carbone pour deux lignées de tumeurs des voies aéro-digestives supérieures et leur sous-population de CSCs, en normoxie et hypoxie.
Resultats : Après avoir confirmé en normoxie l'augmentation de l'invasion/migration en réponse aux photons et la diminution après irradiation par ions carbone, nous avons montré que sous hypoxie, les deux types d'irradiation conduisent à une diminution du processus. Afin de comprendre cette réponse différentielle, les profils de phosphorylation des voies Akt/mTor, STAT3 et ERK/p38/MSK impliquées dans l'EMT ont été établis. En réponse aux photons, l'activation des cascades de kinases est importante pour les 3 voies alors qu'elle l'est plus faiblement en hypoxie, et pas du tout en réponse aux ions carbone quelle que soit la tension en oxygène.
Conclusion : Nos résultats montrent un profil d'activation des trois principales voies de l'EMT fonction du type d'irradiation et de la tension en oxygène. La production de ROS, uniformément répartie dans la cellule en réponse aux photons permet l'activation des voies contrairement aux ions carbone où les ROS sont uniquement localisés dans la trace.

Poster # 78

OPTISTEM Synthetic Medium: An Adapted Serum-Free Alternative for Three-Dimensional Cell Cultures of Triple Negative Breast Cancer Cell Lines

Clémence DUBOIS[1,4], Pierre DAUMAR[1], Corinne AUBEL[2], Jean GAUTHIER[3], Pierre VIDALINC[3], Bernard VIDALINC[3], Emmanuelle MOUNETOU[1], Frédérique PENAULT-LLORCA[4] & Mahchid BAMDAD[1]

1. Université Clermont Auvergne, Institut Universitaire de Technologie, INSERM, U1240, Imagerie Moléculaire et Stratégies Théranostiques, F-63000 Clermont Ferrand, France
2. Université Clermont Auvergne, Faculté de médecine, INSERM, U1240, Imagerie Moléculaire et Stratégies Théranostiques, F-63000 Clermont Ferrand, France
3. Biomarqueurs S.A.S, 10 rue des Boules, 63200 Riom, France
4. Université Clermont Auvergne, Centre Jean Perrin, INSERM, U1240, Imagerie Moléculaire et Stratégies Théranostiques, F-63000 Clermont Ferrand, France

Contact: clemence.dubois@etu.uca.fr

Keywords: serum-free medium, optistem, Triple Negative Breast Cancer cell line, MDA-MB-231, SUM1315, proliferative three dimensional cell culture, spheroid, drug screening

Triple Negative breast cancers are particularly aggressive and of poor prognosis. In order to screen potential targeted therapies, preclinical studies proceed to in vitro cell culture techniques, such as monolayer (2D) or three-dimensional (3D) cell cultures. These techniques need the use of culture media, presenting common components and different supplements. Most media are supplemented with fetal bovine serum, but its contribution is controversial because of the batch-to-batch heterogeneity. Thus, in order to increase in vitro cell culture homogeneity, the development of serum-free formulations has been greatly increasing. Biopass company developed the serum-free medium optistem, initially adapted to the culture of mesenchymal stem cells and meeting all quality controls requirements for the culture of this specific cell type.

In this context, our works aimed to develop monolayer and three-dimensional cell cultures of triple negative breast cancer cell lines MDA-MB-231 and SUM1315 with the new optistem serum-free formulation. In monolayer cell culture, cell adherence, proliferation, viability and phenotype were maintained in optistem medium for both cell lines. Then, spheroid formation was performed with a high reproducibility (superior to 98%) in optistem, and 3D cell cultures presented higher proliferation rates than in the serum-containing reference medium. Moreover, increased drug sensitivity thresholds were highlighted with this culture medium in 3D cell culture, allowing quick high throughput drug screenings. These results open the way to the common use of optistem medium in preclinical cancer research studies.

Poster # 79

Antagonism of EG-VEGF Receptors as Targeted Therapy for Choriocarcinoma Progression In Vitro and In Vivo

Nadia ALFAIDY[3], W TRABOULSI[1,2,3], F SERGENT[1,2,3], H BOUFETTAL[4], S BROUILLET[1,2,3,5], R SLIM[6], P HOFFMANN[1,2,3,5], M BENLAHFID[4], QY ZHOU[7], G BALBONI[8], V ONNIS[8], PA BOLZE[9,10,11], A SALOMON[1,2,3], P SAUTHIER[6], F MALLET[11,12], T ABOUSSAOUIRA[4], JJ FEIGE[1,2,3], M BENHAROUGA[2,3,13]

1. Institut National de la Santé et de la Recherche Médicale, Unité Grenoble, Grenoble, France.
2. University Grenoble-Alpes, Grenoble, France
3. Commissariat à l'Energie Atomique et aux Energies Alternatives (CEA), Biosciences and Biotechnology Institute of Grenoble, Grenoble, France
4. Faculty of Medicine and Pharmacy, University Hassan II Casablanca and Ibn Rochd Hospital of Casablanca, Obstetrics and Gynecology Department, Casablanca, Morocco
5. University Hospital of Grenoble, Department of Obstetrics and Gynaecology, and Laboratoire d'Aide à la Procréation-CECOS, La Tronche, France
6. Department of Human Genetics, McGill University Health Centre Research Institute, Montréal, Quebec, Canada
7. Department of Pharmacology, University of California, Irvine, California
8. Department of Life and Environmental Sciences, University of Cagliari, Cagliari, Italy
9. University of Lyon 1, University Hospital Lyon Sud, Department of Gynecological Surgery and Oncology, Obstetrics, Lyon, France
10. French Reference Center for Gestational Trophoblastic Diseases, University Hospital Lyon Sud, Chemin du Grand Revoyet, Pierre Bénite, Lyon, France
11. Joint Unit Hospices Civils de Lyon-bioMerieux, Cancer Biomarkers Research Group, University Hospital Lyon Sud, Lyon, France
12. EA 7426 Pathophysiology of Injury-induced Immunosuppression, University of Lyon 1 Hospices Civils de Lyon bioMérieux, Hôpital Edouard Herriot, Lyon, France
13. Centre National de la Recherche Scientifique, Unité Mixte de Recherche, Laboratoire de Chimie et Biologie des Métaux, Grenoble, France
14. Institut National de la Santé et de la Recherche Médicale, Unité Grenoble, Grenoble, France

Contact: nadia.alfaidy-benharouga@cea.fr

Keywords: EG-VEGF, choriocarcinoma, mouse model, therapy, cancer progression

Objectives: Choriocarcinoma (CC) is the most malignant gestational trophoblastic disease that often develops from complete hydatidiform moles (CHM). Neither the mechanism of CC development nor its progression are yet characterized. We have recently identified EG-VEGF (endocrine gland-derived vascular endothelial growth factor) as a novel key placental growth factor that controls trophoblast proliferation and invasion. EG-VEGF acts via two receptors PROKR1 and PROKR2. Here, we hypothesized that EG-VEGF receptors can be targeted for CC therapy.
Methods: Three approaches were used, i) a clinical investigation comparing circulating EG-VEGF in control (n=20) and in distinctive CHM (n=38) and CC (n=9) cohorts, ii) an in vitro study investigating EG-VEGF effects on the CC cell line JEG3, and iii) an in vivo study including the development of a novel CC mouse model, through a direct injection of JEG3-luciferase into the placenta of gravid SCID-mice.
Results: Both placental and circulating EG-VEGF levels were significantly increased in CHM and CC (x5) patients. EG-VEGF increased JEG3 proliferation, migration and invasion, in 2D and 3D culture systems. JEG3 injection in the placenta caused CC development with large metastases compared to their injection into the uterine horn. Treatment of the animal model with EG-VEGF receptor's antagonists significantly reduced tumor development and progression and preserved pregnancy. Antibody-array and immunohistological analyses of the placenta further deciphered the mechanism of the antagonist's actions.

Conclusion: Overall, our work describes a novel pre-clinical animal model of CC and bring evidences that EG-VEGF receptors can be targeted for CC therapy. This may provide safe and less toxic therapeutic options compared to the currently used multi-agent chemotherapies.

Poster # 80

A Large Scale Proteome Analysis of the Gefitinib Resistance Overcome by KDAC Inhibition in Mutant KRAS Lung Adenocarcinoma

Sylvia G LEHMANN[1,2, 3,4], Michel SEVE[1,2,3], Laetitia VANWONTERGHEM[5], Sylvie MICHELLAND[1,2, 3], Valérie CUNIN[1,2,3], Jean-Luc COLL[5], Amandine HURBIN[5], Sandrine BOURGOIN-VOILLARD[1,2,3]

1. Univ. Grenoble Alpes, LBFA and BEeSy, PROMETHEE Proteomic Platform, Grenoble, France
2. Inserm, U1055, PROMETHEE Proteomic Platform, Grenoble, France
3. CHU Grenoble Alpes, Institut de Biologie et de Pathologie, PROMETHEE Proteomic Platform, Grenoble, France
4. Univ. Grenoble Alpes, ISTerre, F-38000 Grenoble, France
5. Cancer target and experimental therapeutics, Institute for Advanced Biosciences, INSERM U1209, CNRS UMR5301, Grenoble Alpes University, F-38000 Grenoble, France

Contact: SMichelland@chu-grenoble.fr

Keywords: non-small cell lung cancer, EGFR-TKI, resistance, gefitinib, inhibitors of lysine deacetylases, quantitative proteomics

As previously reported, KDAC inhibitors (KDACi) overcome gefitinib resistance in non-small cell lung cancer (NSCLC) including mutant-KRAS lung adenocarcinoma. To identify which proteins are involved in the restoration of this sensitivity and to provide new therapeutic targets for mutant-KRAS lung adenocarcinoma, we performed an iTRAQ quantitative proteomic analysis of a subcellular fractionation of H358-NSCLC treated with gefitinib and KDACi (TSA/NAM) versus gefitinib alone. The 86 proteins found to have been significantly dysregulated between the two conditions, were mainly involved in cellular metabolism and cell transcription processes. As expected, the pathway related to histone modifications was affected by the KDACi. Pathways known for controlling tumor development and (chemo)-resistance (miRNA biogenesis/glutathione metabolism) were affected by the KDACi/gefitinib treatment. Moreover, 57 dysregulated proteins were upstream of apoptosis and hence provide potential therapeutic targets. Among these 57 proteins, eEF1A2 and STAT1 expressions were inhibited by siRNA, which resulted in a slight decrease in H358-NSCLC viability for eEF1A2 siRNA and no restoration of gefitinib sensitivity for STAT1 siRNA. In addition, siRNA transfections suggested that both STAT1 and eEF1A2 prevent AKT phosphorylation known for enhancing gefitinib resistance in NSCLC. Therefore, altogether our data provide new insights into proteome regulations in the context of overcoming the NSCLC resistance to gefitinib in H358 KRAS mutated and amphiregulin-overexpressing NSCLC cells.

Poster # 81

Anti Netrin 1 Ab Exerts Antitumor Activity in Combination With Doxorubicin and Modulates Tumor Immune Environment in Osteosarcoma Models

Morgane MONCHANIN[1], Iseulys RICHERT[1], Paul BERCHARD[1], Jean Baptiste LANGLOIS[3], Agnès BERNET[2], Nicolas GADOT[4], Jean Yves BLAY[1 5], Aurélie DUTOUR[1]

1. Apoptosis and pediatric sarcoma team, CRCL, UMR, INSERM, U1052, Centre Léon Bérard, Lyon, France
2. Apoptose Cancer et Development team, CRCL, Centre Léon Bérard, Lyon, France
3. Animage imaging platform. CERMEP –Bron, France
4. Anatomopathology research platform, CRCL, Lyon France
5. Department of medicine, Centre Léon Bérard, Lyon, France

Contact: Morgane.MONCHANIN@lyon.unicancer.fr

Keywords: osteosarcoma relapse, metastases, tumor microenvironment, chemotherapy

Despite the intensification of chemotherapy regimen, 5 years survival rates for metastatic or relapsed osteosarcoma (OS) remains of 20%. The secreted factor netrin 1 (Nt1) is overexpressed in many human cancers and recent studies showed that blocking Nt1 interaction with its receptors potentiates chemotherapy efficacy. Combining chemotherapies with Nt1 interference could be a promising approach for chemoresistant tumors like OS. Molecular analyses performed on human sarcomas samples showed that OS is the Sarcoma with complex genomic expressing NT1 at highest level ($p<0.002$). Molecular analysis of an OS cohort demonstrated that chemotherapies increased Nt1 expression in primary OS ($p<0.001$) indicating that Nt1 could be a potential target for OS treatment. Thus, we evaluated the antitumoral effects of anti Nt1 monoclonal antibody (aNt1) combined to doxorubicin (Dox) in a rat syngeneic and metastatic OS model either on progressive OS or post operatively to prevent OS relapse.

Given on progressive OS, Dox+aNt1 caused a marked delay in OS progression ($p<0.02$) and dramatically slowed down metastatic spreading: lung metastases were found respectively in 75% and 17% of Dox and Dox+aNt1 treated rats. As post-operative treatment, Dox+aNt1 significantly delayed tumor relapse: 19 days after tumor resection, 10% of the Dox treated tumors hadn't relapsed versus 40% in the Dox+aNt1 treated group. immunohistochemical analyses performed on tumor samples showed that, Dox+aNt1 decreased T effectors $CD8^+$ recruitment and inhibited M2 macrophages $CD163^+$ infiltration. *In vitro* macrophages polarization assays were performed, and confirmed that aNt1, caused a decrease of CD163+ membrane expression.

Our study reporting the anti-proliferative and anti-metastatic effects and of Dox+aNt1 in OS indicate that this combined treatment could be a way to overcome OS chemoresistance by modifications of the tumor microenvironment.

Poster # 82

DNA Repair Enzyme Signature Reveals Subtypes of Responses to Targeted Therapies in Melanoma Cell Lines

Sylvie SAUVAIGO[1], Manel BENKHIAT[4], Florian BRAIZAS[4], Florence de FRAIPONT[2], Caroline ASPORD[3], Stéphane MOURET[4], Joël PLUMAS[3], Fanny BOUQUET[5], Marie-Thérèse LECCIA[3,4]

1. LXRepair, 7 parvis Louis Néel, Grenoble, France
2. UM Biochimie des Cancers et Biothérapies, CHU Grenoble Alpes, France
3. EMR EFS-UGA-INSERM U1209- CNRS, Immunobiology and Immunotherapy of Chronic Diseases
4. Grenoble, France
5. Service de Dermatologie, Allergologie et Photobiologie, CHU Grenoble Alpes, France
6. Institut Roche, 30, cours de l'Ile Seguin, Boulogne-Billancourt, France

Contact: sylvie.sauvaigo@lxrepair.com

About 50% of melanomas carry activating mutation in BRAF or NRAS genes. BRAF/MEK inhibitors elicit a transient effective response but resistance rapidly develops through various MAPK pathway activating mechanisms. As DNA Repair mechanisms are regulated by these signaling pathways we hypothesized that effective inhibition of the MAPK pathway should translate into modifications of DNA Repair capacities.

To gain insights into this hypothesis we characterized various DNA Repair systems of 12 melanoma cell lines treated or not by BRAF and MEK inhibitors (respectively Vemurafenib V and Cobimetinib C), alone and in combination. We thus obtained a comprehensive overview of the cell lines DNA Repair capacities.

Qualitative and quantitative differences were observed between the DNA Repair profiles of the 3 mutation groups in non-treated cells.

Globally DNA Repair capacities of BRAFm cells significantly decreased following treatment by V and V+C. When the cell lines were examined individually, interesting features were observed. 3/7 showed drastic decrease of DNA repair with V and V+C treatment. On the contrary, C alone activated repair in 3/7, possibly reflecting a paradoxical activation of some pathways.

Among the 3 NRASm cell lines, only 1 exhibited a marked decreased of DNA Repair after C treatment. Surprisingly V and V+C activated some repair activities in one WT cell line, possibly reflecting some paradoxical activation of the complex kinase network.

Our results suggest that mutations in kinase signaling pathways impact the DNA Damage Response and translate into specific DNA Repair Enzyme Signatures. We thus showed that it is possible to take advantage of this intricate regulation through characterization of DNA Repair to gain information on the inhibition efficacy of targeted drugs. Interestingly this approach can be conducted on clinical samples.

This study was sponsored by Institut Roche.

Poster # 83

α-Sulfamidophosphonates via MCR: Green Synthesis and Cytotoxic Activity

Khaoula BECHLEM[a], Billel BELHANI[a], Zouhair BOUAZIZ[b], Marc LE BORGNE[b], Seifeddine DJOUAD[a,c], Riadh BEN MANSOUR[d], Mohamed BOUAZIZ[d], Malika BERREDJEM[a]

a) Laboratory of Applied Organic Chemistry LCOA, Synthesis of biomolecules and molecular modelling Group, Badji-Mokhtar - Annaba University, Box 12, 23000 Annaba, Algeria
b) EA 4446 Bioactive Molecules and Medicinal Chemistry, SFR Santé Lyon-Est CNRS UMS3453-INSERM US7, Faculté de Pharmacie-ISPB, Université Claude Bernard Lyon 1, 8 avenue Rockefeller, F-69373 Lyon CEDEX 8, France
c) Laboratory of Therapeutic Chemistry, CHU Benflis Touhami de Batna, Algeria
d) Université de Sfax, Institut Supérieur de Biotechnologie de Sfax, Laboratoire d'Electrochimie et Environnement, Tunisia

Contact: bechlemkhaoula92@yahoo.com

Keywords: multicomponent reaction, microwave synthesis, α-sulfamidophosphonates, cytotoxic activity

Cancer is a major public health problem and a leading cause of death worldwide. More than half of all cancer cases and 60% of deaths from cancer appear in less developed countries.
α-Aminophosphonates have been reported to exert several pharmacological activities such as peptide mimics, antibiotics and pharmacological agents. For that reason, the synthesis of α-aminophosphonates has received considerable attention and significant progress has been made to develop more efficient methods for the synthesis of these compounds.
In this work, a series of novel α-sulfamidophosphonate derivatives was rationally designed and synthesized following the principle of the superposition of bioactive substructures. A multicomponent reaction (MCR) approach was then used to combine three chemical building blocks, namely sulfamide, benzaldehyde and triethylphosphite.
A microwave-assisted synthesis was carried out to access quickly to the target compounds. All structures were confirmed by 13C, 1H NMR, MS, IR, and elemental analysis.
The relative cytotoxicity of these derivatives is reported.

Poster # 84

Characterization of Alternative Splicing Signatures of Glioblastoma Stem Cells Deriving from Human Xenografts

Nabila BERABEZ[1,3], Nuno L. Barbosa MORAIS[4], David MEYRONET[1,2,3], François DUCRAY[1,2,3], Mathieu GABUT[1,3]

1. Cancer Research Centre of Lyon (CRCL, UMR Inserm 1052 CNRS 5286), Centre Léon Bérard, Lyon, France
2. Department of Neurology, Hôpital Pierre Wertheimer, Hospices civils de Lyon, Lyon, France
3. University Claude Bernard Lyon 1 (UCBL), Lyon, France
4. Instituto de Medicina Molecular, Lisbon, Portugal

Contact: nabila.berabez@lyon.unicancer.fr

Keywords: Cancer stem cell, alternative splicing, glioblastoma

Glioblastomas (GBM) are the most aggressive tumors in the adult brain. They contain a small number of treatment-resistant cells, the Glioblastoma Stem Cells (GSCs), which are responsible for tumor initiation, growth, and relapse after standard treatments. Understanding the mechanisms underlying the survival and tumorigenic capacities of GSCs is needed to develop innovative and efficient therapies that are lacking to date. Alternative splicing is a major driver of transcriptome diversity and splicing alterations are known to promote tumorigenesis and invasion in solid cancers. As it remains unclear to what extent alternative splicing regulation favors GBM initiation and progression, we propose to investigate the alterations of splicing programs in 5 GSC in vitro models.

Using an RNA-Seq approach, we identified two alternative splicing factors enriched in GSC compared to differentiated samples. We are currently investigating their implication in the GSC phenotype using a loss-of-function strategy. In addition, using bio-informatics algorithms, we are analyzing the 5 GSC models transcriptome in order to identify specific splicing variants that might be regulated by our two candidates.

The perspective of this study aims at identifying splicing programs (qualitative changes) and gene signatures (quantitative changes) enriched in GSC comparing the transcriptomes of GSC, neural stem cells, and in vitro differentiated samples. This analysis will further establish a molecular signature of these aggressive cells, and potential new targets emerging from this work will be considered to improve the clinical outcome of patients with personalized treatments.

Poster # 85

snoRNA-Induced Alterations of Ribosomal RNA 2'-O-Ribose Methylation Contribute to Resistance to Tyrosine Kinase Inhibitor in Non-Small-Cell Lung Cancer (NSCLC)

Thomas BOYER[1], Janice KIELBASSA[2], Virginie MARCHAND[3], Yuri MOTORIN[3], Alain VIARI[2], Pierre SAINTIGNY[4], Sandra ORTIZ-CUARAN[4], Jean-Jacques DIAZ[1] and Virginie MARCEL[1]

1. Cancer Research Center of Lyon, UMR INSERM 1052 CNRS 5286, Centre Léon Bérard, Université Lyon 1, Nuclear Domains and Pathologies team, Lyon, France
2. Gilles Thomas Bioinformatic Platform, Fondation Synergie Lyon Cancer, Centre Léon Bérard, Lyon, France
3. NGS platform, Bioingénérie Moléculaire Cellulaire et Thérapeutique, Université de Lorraine, Vandoeuvre-les-Nancy, France
4. Translational Research Laboratory, Centre Léon Bérard, Lyon, France

Contact: thomas.BOYER@lyon.unicancer.fr

Keywords: Ribosome rRNA snoRNA NSCLC TKI-resistance

Contrary to what is expected, it appears that ribosomes play a direct role in regulating translation. Ribosomes can adopt different compositions that display distinct translational activities. The main source of ribosome diversity comes from the ribosomal RNA (rRNA) that undergoes chemical modifications, including 2'-O-ribose methylation. These methylations occur at 106 sites and are catalysed by ribonucleoprotein complexes containing small nucleolar RNA (snoRNA) that guides the enzyme on the site to be methylated and thus provides nucleotide specificity. Our team showed that alteration of rRNA methylation profile directly contributes to translational regulation of Internal Ribosome Entry Sites (IRES)-containing mRNAs, such as IGF-1R (Marcel et al, Cancer Cell 2013; Erales et al, PNAS 2017). It has been recently reported that IGF-1R activation drives crizotinib resistance of NSCLC characterized by ALK-EML4 fusion (Lovly et al, Nature Med 2014). Our project aims to determine the role of snoRNA-induced alteration of rRNA methylation in IGF-1R activation in resistance to crizotinib.

Using innovative genome-wide approaches, we identified by RNA-seq four snoRNAs whose expression is altered in H3122 crizotinib resistant cells compared to parental ones, and by RiboMETH-seq, a dozen of rRNA methylation sites whose levels are altered. To knock-down snoRNA expression and its associated rRNA methylation levels, we developed Locked Nucleic Acids tools. Reduction of rRNA methylation level by specifically targeting expression of the corresponding snoRNA allowed to determine the role of rRNA methylation in resistance to crizotinib and in translational regulation of IGF-1R.

Altogether, our data suggest that snoRNA-induced alterations of rRNA methylation play a role in resistance to crizotinib. In addition, our data identified rRNA methylation and/or snoRNA profiling as original biomarkers and therapeutic targets suitable for management of TKi resistance.

Poster # 86

Lysine Methylation of P53 As An Alternative Mechanism to Overcome P53-Mediated Tumor Suppression in Melanoma

Alexandre CASANOVA[1], Gael ROTH[1,2], Pierre HAINAUT[1], Nicolas REYNOIRD[1]

1. Institute for Advanced Biosciences, INSERM 1209 CNRS 5309 Université Grenoble-Alpes, Grenoble, France
2. Clinique Universitaire d'Hépato-Gastroentérologie, Pôle Digidune, CHU Grenoble-Alpes, Grenoble, France

Contact: alex_casanova_75@hotmail.fr

Keywords: Lysine methylation, p53, Melanoma

Melanoma is the most aggressive form of skin cancer. While TP53 is identified as the most mutated gene in cancers, melanoma is surprisingly rarely mutated on TP53 (around 10%). Thus, p53 functions must be down regulated by yet unknown mechanisms in melanoma. The p53 protein is regulated by multiple Post-Translational Modifications (PTMs) including lysine methylation. Deregulation of PTMs is a common feature of human diseases and several studies suggest that lysine methylation potentially mediates a repressive status of p53. However, how these multiple PTMs are coordinated to mediate the wide repertoire of p53 biological effect is still poorly understood. The presence of multiple post-translational marks in the p53 C-terminal domain suggests that the principles of the "histone code" may provide a frame-work for understanding the complex regulation of non-histone proteins such as p53, resulting in a more generalized concept of a 'protein code'. Our working hypothesis is that imbalance in p53 methylation may significantly contribute to p53 inactivation in melanoma with wild-type TP53, thus contributing to novel alternative ways to overcome p53 mediated tumor suppression. The detailed cartography and dynamics of p53 lysine methylation is still largely unknown, and there is no previous data on p53 methylation in melanoma. Thus, the specific objectives of the project are: (1) To develop a precise cartography of p53 lysine methylation in melanoma and melanocytes and evaluate the dynamics of p53 lysine methylation in response to stimuli activating p53 suppressor functions; (2) To identify KMTs responsible for these p53 lysine methylation marks and to characterize these events by deciphering their molecular consequences. (3) To analyze the expression of KMTs in melanoma harboring wild-type p53 and to examine whether experimental inhibition of these KMTs may reactivate p53 suppressor function and be of therapeutic interest for melanoma patients.

Poster # 87

Evidence for rRNA 2'-O-Methylation Plasticity: Control of Intrinsic Translational Capabilities of Human Ribosomes

J. ERALES[1,2], V. MARCHAND[3], B. PANTHU[2,4,5], M. GARCIA[1,2], F. LAFORETS[1,2], V. MARCEL[1,2], A. BAUDIN-BAILLIEU[6], P. BERTIN[6], Y. COUTE[7], A. ADRAIT[7], M. MEYER[8], G. THERIZOLS[1,2], M. YUSUPOV[8], O. NAMY[5], T. OHLMANN[2,4,5], Y. MOTORIN[9], F. CATEZ[1,2] and J.J. DIAZ[1,2]

1. Centre de Recherche en Cancérologie de Lyon UMR Inserm 1052 CNRS 5286, Centre Léon Bérard, F-69373, Lyon, France
2. Université de Lyon, F-69003, Lyon, France
3. Next-Generation Sequencing Core Facility, FR3209 BMCT CNRS-Lorraine University, F-54505, Vandoeuvre-les-Nancy, France
4. CIRI, Université de Lyon, Lyon, France
5. Ecole Normale Supérieure de Lyon, France
6. Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS, Université Paris-Sud, Université Paris-Saclay, France
7. Laboratoire Biologie à Grande Échelle, Institut de Biosciences et Biotechnologies de Grenoble, Université Grenoble Alpes, Commissariat à l'énergie atomique et aux énergies alternatives, INSERM, 38000 Grenoble, France
8. Institut de Génétique et de Biologie Moléculaire et Cellulaire, CNRS UMR 7104 Inserm U 964, Illkirch F-67404, France
9. IMoPA UMR7365 CNRS, Université de Lorraine, Vandoeuvre-les-Nancy, F-54505, France

Contact: frederic.catez@lyon.unicancer.fr

Keywords: ribosome, rRNA, translation control, RNA epigenetics

Ribosomal RNAs (rRNAs) are main effectors of mRNA decoding, peptide-bond formation and ribosome dynamics during translation. Ribose 2'-O-methylation (2'-O-Me) is the most abundant rRNA chemical modification, and display a complex pattern in rRNA. 2'-O-Me was shown to be essential for accurate and efficient protein synthesis in eukaryotic cells. However, whether rRNA 2'-O-Me is an adjustable feature of the human ribosome and a means of regulating ribosome function remains to be determined. Here we challenged rRNA 2'-O-Me globally by inhibiting the rRNA methyl-transferase fibrillarin (FBL) in human cells. Using RiboMethSeq, a non-biased quantitative mapping of 2'-O-Me, we identified a repertoire of 2'-O-Me sites subjected to variation and demonstrate that functional domains of ribosomes are targets of 2'-O-Me plasticity. Using the cricket paralysis virus (CrPV) IRES element, coupled to in vitro translation, we show that the intrinsic capability of ribosomes to translate mRNAs is modulated through 2'-O-Me pattern and not by non-ribosomal actors of the translational machinery. Our data establish rRNA 2'-O-methylation plasticity as a mechanism providing functional specificity to human ribosomes.

Poster # 88

Evaluation of New Platinum Compounds for Melanoma Treatment

Elsa CHARIGNON[1,2], Gabriel ICHIM[2], Hichem MERTANI[2], Mathilde BOUCHÉ[3], Stéphane BELLEMIN[3], Philippe BOUVET[2], Claire BILLOTEY[1]

1. Université de Lyon, EMR 3738, Hospices civils de Lyon 69600 Oullins France
2. Centre de Recherche en Cancérologie de Lyon (CRCL), INSERM U1052, CNRS
3. UMR5386, Centre Léon Bérard 69008 Lyon France.[3]InsFtut de Physique et Chimie des Matériaux de Strasbourg (IPCMS) 67200 Strasbourg, France.

Contact: Elsa.CHARIGNON@lyon.unicancer.fr

Keywords: melanoma, new platinum compounds

Melanoma is a related to a cancerous transformation of melanocytes affecting principally the skin and more rarely the mucous membranes eyes and under the nails. Although melanomas represent only 10% of the skin cancers, they are responsible for 80% of the mortality related to skin cancer. The depth local invasion of the melanoma is the main prognostic factor, with a resulting major difference of superficial form of melanoma treated by surgical excision with a very favourable prognostic (95% survival over 5 years), and the other forms related to a high metastatic potential (15% survival over 5 years.

The recent emergence of the targeted therapy and immunotherapy strongly change the prognostic of the metastatic patient with an enhancing of their time-survival.

However, a large part of these patients develop a resistance. In this case only chemotherapy can be used.

Therefore, it is necessary to develop new therapeutic strategies and understand their mechanism of action to treat metastatic melanomas efficiently.

Some studies were demonstrated that Platine grafted with N-heterocyclic carbenes (NHC), NHC-Platinum (NHC-Pt) compounds have a greater toxic effect than Cisplatin (platinum salt usually use in chemotherapy) as evidenced by the comparison of the IC50 in different types of cancer cells.

In our team, we have evidenced that these compounds have also cytotoxic effects on human melanoma cell lines.

These effects were evidenced using a real-time analysis system (Xcelligence), allowing to show that new NHC-Pt complexes induced a rapid toxicity (in a matter of hours) whereas cisplatin induce a slower toxicity and dacarbazine a cytostatic effect.

NHC-Pt are therefore a promising new compounds for the treatment of melanoma.

Poster # 89

Exosomal Transfer of Adrenocortical Cancer Cell-Derived Mir-483-5p and Mir-139-5p Promote Endothelial Cell Angiogenesis

Rosy GHANEM[1,2,3], Jonathan LAUGIER[1,2,3], Claire AGOSTA[1,2,3,4], Josiane DENIS[1,2,3], Jean-Jacques FEIGE[1,2,3], Olivier CHABRE[1,2,3,4], Nadia CHERRADI[1,2,3]

1. Institut National de la Santé et de la Recherche Médicale, Unité 1036, Grenoble, France
2. Commissariat à l'Energie Atomique, Institut de Biosciences et Biotechnologies de Grenoble, Biologie du Cancer et de l'Infection, Grenoble, France
3. Université Grenoble Alpes, Unité Mixte de Recherche-S1036, 38000, Grenoble, France
4. University Hospital Albert Michallon, Department of Endocrinology, Grenoble, France

Contact: nadia.cherradi@cea.fr

Keywords: adrenocortical cancer-microRNAs-exosomes-endothelial cells-angiogenesis-intercellular communication

Adrenocortical carcinoma (ACC) is a rare and highly aggressive cancer with poor prognosis and limited therapeutic options. We have previously shown that microRNAs (miRNA) miR-483-5p and miR-139-5p are upregulated in ACC tumor tissue as well as in the serum of ACC patients. Both miRNA displayed strong diagnostic and prognostic values. However, the mechanisms underlying the role of miRNA in ACC aggressiveness remain largely unknown. Increasing evidence indicates that extracellular vesicles (EVs)-mediated interaction between cancer cells and their surrounding cells within tumor microenvironment confers advantages for cancer initiation and progression. In this study, our aim was to evaluate whether circulating ACC-derived miR-483-5p and miR-139-Sp were embedded in nano-sized EVs called exosomes and whether they could be transferred through exosomes to vascular endothelial cells (EC) and induce their reprogramming. We isolated and characterized exosomes from the ACC cell line NCI H295R conditioned medium (CM) and evaluated their effects on human umbilical endothelial cells (HUVECs). Both miR-483-5p and miR-139-5p were found in exosomes. Fluorescent-labeled exosomes were efficiently internalized by living HUVEC and promoted their migration and organization during tubular differentiation on Matrigel. These effects were accompanied by increases in miR-483-5p and miR-139-5p levels in endothelial cells as well as activation of MAP-Kinase pathways and potentiation of the response to Vascular Endothelial Growth Factor (VEGF). Collectively, our results suggest that ACC cell-derived exosomal miRNAs can be transferred to endothelial cells and promote their angiogenic activity. Detailed investigation of these mechanisms could help elucidate a novel pathway in the progression of ACC metastasis.

Poster # 90

The Interplay Between IGF1R and ERα in Breast Cancer Involves Methylated ERα

Ali CHOUCAIR[1,2,3], Soleilmane OMARJEE[1,2,3], Julien JACQUEMETTON[1,2,3], Ha Ta PHAM[1,2,3], Loay KASSEM[4], Olivier TREDAN[5], Juliette RAMBAUD[1,2,3,6], Elisabetta MARANGONI[7], Laura CORBO[1,2,3], Isabelle TREILLEUX[1,2,3,8] and Muriel LE ROMANCER[1,2,3]

1. INSERM U1052, Centre de Recherche en Cancérologie de Lyon, Lyon, France
2. CNRS UMR5286, Centre de Recherche en Cancérologie de Lyon, Lyon, France
3. Universite Lyon 1, Lyon, France
4. Clinical Oncology Department, Faculty of Medicine, Cairo University, Cairo, Egypt
5. Centre Leon Bérard, Oncology Department, Lyon, France
6. Genoway
7. Institut Curie, Translational Research Department, 75005 Paris, France
8. Centre Leon Bérard, Pathology Department, Lyon, France

Contact: ali.choucair@hotmail.com

Keywords: insulin-like growth factor 1, estrogen receptors a, breast cancer, estrogen signaling, arginine methylation

Besides nuclear action, oestrogen also mediates its effects through cytoplasmic signalling. Our team has shown that ERα methylation is central to the rapid transduction of estrogen signaling. Crosstalk between oestrogen and growth factors signalling involving phosphorylation of ERα has been largely described. Here, we investigated whether growth factors can regulate ERα methylation. Among several growth factors, we found that IGF-1 treatment of MCF-7 cells induced rapid ERα methylation by the arginine methyltransferase PRMT1. By several approaches, we showed that IGF1 triggers PRMT1 interaction with IGF1R and its enzymatic activation, event involving the adaptor Shc but not IRS1. ERα methylation is a key step for IGF1 signalling, as it is required for the binding of IGF1R to its partners Src, PI3K, Shc and IRS1 as well as for the downstream signalling mediated by Akt and ERK. Moreover, IGF1R binds directly and phosphorylates ERα on the Y219, a docking site stabilizing their interaction. In addition, in a cohort of breast tumours, we found that IGF1R expression is correlated with ERα/Src and ERα/PI3K, reinforcing the link between IGF1 and ERα methylation.
These results report new insights into estrogen and IGF-1 interference and open new perspectives of combining therapies targeting PRMT1 activity.

Poster # 91

Optogenetic Control of Cell Invasion

Adèle KERJOUAN[1], Cyril BOYAULT[1], Christiane ODDOU[1], Edwige HIRIART-BRYANT[1], Alexei GRICHINE[1], Alexandra KRAUT[2], Yohan COUTE[2], Mylène PEZET[1], Martial BALLAND[3], Isabelle BONNET[5], Eva FAUROBERT[1], Yohan COUTE[2], Corinne ALBIGES-RIZO[1], Bertrand FOURCADE[4] and Olivier DESTAING

Institute for Advanced Biosciences

Contact: olivier.destaing@univ-grenoble-alpes.fr

Keywords: optogenetic, invadosome

A cell transmits information from the extracellular environment through intercellular signaling node to adapt and alter cell fate. However, how one signaling node can understand multiple stimuli and diffuse the appropriate information remains poorly understood. Further, recent data suggest that signal integration in space and time is critical for proper signal transduction in mechanotransduction.

To challenge the spatiotemporal aspect of protein regulation, we focus our study on the proto-oncogene and a pleiotropic tyrosine kinase, c-Src, which is one such node known to drive many cellular processes, such as migration, invasion, degradation, and cell division. In that respect, we designed a tool able to control Src activity in space and time and then the invasion processes. Such strategy allows, for the first time, to distinctly and precisely control differential cellular adhesive in an epithelial cell type.

Poster # 92

Integrated Analysis Highlights APC11 Protein Expression as a New Independent Predictive Marker for Colorectal Cancer

Youenn DROUET[1], Isabelle TREILLEUX[3], Mojgan DEVOUASSOUX[4,5,6,7,8,9,10], Nicolas VOIRIN[1,7,10], Brigitte MANSHIP[4], Christelle de la FOUCHARDIERE[4], Alain PUISIEUX[4,5,6,7,8,9], Christine LASSET[1,2], Caroline MOYRET-LALLE[4,5,6,7,8,9]

1. Centre Léon Bérard, Département de Santé Publique, Lyon, F-69008, France;
2. CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Lyon, F-69373;
3. Centre Léon Bérard, Service d'Anatomopathologie, Lyon, F-69008, France;
4. Centre Léon Bérard, Lyon, F-69008, France;
5. INSERM U1052, Cancer Research Center of Lyon, Lyon, F-69008, France;
6. CNRS UMR 5286, Cancer Research Center of Lyon, Lyon, F-69008, France;
7. Université de Lyon, Lyon, F-69622, France;
8. Université Lyon1, ISPB, Lyon, F-69008, France;
9. LabEx DEVweCAN, Université de Lyon, F-69000 Lyon, France; (10) Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, F-69008, France

Contact: youenn.drouet@lyon.unicancer.fr

Keywords: APC/C, APC11, catalytic subunit, CRC, metastases

Approximately 50% of colorectal cancer (CRC) patients develop advanced and poorly predictable metastatic CRC (mCRC). We investigated the predictive and prognostic potential of APC11, the catalytic subunit of the anaphase-promoting complex/cyclosome (APC/C), which has never been examined in the context of CRC.

The expression of APC11 was assessed in 21 CRC cell lines and in tissue microarrays (TMAs) from a cohort of 82 patients at different stages of the disease. Overexpression of APC11 was associated with chromosomal instability (P = 0.0005) in CRC cells, while in primary TMAs, statistical associations were found with residual tumor (odds ratio: OR = 6.77, P = 0.004), vascular invasion (OR = 3.92, P = 0.01), tumor size (OR = 3.35, P = 0.03), stage (OR = 2.47, P = 0.05), node involvement (OR = 2.47, P = 0.05), metastasis at diagnosis (OR = 3.95, P = 0.01) and pre-operative carcinoembryonic antigen (CEA) (OR = 3.01, P = 0.04). Furthermore, patients with elevated APC11 levels also had a higher risk of disease progression (hazard ratio: HR = 2.60, P = 0.01) and a higher mortality rate (HR = 2.69, P = 0.007). However, stratified analysis showed that this poorer survival rate for patients with elevated APC11 levels came from their metastatic statuses at diagnosis and not from metastatic relapses.

APC11 expression in primary colon tumors thus represents a potentially novel theranostic marker of mCRC. Further studies are needed to confirm these results.

Poster # 93

Association Between Hepatitis B Virus Pre-S2 Deletion and Increased Risk of Hepatocellular Carcinoma: A Case-Control Study in West Africa

Damien COHEN[1], Sumantra GHOSH[1], Yusuke SHIMAKAWA[2], Janet HALL[1], Clement GUILLOT[1], Njie RAMOU[2], Maud LEMOINE[3], Maimuna MENDY[4], Sophie ALAIN[5], Gibril NDOW[2], Maimuna MENDY[4], Fabien ZOULIM[1,6], Mark THURSZ[3], Isabelle CHEMIN[1]

1. CRCL, INSERM U1052, CNRS 5286, Université de Lyon, 151 cours A Thomas, 69424, Lyon, France.
2. Medical Research Council Laboratories, The Gambia Unit, Fajara, The Gambia.
3. Department of Medicine, Imperial College London, St Mary's Campus, South Wharf Road, London, UK.
4. International Agency for Research on Cancer, 150 cours Albert Thomas, 69372, Lyon, France.
5. Univ. Limoges, INSERM UMR 1092, CHU Limoges, Laboratoire de Bactériologie-Virologie-Hygiène, National Reference Center for Cytomegaloviruses, 87025, Limoges, France.
6. Hepatology Department, Hospices Civils de Lyon, 69004, Lyon, France.

Contact: damien.cohen@inserm.fr

Hepatitis B virus (HBV)-related cirrhosis and HCC (Hepatocellular Carcinoma) are highly endemic in Sub-Saharan Africa (SSA). Previous results from the PROLIFICA (Prevention of Liver Fibrosis and Cancer in Africa) European Commission (FP7) project have shown that although individuals in this region often have low viral loads (2,000 UI/mL), an early onset of cirrhosis and a high frequency of liver tumors, associated with low survival rates, is frequently found (Lemoine et al., 2016). Within this study population a high frequency of PreS2 HBV deletion mutations was found (Ghosh et al., 2016). The PreS2 mutations profile is distinct from those reported in other regions of the world as one region of the PreS2 gene is targeted, in addition their frequency increased with disease progression: mutant virus was found in 24% of chronic HBV carriers, 38% of cirrhotic patients and up to 55% of HCC patients. These PreS2 mutations occur in regions encoding the viral envelope implicated in the host cell's immune response to viral infection and can lead to the accumulation of the viral envelope in the endoplasmic reticulum an event linked to an increased genetic instability that could accelerate hepatocarcinogenesis. Interestingly, in cell lines infected with a PreS2 deleted HBV it has been reported that the NBS1 DNA repair enzyme is sequestrated in the cytoplasm and is associated with lower levels of homologous recombination repair (Hsieh et al. 2015). As low levels of nuclear NBS1 expression has been associated with PARP inhibitor sensitivity this observation opens up the possibility that HCCs carrying preS2 mutations might be sensitive to the cytotoxic effects of PARP inhibitors. Further in vitro and in vivo studies are needed to investigate this possibility and to establish the cause of these PreS2 deletion mutants and their role in the development of HCC in SSA.

Poster # 94

DNA Double-Strand Breaks Induced by Combined Treatement with Doxorubicin and Ultrasound Cavitation in Murine Mammary Tumor Cells

C FANT[1], A Granzotto[2], T Moraes Vieira[1], J-L Mestas[1], J Ngo[1], M. Lafond[1], C Lafon[1], N Foray[2], F Padilla[1,3,4]

1. LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ-Lyon, F-69003, LYON, France
2. Inserm, U1052 unit, Groupe de Radiobiologie, 69008, Lyon ,France
3. Department of Radiation Oncology, University of Virginia School of Medicine, Charlottesville, VA, USA
4. Focused Ultrasound Foundation, Charlottesville, VA, USA

Contact: cecile.fant@inserm.fr

Keywords: Doxorubicin, ultrasound, DNA damage, synergy

Doxorubicin (DOX) induces cell cytotoxicity through DNA damage. Recent studies reported DNA damage in different cell lines exposed to therapeutic ultrasound. We hypothesized that a combined treatment with doxorubicin and therapeutic ultrasound would increase DNA damage in cells and decrease cell viability.

4T1 cells, a mouse mammary cancer cell line, were treated in vitro using an ultrasound confocal device to generate and monitor acoustic cavitation, with or without addition of DOX. After treatment, DNA damage were assessed by scoring □□H2AX foci number in cell nuclei by immunofluorescence. The role of a bystander effect, mediated by calcium release, was assessed by exposing untreated cells to the supernatant of sonicated cells with or without the addition of a calcium chelator (PBS). Cell viability and cell proliferation were assessed at 72h post treatment by cell counting and clonogenecity assays.

In cells treated with stable ultrasound cavitation (US), with or without DOX, double strand breaks (DSB) were observed. However, without DOX, these DSB did not impact cell proliferation nor viability. The combination of ultrasound cavitation and DOX led to premature DSB from 1h post treatment compared to DOX alone where DSB were observed only from 4h post treatment. Significant decrease in cell viability and proliferation were observed for the US+DOX group compared to the DOX group. The exposure of untreated cells to sonicated cells supernatant showed 40% of untreated cells with DSB from 10 min after treatment. The addition of PBS in the supernatant prevented the occurrence of g-H2AX foci in the cells.

A combined US+DOX treatment of 4T1 tumor cells led to premature DSB, possibly induced by a bystander effect, and to significant decreases in cell proliferation and viability compared to a treatment with DOX or US alone. These data suggest that cavitational ultrasound may potentiate the action of DOX through induction of DSB, therefore increasing the cytotoxicity of DOX.

Poster # 95

Lipoic Acid Modulates Proliferative/Survival Pathways and Reduces ER α Protein Level in Human Breast Cancer Cell Lines

Diana FARHAT[1, 2, 3, 4], Sandra E. GHAYAD[5], Nader HUSSEIN[4], Muriel LE ROMANCER[1, 2, 3] and Hubert LINCET[1, 2, 3, 6]

1. Université Lyon 1, Lyon, France
2. Inserm U1052, Centre de Recherche en Cancérologie de Lyon (CRCL), Lyon, France
3. CNRS UMR5286, Centre de Recherche en Cancérologie de Lyon (CRCL), Lyon, France
4. Department of Chemistry-Biochemistry, Laboratory of Cancer Biology and Molecular Immunology, EDST-PRASE, Lebanese University, Faculty of Sciences, Hadath- Beirut, Lebanon
5. Department of Biology, Faculty of Science II, Lebanese University, Fanar, Lebanon
6. ISPB, Faculté de Pharmacie, Lyon, France

Contact: diana.farhat123@outlook.com

Keywords: breast cancer; lipoic acid; glucose metabolism; cellular proliferation

Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women (25% of all cancers). Despite advances in chemotherapy, hormonotherapy and targeted therapy in combination or not with surgery, mechanisms of resistance remain the underlying cause of morbidity and mortality for women. It is known that glucose metabolism is profoundly disrupted in many tumor lines and that tumor cells adapt their biochemical metabolism to establish mechanisms of resistance to therapeutic treatments. The increased glucose metabolism provides several advantages notably a high level of ATP, biosynthesis of macromolecules and maintenance of a redox status compatible with the cellular survival.

Our study intends to explore the effect of citrate (Ct) or lipoic acid (LA) alone or combined on breast cancer cell lines to pave the way for reducing the tumoral proliferation. LA is an essential mitochondrial co-factor, that has both antioxidant and oxidant properties, while citrate is an intermediate in the TCA cycle and an allosteric inhibitor of PFK1.

Many breast cancer cell lines with or without estrogen receptors (ERα + or ERα-) have been treated with different concentrations of Ct, LA, or by their combination. IncuCyte™ ZOOM was applied to detect the drugs influence on breast cancer cell proliferation. This combination has more or less synergic effect according to the treated cell line. Western blot was performed to study the effects of LA and Ct on several proliferative/survival pathways. Whatever the ER status, our results have shown that LA inhibits cell proliferation much more effectively than Ct. Moreover, our results showed that LA inhibits several signaling pathways by down-regulating phospho-AKT, phospho mTOR downstream effectors and phospho-ERK by western blot. AMPK, a cellular sensor of ATP level was studied in response to LA treatment, we have found a high induction of its phosphorylation leading its activation. On the other hand, LA induces the endoplasmic reticulum stress protein, CHOP which is known as a particular transcriptional activator of Bim.

Interestingly in ERα+ breast cancer cell lines, we demonstrated that LA abolishes the ERα protein expression level but not on transcriptional activity. This loss of expression was accompanied with an induction of p38 phosphorylation

To shorten, our study mainly proves an anti-proliferative effect of LA in breast cancer cell lines, as well as the effect of Ct. The molecular mechanisms of ERα downregulation are not elucidated yet. Furthermore, we look forward to increase the effects of the conventional therapy and prevent the mechanisms of resistance by such molecules.

Poster # 96

A new signaling cascade linking BMP4, BMPR1A to ΔNp73 and NANOG impacts immature-like AML cell properties and patient outcome

Mario FLORES-VIOLANTE[1,2,3,4,5*], **Thibault Voeltzel**[1,2,3,4,5,*], Florence ZYLBERSZTEJN[1,2,3,4,5], Sandrine JEANPIERRE[1,2,3,4,5,6], Gaelle FOSSARD[1,2,3,4,5,7], Amine BELHABRI[1,2,3,4,5,6], Etienne PAUBELLE[7], Xavier THOMAS[7], Fawzia LOUACHE[8], Franck-Emmanuel NICOLINI[1,2,3,4,5,6,7], Claude CARON de FROMENTEL[1,2,3,5], and Véronique MAGUER-SATTA[1,2,3,4,5]

1. CNRS UMR5286, Centre de Recherche en Cancérologie de Lyon, F-69000 Lyon, France
2. Inserm U1052, Centre de Recherche en Cancérologie de Lyon, F-69008 Lyon, France
3. Université de Lyon, F-69000, Lyon, France
4. Department of tumor escape signaling, F-69000, Lyon, France
5. Université de Lyon 1, F-69000, Lyon, France
6. Centre Léon Bérard, 69000 Lyon, France
7. Hospices Civils de Lyon, Hematology Department, Centre Hospitalier Lyon Sud, F-69495 Pierre Bénite, France;
8. Inserm, UMR1170, Villejuif, F-94000, France

Contact: qfbmarioflores@hotmail.com

Keywords: AML, BMP, Microenvironment, Leukemic Stem Cell, p73

Acute myeloid leukemias (AML) are heterogeneous hematological malignancies characterized by the accumulation of immature and non-functional cells in bone marrow and peripheral blood. Despite the achievement of initial "complete" remission the majority of patients relapse facing a poor prognosis. The presence of leukemic stem cells (LSC) may play a key role in patients' relapse through chemotherapy resistance and this likely involves an altered bone marrow microenvironment. The BMP (Bone Morphogenetic Proteins) pathway is involved in stem cell fate and contributes to transformation, expansion and persistence of immature cells, as demonstrated in Chronic Myeloid Leukemia and breast cancer. Here, we identified intrinsic and extrinsic alterations of the BMP pathway in AML bone marrows, with high concentrations of BMP4, produced by the leukemic microenvironment with an increase of 3.6 fold as compared to normal bone marrow. Intrinsically, we observed overexpressions of BMPR1A (receptor) and Id1 (target gene) and evidenced that induction of these two was correlated with ΔNp73 (p53 family) expression. We further demonstrated that ΔNp73 directly induces NANOG and that both expressions are associated with immature features of leukemic cells. Thus, our team identified a new signaling cascade starting with BMP4/BMPR1A driving ΔNp73 and NANOG expressions, and leading to immature-like properties. Furthermore, in relation with clinical data, we have identified NANOG, ΔNp73 and BMPR1A as potential powerful markers to predict relapse in AML patients at the time of diagnosis.

Poster # 97

Unveiling the Mechanisms of the RNA-Binding Protein Musashi1in Stemness qnd Drug Resistance of Intestinal Epithelial Cells

Carla FRAU, Gabriela GUARDIA, Matthias GODART, Joel UCHUYA CASTILLO, Clémentine LE NEVE, Pedro GALANTE, Luiz PENALVA, Michelina PLATEROTI

CRCL-CLB
Contact: carla.frau@inserm.fr

Keywords: stem cells, cancer stem cells, drug resistance, intestinal cancer

Object: The new concept of ''cancer stem cells'' is revolutionizing tumor comprehension and the development of new therapeutic approaches. In colorectal cancer, CSCs seem to be not only at the origin of tumor initiation but also responsible for drug failure and drug resistance. The RNA-binding protein Musashi1 (Msi1) in the intestine is a marker of stem cells and regulates stem cell homeostasis. However, an up-regulation of its expression is exerts a tumorigenic potential. In addition a link between high Msi1 expression levels and poor prognosis and drug resistance has also been suggested. The aim of my project is to elucidate the role of Msi1 in stemness and drug resistance. In order to achieve this aim we developed a bi-transgenic mouse model that specifically overexpress Msi1 in the intestinal epithelium and in which stem cells are labelled by GFP.

Method: By using an approach of 3D crypts culture, a powerful tool recapitulating the intestinal epithelium organization, we studied the effect of 5-FU in organoids overexpressing or not Msi1.

Results and conclusions: Our results clearly demonstrate that when Msi1 is overexpressed, organoids are more resistant to the toxic effect of the drug. Interestingly, 5-FU in WT organoids targets the GFP-positive stem cells while in transgenic organoids stem cells are not affected. Altogether, we observed that Msi1 is crucial for protecting cells against the cytotoxic effect of the drug and that this protein seems to be strongly involved in the development of a cancer stem cell-linked drug-resistant phenotype. In order to elucidate possible mechanisms responsible for the resistant phenotype associated with Msi1 overexpression we analyzed key enzymes involved in the mechanism of action of 5-FU (TYMP, TYMS and DPYD) revealing that the overexpression of Msi1 is able to impact processes of activation and inactivation of the drug toward a resistant phenotype. These enzymes are important biomarkers to predict the response of a patient to 5-FU. Our results could have therefore an important clinical value for the development of new therapies able to specifically target CSCs. In order to test this hypothesis, in collaboration with platforms of the Centre Leon Berard we started to develop human intestinal organoids from normal parts and tumor specimens in order to investigate Msi1-linked drug resistance. The last step will be to screen for small molecules to inhibit Msi1 action.

Poster # 98

Identification and Characterisation of a Novel Obstacle Towards Oncogenic and Pluripotent Reprogramming

G FURLAN[1], A HUYGHE[1], P WADJA[1], R GASA[2], F LAVIAL[1]

1. Cellular Reprogramming and Oncogenesis Laboratory – Lyon University, Claude Bernard Lyon 1 University, INSERM 1052, CNRS 5286, Centre Léon Bérard, Cancer Research Center of Lyon, 69008 Lyon, France.
2. Diabetes and Obesity Research Laboratory, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Contact: giacomo.furlan@lyon.unicancer.fr

Keywords: oncogenic reprogramming, c-Myc, pluripotent reprogramming, Atoh8, bHLH

A crucial objective in cancer biology is to understand why a given cell is susceptible to become tumorigenic. Nevertheless, little is known about the mechanisms protecting somatic cells from such conversion. In the first step of tumorigenesis, cells acquires a new plasticity, followed by epigenetic rewiring: cells lose their somatic protections and become sensitive to oncogenic insult. We can describe these first steps as the oncogenic reprogramming (OR). This concept emerged recently and its characterization is very limited. In this context, the development of alternative models is crucial to decipher our understanding of tumorigenesis.

In the lab, we propose to compare oncogenic reprogramming to another process characterized by loss of somatic identity and acquisition of plasticity: the pluripotent reprogramming (PR), the conversion of an adult differentiated cell to an embryonic-like induced pluripotent stem cell (iPSC).
We can thus consider the early stages of oncogenic and pluripotent reprogramming (PR) as novel models to decipher the molecular mechanisms that render a somatic cell prone to change identity and reacquire plasticity.

In this context, we identified the basic helix loop helix (bHLH) transcription factor Atoh8 as a common obstacle to both reprogramming processes. Its loss renders a cell more prone to reprogram in both scenarios. In other terms, the loss of the somatic barrier Atoh8 sensitizes the cell to the oncogenic insults carried by c-Myc and KRasG12D. We also showed that c-Myc is responsible for Atoh8 loss of expression in the somatic cell.

Altogether, our data give new insights on the mechanisms triggering the oncogenic reprogramming and highlight a new cellular identity gatekeeper negatively modulated by the oncogene c-Myc.

Poster # 99

Adipocyte-Released Agents Induce Resistance of Breast Cancer Cells to Lapatinib

A. GENESTE[1], MN. DUONG[2], S. BEAUMEL[1], A. CLERET[1], K. CHETTAB[1], E. DELAY[3], P. VALET[5], L.P. JORDHEIM[1], C. DUMONTET[1,4]

1. Centre de Recherche en Cancérologie de Lyon (CRCL), INSERM UMR 1052, CNRS 5286, 8 Avenue Rockefeller, 69008 Lyon, France
2. Department of Oncology, Lausanne University Hospital Center (CHUV) and University of Lausanne, Epalinges, Switzerland
3. Centre Léon Bérard, Chirurgie plastique reconstructrice et esthétique, 28 Promenade Léa et Napoléon Bullukian, 69008 Lyon, France
4. Hospices Civils de Lyon, Services d'Hématologie, 165 Chemin du Grand Revoyet, 69310 Pierre-Bénite, France
5. Université de Toulouse, UPS, Institut de Médecine Moléculaire de Rangueil, Equipe n°3, UMR INSERM 1048, IFR31, Toulouse, France

Contact: aline.geneste@univ-lyon1.fr

Keywords: adipocyte, breast cancer, targeted therapies, resistance, lapatinib

Several studies have shown an adipocyte-mediated resistance effect to various anticancer therapies. However, the responsible agent(s), the mechanism(s) and the signaling pathway(s) involved in this resistance remain unclear.

In the present study, we assessed the cytotoxic effect of lapatinib on several breast cancer cell lines in the presence or absence of adipocyte-conditioned medium. We performed different treatments on these conditioned media in order to separate and identify the different molecules and agents involved. In parallel, we investigated the changes that occurs in breast tumor cells following the contact with adipocyte-conditioned medium and the exposure to lapatinib. We also created a mouse model reproducing the contact between adipose tissue and tumors.

Our results showed that tumor cells exposed to adipocyte-conditioned medium were less sensitive to lapatinib-mediated cytotoxic effects and cell cycle blockade than cells grown in standard culture medium. This resistance was observed with the conditioned medium and confirmed on different breast tumor cell lines overexpressing HER2. Using a xenograft of normal human adipose tissue with implantation of tumor cells in contact to this adipose tissue, we also confirmed the protective effect against the antitumoral activity of lapatinib in vivo. The nature of the responsible agents of the resistance has been partly elucidated as well as the mechanisms. Indeed, it seems that the presence of soluble factors released from adipocytes such as lipolysis and metabolism products are required to limit the effect of lapatinib on tumor cells.

Briefly, compounds released from adipocytes reduced the lapatinib induced cytotoxicity on breast cancer cells overexpressing HER2 by interfering with the AKT signaling pathway. These results suggest possible strategies to counteract tumor cell resistance to lapatinib, by targeting adipocyte-released mediators.

Poster # 100

Does Kremen-1 Induce Autophagic Cell Death?

Clara GENESTE, Ana-Maria NEGULESCU, Olivier MEURETTE, Patrick MEHLEN

Cancerology Research Center of Lyon (CRCL), "Apoptosis, Cancer and Development" Team
Contact: Clara.GENESTE@lyon.unicancer.fr

Keywords: Kremen1, autophagy, cell death

The transmembrane receptor Kremen1 (K1) has first been described as a receptor for Dickkopf ligands (DKK1, 2, 3 and 4) and its ability to block the WNT (winglessrelated integration site) signalling. More recently, K1 was demonstrated to mediate cell death independently of its ability to inhibit Wnt signalling through a dependence receptor function. These receptors have a dual signalling ability depending on the availability of ligands. As such, K1 is inducing cell death unless bound to DKK1.

We showed that K1 is lost in many different cancers whereas DKK1 is upregulated in cancers. In breast cancer carcinoma, K1 high expression is also a factor of good prognosis in patients in which DKK1 expression is low, showing a possible conditional tumour suppressive activity. We tested the ability of K1 to induced cell death in breast cancer cells. We showed that K1 overexpression or downregulation of DKK1 induces an atypical cell death mechanism, which is not inhibited by apoptosis or necroptosis inhibitors and that has autophagic phenotypic features. We confirmed autophagy induction by western blotting for the lipidated form of LC3B following expression of K1. Furthermore, this cell death is rescued by 3-methyladenine (an autophagy inhibitor) and enhanced by blocking the autophagic flux. We are currently validating putative partners obtained by a shRNA screen to decipher the precise mechanism of this pathway.

Poster # 101

NMR Metabolomics Investigation of the Effect of Adipose Cells on Breast Cancer Cells

Manhal MILI[1], Aline GENESTE[2], Elodie JOBARD[1], Charles DUMONTET[2], Bénédicte ELENA-HERRMANN[1]

1. Université de Lyon, Institut de Sciences Analytiques (UMR 5280 CNRS / ENS-Lyon / UCB Lyon 1), Centre de RMN à Très Hauts Champs, 69100 Villeurbanne, France
2. Centre de Recherche en Cancérologie de Lyon (CRCL), INSERM UMR 1052/CNRS 5286, Lyon, France

Contact: manhal.mili@ens-lyon.fr

Keywords: nuclear magnetic resonance, metabolomics, breast cancer, targeted-therapies

Objective: HER2-positive Breast Cancer is defined by an overexpression of human epidermal growth factor receptor 2 (HER2) which occurs in 20-30% of breast cancer tumors. this overexpression is linked to a more agressive disease and a worse prognosis.
The development of HER2-directed therapies has revolutionized HER2-positive breast cancer treatment. Trastuzumab is the prototype HER2-targeting agent. However, intrinsic and acquired resistance to trastuzumab appear to be a major challenge in the management of HER2-positive breast cancer.
Duong et al. demonstrated that adipose cells are implicated in HER2-positive breast cancer cells resistance to trastuzumab treatment via the secretion of soluble factors.
Our study aims to elucidate the underlying mechanisms of cancer cells resistance to trastuzumab treatment by determining the changes that occur in the metabolism of HER2-positive breast cancer cells when exposed to preadipocytes and adipocytes secreted factors.

Methods: We conducted a 1H NMR-based metabolomic study to compare supernatants of culture of HER2-positive breast cancer cells (BT474 cells) incubated or not in preadipocytes (3T3-F442) and adipocytes (#3T3-F442) conditioned-media. Drugs were added to act on specific metabolic pathways in the cells. Metabolites were identified and quanified in each medium to enable comparison of the evolution of metabolic profiles.

Results and Conclusion: BT474 cells have a strong metabolism in adipose-conditioned media.
The metabolism of BT474 cells is different in preadipocytes and inadipocytes conditioned-media.
Metabolomics may allow identifiying metabolic changes associated with the effect of preadipocytes and adipocytes on HER2-positive cancer cells.
Endometabolome analysis provided after cell extraction may provide more information about implicated metabolic pathways.

Poster # 102

5'-Nucleotidases are Involved in the Biology of Human Lung Cancer Cell Lines

Muhammad-Zawwad RAZA, Emelline CROS-PERRIAL, Octavia CADASSOU, Charles DUMONTET, Lars Petter JORDHEIM

Univ Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Centre Léon Bérard, Centre de Recherche en Cancérologie de Lyon, Lyon, 69008, France
Contact: muhammad-zawwad.raza@univ-lyon1.fr

Keywords: 5'-nucleotidases

Cytosolic-5'-nucleotidase II (cN-II) and ecto-5′-nucleotidase (ecto-5′-NT, eN, CD73) are enzymes involved in the nucleotide metabolism by dephosphorylating intracellular and extracellular nucleotide monophosphates, respectively. Both enzymes have been shown to be involved in cancer by modifying anticancer drug activity, cancer cell biology and immune modulation. We have successfully developed the lung cancer cell models (NCI-H292) with a complete knockout of either/both of these enzymes using the CRISPR-Cas9 technique. These cell models are used to study the relative effect on cell proliferation, anti-cancer drugs sensitivity and migration of these cells using CFSE staining, Incucyte relative confluence assay and Incucyte wound healing techniques respectively. Our results show that there is no significant difference in proliferation between different cell models exposed or not to different concentrations of either adenosine or AMP. However, cN-II deficient cells showed higher sensitivity towards certain cytotoxic drugs as compared to the other phenotypes. Furthermore, CD73-deficient cells migrate slower than their corresponding control cells. Upcoming experiments should help us understand the molecular mechanisms between the observed differences.

Poster # 103

Deciphering Chondrosarcomas Immune Environment Indicates that Macrophages are the Population to Target

I Richert[1], C Bouvier[2, 3], A Gomez-Brouchet[4], N Gadot[5], M Karanian[5], JY Blay[6], A Dutour[1]

1. Cancer Research Center of Lyon, INSERM UMR 1052, CNRS UMR 5286,
2. Department of Neuropathology and APHM Tumor Bank, LaTimone Hospital, Marseille, France
3. UMR911, Equipe 4, Faculté de Médecine de Marseille, 27 Boulevard Jean Moulin, Marseille, France
4. Department of Pathology, IUCT-Oncopole, University of Toulouse, Toulouse, France
5. Pathology Department, Centre Leon Berard, Lyon, France
6. Department of Medical Oncology, Centre Leon Berard, Lyon, France

Contact: iseulys.richert@lyon.unicancer.fr

Keywords: chondrosarcoma, immune infiltrates, macrophages, immune checkpoints

Chondrosarcoma (CHS) is the second most common skeletal malignancy after osteosarcoma. If different subtypes of this sarcoma are described, they are all characterized by the synthesis of cartilaginous matrix and their resistance to chemo and radiation therapies. If the chondrogenic nature of its extracellular matrix and hypoxia are some of the major limitations of CHS response to conventional therapies, little is known regarding the implication of immune environment in CHS progression.

Recently, we described conventional CHS immune environment and reported that its composition is correlated with tumor's agressivity. Moreover, we showed in a rat CHS model that immunomodulation could be effective in this tumor.

We pursued the exploration of CHS immune environment by analyzing more in depth immune populations, the expression of ICP (immune checkpoint) and modulatory markers in a larger cohort of CHS regrouping conventional and dedifferentiated subtypes. Lymphocytes and macrophages were characterized by immunohistological staining while the expression of ICP (TIM3, LAG3, CTLA4, PDL1) and macrophages modulatory markers (CSF1, CSF1R) was assessed by RT qPCR.

In both subtypes of CHS we confirm the presence of immune infiltrates mainly composed of lymphocytes CD3+ CD8+ and macrophages CD68+ and CD163+. Immune cells were found at the peritumoral area of conventional CHS and in the intratumoral dedifferentiated part of dedifferenciated CHS. Preliminary analyses confirmed the correlation existing between high ratio of CD163 and tumor agressivity. Molecular analyses indicated that while some ICP are not expressed in CHS subtypes, B7H3 and the macrophage modulators markers CSF1/CSF1R were expressed at high levels. Both of these receptors are expressed on APC, such as macrophages, and can prevent anti-tumoral immunity.

Our results indicate that an immunomodulation of macrophages using macrophage modulator or CSF1R inhibitor could be a new therapeutic approach against CHS.

Social Sciences, Prevention

Poster # 104

Ethical Issues and Cancers

S. SEDDIKI, Z. BOUCIF, F.Z. EL KEBIR

Laboratory of Biology and Development University of Oran 1. Ahmed Ben bella
Contact: sonia13_2000@yahoo.fr

Keywords: cancer, ethics, health, prevention

Cancer, Ethics, Health, Prevention Cancer is responsible for considerable morbidity and mortality. Yet our epidemiological knowledge indicates that about 80% of cases of this pathology could be avoided, thanks to a modification of the way of life of people and their environment.

The objective of this work is to propose reflections on the ethical questions and the procedures to follow for people with cancer (breast cancer, prostate cancer, lung cancer, etc.).

We found that two complementary approaches exist. The first is a holistic approach to promoting health, based essentially on the adoption of behaviors and lifestyle for the physical, moral and social well being of individuals, the second approach and to set up an important device such as that information campaigns and awareness on the risks of exposure to certain agents as such as tobacco, UV, pollution, food ... etc. . Various protection measures and screening programs are implemented under the responsibility of health professionals for the prevention of certain cancers. The field of pharmaco-prevention is still only at the stage of preliminary research. Only vaccinations have demonstrated an undeniable protective effect against infections and can play a role in the occurrence of cancers. The other modalities of chemoprevention, by vitamin supplements and especially by antihormones, present iatrogenic effects such as their use in healthy population, this leads us to ask important questions on the principles of ethics in oncology.

Poster # 105

Analyse psychosociale de la radioprotection dans le domaine médical : le dépistage du cancer du sein

Manon BRITEL[2], Michel Bourguignon[1], Marie Préau[2]

1. IRSN, 31 Avenue de la Division Leclerc, 92260 Fontenay-aux-Roses
2. GRePS, Université Lyon 2 5 Avenue Pierre Mendès France 69676 Bron

Contact: manon.britel@inserm.fr

Keywords: représentations sociales ; mammographie ; cancer du sein ; rayonnements ionisants

Contexte : Dans un contexte d'augmentation significative et durable de l'exposition aux faibles doses de rayonnements ionisants (RI) en imagerie médicale, notamment en mammographie, l'IRSN a pu constater que le grand public ne semble pas avoir de connaissances appropriées de ce sujet. Cependant, communiquer autour des RI revient à se confronter aux croyances, représentations et peurs qui construisent les représentations autour du « nucléaire ». Afin de faciliter la compréhension et orienter les comportements dans le sens de la prévention promue par l'IRSN, il est nécessaire d'investiguer à travers une étude psychosociale les représentations sociales du nucléaire dans le cas du dépistage du cancer du sein en mammographie.

Méthodes : Afin d'investiguer les représentations des RI en mammographie, nous avons réalisé une analyse de la presse grand public. Cette méthode permet de mettre en évidence les éléments de communication présents dans la presse afin de savoir ce qui peut alimenter les représentations des lecteurs (les femmes comme les professionnels) et de quelle manière les recommandations nationales à propos du cancer du sein ont été transmises dans la presse (nous tenons compte du type de revue). Cette méthode permet d'accéder aux représentations véhiculées autour d'un objet, dans le contexte social étudié. La presse peut ainsi être considérée comme reflétant certains éléments de pensée d'une société.

Résultats et perspectives : Ce travail a permis de mettre en évidence la présence dans le corpus d'éléments de cette représentation, comme la transmission rigoureuse des recommandations nationales sur l'âge et la fréquence de dépistage. Il a également permis de montrer un paradoxe intéressant : la présence moindre, ou l'absence de certains éléments de précaution, notamment ceux relatifs aux rayonnements ionisants en mammographie.
Ce travail ouvre des perspectives intéressantes de recherche auprès des différents acteurs du dépistage du cancer du sein.

Poster # 106

Sustainable Return to Work After Breast Cancer: Towards an Integrative Theoretical Framework to Guide Intervention Research

Guillaume BROC[1], Marion LAMORT-BOUCHE[2], Julien CARRETIER[3], Philippe SARNIN[4] & Jean-Baptiste FASSIER[1]

1. Univ Lyon, Université Claude Bernard Lyon 1, Unité mixte de recherche Epidémiologique et de Surveillance Transport Travail Environnement, UMRESTTE UMR T 9405, 8 avenue Rockefeller, F-69008 LYON, France
2. Univ Lyon, Université Claude Bernard Lyon 1, Collège Universitaire de médecine générale, 8 avenue Rockefeller, F-69008 LYON, France
3. Univ Lyon, Université Claude Bernard Lyon 1, Health Services and Performance Research, HESPER Université Lyon 2 - LYON, France
4. Univ Lyon, Université Lumière Lyon 2, GREPS - EA 4163 (Groupe de recherche en psychologie sociale), LYON, France

Contact: gbroc33@gmail.com

Keywords: return to work, breast cancer, integrative intervention model, systematic review, qualitative methods

Objective: Employment issue from breast cancer encompasses an intersectoral problem at the crossroads of different systems (patient, healthcare, insurance, and workplace) where stakeholders interact at different ecological levels. In such context, developing and validating a shared intervention theory and logic model remains consequently more necessary than ever to help the stakeholders implementing theory-based interventions, hence the interest of our study.

Methods: A systematic literature search of theoretical frameworks that yielded 1239 references from which 14 were included in a qualitative meta-analysis was conducted to build a unifying meta-model. Then, this model was tested to analyse qualitatively 17 semi-structured interviews focusing on professional trajectory of french women with breast cancer.

Results: A parsimonious Sustainable return to work (SRTW) model combining both ecological and phase dimensions was proposed to overcome the shortcomings highlighted by the metasynthesis (study 1). This model enabled capturing the women's need during and after breast cancer (study 2). It could discriminate time varying and unvarying individual and environmental factors involved in work issues. Policy implications: SRTW guide the development of theory-based interventions tailored to the needs of both women and stakeholders involved.

Poster # 107

Utilisation des réseaux sociaux en ligne et comportements à risques pour la santé chez les jeunes

Boris CHAPOTON[1], Valentin FLAUDIAS[2], Fabien TINQUAUT[3], Véronique REGNIER-DENOIS[3], Franck CHAUVIN[1]

1. Univ. Lyon, Université Saint-Etienne, HESPER EA 7425, F-42023 Saint-Etienne, France
2. Université Clermont Auvergne, Université d'Auvergne, EA NPsy-Sydo, BP 10448, F-63000 Clermont-Ferrand, France
3. Centre Hygée, Département de Santé Publique de l'Institut de Cancerologie Lucien Neuwirth, Hesper EA 7425, Saint-Priest en Jarez, France

Contact: boris.chapoton@univ-st-etienne.fr

Mots clés : réseaux sociaux, adolescents, alcool, tabac

Contexte : Le tabac, en cause dans 1 cas sur 2 des cancers et 1ère cause de morts et de maladies évitables en France, ainsi que l'alcool, cancérogène avéré et 2nde cause de décès prématurés font partie des priorités nationale et européenne en tant que facteurs à cibler dans une optique de réduction des risques. Très tôt, les représentations de plaisir, de convivialité et de liberté liés au tabac et à l'alcool sont construites et maintenues à travers certains facteurs psychologiques, économiques et culturels parmi lesquels sont comptés les pratiques familiales et les pairs. Une possible source d'influence à risque récemment mise en avant est celle des Réseaux Sociaux en Ligne (RSL). Utilisés par plus d'un adolescent sur deux qui y affirme sa personnalité, les RSL tendent à se multiplier (Facebook, Instagram, Snapchat, …) et font office de terrains particulièrement propices au développement et à la transmission de valeurs associées à ces substances. Pourtant les données quant à l'utilisation de ces RSL par les adolescents et son lien avec l'adoption de comportements potentiellement protecteurs ou risqués pour la santé sont encore peu développées dans le contexte français.

Méthode : Un questionnaires a été réalisé auprès d'élèves de 4ème et 3ème (13-15ans) au sein de leur établissement scolaire. Des questions relatives aux variables socio-démographiques, à l'utilisation des réseaux sociaux et à la publication de posts relatifs à l'alcool et au tabac sur les réseaux sociaux ont été posées.

Résultats-Conclusion : Les données, en cours d'analyse, seront présentées lors de la 13ème édition du Forum de la Recherche en Cancérologie et permettront de dresser un premier état des lieux sur les caractéristiques associées à l'utilisation des réseaux sociaux en ligne par les adolescents et la publication de messages alcool et/ou tabac.

Poster # 108

Hospital Staff's Opinion on a Smoke-Free Policy: A Survey at the Centre Léon Bérard Cancer Center of Lyon

S CORBIN, Y DROUET, G BARONE, E PEYSSON, C BIOTA, C BORYS, D SEBILEAU, D TRIVIAUX, C LASSET

Centre Léon Bérard, Département de Santé Publique, Lyon, F-69008, France
Contact: sara.corbin@lyon.unicancer.fr

Keywords: tobacco, smoke-free policy, smoking cessation, survey

Introduction: The Centre Léon Bérard cancer center is starting a new smoke-free policy (forbidding smoking for anybody anywhere, hospital grounds included), in agreement with the 2016 INCa recommendations which place smoking cessation as a part of cancers treatment. This survey assesses smoking prevalence and staff's opinion about this new policy.

Methods: An anonymous questionnaire was distributed to the 1685 employees, 611 (37%) answers were collected. Quantitative scores (1 = "disagree totally" to 4 = "agree totally") were analyzed with multiple linear regression models.

Results: Overall, 9.7% (N = 58) of the respondents smoked on a daily basis, 6.7% (N = 40) smoked occasionally, 15.7% (N = 94) were former smokers and 68% (N = 407) were nonsmokers. On average, daily and occasional smokers were younger than former and nonsmokers (respectively 34, 35, 38 and 42 years old, $P < 0.0001$). About the new tobacco-free policy, employees were broadly in favor of the nonsmoking on hospital grounds new rule (mean score = 3.71). Nonetheless, we found disparities based on department and smoking status, smoking caregivers represented the most reluctant staff category towards that restriction (mean score= 2.81). When asked if they saw themselves as a role model to patients, the staff's answers differed between departments (mean scores= 3.12, 2.72, 2.65 respectively for caregivers, non-nursing and research staff, $P < 0.001$) and smoking status (mean scores= 3.01, 2.95, 2.92, 2.16 respectively for nonsmokers, former, occasional and daily smokers, $P < 0.001$). Finally, 44% of respondents reported tensions between hospital smokers and nonsmokers, and surprisingly smoking status didn't seem to impact this perception ($P = 0.8$).

Conclusion: Overall, employees of the Centre Léon Bérard cancer center seemed to be in favor of a smoke-free hospital. Nonetheless, this survey highlights some differences of opinion. This study will be helpful for the organization of targeted preventive actions.

Poster # 109

Self-Management Support for Breast Cancer Survivors: Qualitative Study on Collaborative Care in the Lyon Area

Maha GANEM[1], A DIMA[1], , E VAN GANSE[1], M PREAU[2,3], A-M SCHOTT[1]

1. Univ Lyon, Université Claude Bernard Lyon 1, Université Saint-Étienne, HESPER EA 7425, F-69008 Lyon, F-42023 Saint-Etienne, France
2. Aix Marseille Univ, INSERM, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, 3. GREPS, Institut de Psychologie, Université Lumière Lyon 2

Contact: mahaganem@gmail.com

Keywords: self-management support; integrated care; care coordination

Objective: To maintain long-term quality of life, breast cancer survivors need to perform several behaviours regularly, such as adherence to long-term medication regimens, attendance to monitoring appointments, self-monitoring of recurrence symptoms, following nutrition advice, or physical exercise. Supporting these behaviors is part of chronic cancer care, and several health care professionals, such as general practitioners, specialists, therapeutic patient education (TPE) providers, pharmacists, nurses, nutritionists, physiologists, etc., may provide different types of self-management support (SMaS). These interventions need to be coordinated for optimal results. While there has been a sustained improvement in cancer survivorship services recently, SMaS coordination is less developed. We conduct a qualitative study of breast cancer survivors, caregivers and health care professionals involved in cancer care, in order to explore their experiences and representations of SMaS and coordination of care in this domain, and any improvement they envisage.

Method: We recruit participants via patient and professional organizations and perform semi-structured interviews (estimated sample size 50). Verbatim transcripts will be analyzed via thematic and lexicometric analyses to identify current SMaS practices, needs, and solutions, and develop a conceptual framework to guide intervention

Results: The study is currently recruiting. Preliminary results will be presented.
Conclusion: This study is to our knowledge the first to describe current collaborative SMaS practices for breast cancer survivors in the Lyon area. It will be the first step of a larger community-based participatory research project to improve coordination of SMaS services in the region.

Poster # 110

Faciliter et soutenir le retour au travail après un cancer du sein (FASTRACS) : élaboration d'un modèle logique du problème avec le protocole de l'Intervention Mapping

Jean-Baptiste FASSIER[1,2], Marion LAMORT-BOUCHE[1,3], Guillaume BROC[1], Laure GUITTARD[4,5], Julien PERON[6,7], Sabrina ROUAT[8], Julien CARRETIER[9], Béatrice FERVERS[9,10], Laurent LETRILLIART[3,4], Philippe SARNIN[8]

1. Univ Lyon, Université Claude Bernard Lyon 1, Unité mixte de recherche Epidémiologique et de Surveillance Transport Travail Environnement, UMRESTTE UMR T_9405, Lyon, France
2. Hospices civils de Lyon, service de médecine et santé au travail, Lyon, France
3. Univ Lyon, Université Claude Bernard Lyon 1, Collège universitaire de médecine générale, Lyon, France
4. Univ Lyon, Université Claude Bernard Lyon 1, Health Services and Performance Research, HESPER
5. Hospices civils de Lyon, Pôle IMER, Lyon, France
6. Univ Lyon, Université Claude Bernard Lyon 1, Laboratoire de Biométrie et Biologie Evolutive LBBE – UMR 5558, Lyon, France
7. Service d'oncologie médicale. Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), Pierre-Bénite, France
8. Univ Lyon, Université Lumière Lyon 2, GRePS - EA 4163 (Groupe de Recherche en Psychologie Sociale), Lyon, France
9. Centre Léon Bérard, Département Cancer et Environnement, Lyon, France
10. Université Claude Bernard Lyon 1, Faculté Lyon Est, Lyon, France

Contact : jean-baptiste.fassier@univ-lyon1.fr

Mots clés : cancer du sein, inégalités sociales, réadaptation professionnelle, maintien en emploi, intervention mapping, programme de santé

Le retour au travail des femmes après un cancer du sein est une étape importante pour leur participation sociale et leur autonomie. Cependant, elles font face à de nombreuses barrières qui touchent plus particulièrement les femmes plus âgées et celles qui ont un plus faible niveau d'études. Les acteurs de la santé, du travail et de l'assurance-maladie collaborent faiblement dans le processus du retour au travail. Aucune intervention à ce jour n'a prouvé son efficacité pour réduire les inégalités sociales devant l'emploi après un cancer du sein. Il est rapporté dans la littérature scientifique des échecs à la fois de la théorie et de l'implantation des interventions de retour au travail. En vue de prévenir de tels échecs, le protocole de l'Intervention Mapping est utilisé pour développer, implanter et évaluer une intervention visant à faciliter le retour au travail après un cancer du sein à l'échelle de la métropole de Lyon (le projet FASTRACS). L'objectif de cette étude est de décrire le processus et les résultats de l'évaluation des besoins, avec les défis et les opportunités rencontrées. Différentes méthodes ont été suivies pour 1) établir et travailler avec un comité stratégique et 2) conduire une évaluation des besoins. Un comité stratégique a rassemblé les différentes parties prenantes (patientes et associations, employeurs, professionnels de santé, institutions) pour collaborer avec l'équipe de recherche. Une revue de la littérature a été conduite. Une enquête qualitative de terrain a été menée auprès des parties prenantes avec 12 focus groupes et 48 entretiens individuels semi structurés pour explorer leurs besoins et leur expérience. Une charte de partenariat a été élaborée pour structurer le processus participatif. Un modèle logique du problème a été élaboré à partir de la revue de littérature, des indicateurs et de l'enquête qualitative. Cette première étape conduira à développer, implanter puis évaluer une intervention adaptée aux besoins identifiés.

Poster # 111

Interventions Developed with the Intervention Mapping Protocol in the Field of Cancer: A Systematic Review

Marion LAMORT-BOUCHE[1,2], Philippe SARNIN[3], Gerjo KOK[4], Sabrina ROUAT[3], Julien PERON[5,6], Laurent LETRILLIART[2,7], Jean-Baptiste FASSIER[1,8]

1. Univ Lyon, Université Claude Bernard Lyon 1, Unité mixte de recherche Epidémiologique et de Surveillance Transport Travail Environnement, UMRESTTE UMR T 9405, F-69008 Lyon, France
2. Univ Lyon, Université Claude Bernard Lyon 1, Collège Universitaire de médecine générale, F-69008 Lyon, France
3. Univ Lyon, Université Lumière Lyon 2, GREPS - EA 4163 (Groupe de recherche en psychologie sociale), Lyon, France
4. Department of Work and Social Psychology, Maastricht University, Maastricht, The Netherlands
5. Univ Lyon, Université Claude Bernard Lyon 1, Laboratoire de Biométrie et Biologie Evolutive LBBE – UMR 5558, Lyon, France
6. Service d'oncologie médicale. Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), Pierre-Bénite, France
7. Univ Lyon, Université Claude Bernard Lyon 1, Health Services and Performance Research, HESPER Université Lyon 2 - Lyon, France
8. Hospices civils de Lyon, service de médecine et santé au travail, Lyon, France

Contact: marion.lamort-bouche@univ-lyon1.fr

Keywords: cancer, health promotion, intervention mapping, oncology, program development, program evaluation

Objectives: The Intervention Mapping (IM) protocol provides a structured framework to develop, implement and evaluate complex interventions. The main objective of this review was to identify and describe the content of the interventions developed in the field of cancer with the IM protocol. Secondary objectives were to assess their fidelity to the IM protocol and to review their theoretical frameworks.

Methods: Medline, Web of Science, PsycINFO, Pascal, Francis, and BDSP databases were searched. All titles and abstracts were reviewed. A standardized extraction form was developed. All included studies were reviewed by two reviewers blinded to each other.

Results: Sixteen studies were identified, and these reported 15 interventions. The objectives were to increase cancer screening participation (n=7), early consultation (n=1) and aftercare / quality of life among cancer survivors (n=7). Six reported a complete participatory planning group and seven described a complete logic model of the problem. Ten studies described a complete logic model of change. The main theoretical frameworks used were the theory of planned behaviour (n=8), the transtheoretical model (n=6), the health belief model (n=6) and the social cognitive theory (n=6). The environment was rarely integrated in the interventions (n=4). Five interventions were reported as effective.

Conclusions: Culturally relevant interventions were developed with the IM protocol that were effective to increase cancer screening and reduce social disparities, particularly when they were developed through a participative approach and integrated the environment. Stakeholders' involvement and the role of the environment were heterogeneously integrated in the interventions.

Poster # 112

Quels sont les risques individuels de cancers perçus en Région Auvergne-Rhône-Alpes ? Quels liens avec l'adoption de comportements en santé ? Données d'une enquête transversale

Marine GENTON, Julien CARRETIER, Nora MOUMJID

Département Cancer et Environnement, Centre Léon Bérard
Université de Lyon, Université Claude Bernard Lyon 1, HESPER EA 7425
Contact: marine.genton@lyon.unicancer.fr

Mots clés : perceptions des risques, cancers, facteurs environnementaux, enquête transversale, Auvergne-Rhône-Alpes

Contexte : Un tiers des cancers pourrait être évité par l'adoption de stratégies de prévention individuelles notamment en lien avec les comportements de consommation (OMS, 2018). De nombreux modèles et études en sciences sociales ont montré que les perceptions individuelles jouent sur l'adoption de comportements.

Objectif : Explorer les perceptions individuelles des risques de cancers toutes causes confondues et liés aux facteurs environnementaux au sein de la Région AURA et analyser leurs liens avec l'adoption de comportements en santé.

Méthode : Enquête transversale conduite en ligne par l'intermédiaire d'IPSOS en octobre 2016 sur un échantillon représentatif de la population âgée de 18 à 75 ans.

Résultats : Le questionnaire a été complété par 674 individus résidant en région AURA. 38% ont déclaré ne pas savoir comment percevoir leur risque de développer un cancer au cours de leur vie, 40% ont déclaré percevoir leur risque élevé et 22% faible. Près de la moitié des individus ont déclaré percevoir au regard de leur mode de vie leurs risques de développer un cancer lié à la pollution de l'air, au stress et à l'exposition aux pesticides élevés. A contrario, la majorité des répondants a déclaré percevoir son risque lié aux produits cosmétiques et à une alimentation riche en viandes rouges faible. Ne pas savoir comment percevoir son risque de développer un cancer lié à la pollution de l'air, à l'alimentation et au stress, tout comme percevoir son risque de développer un cancer lié au tabagisme, aux pesticides, à l'alimentation et au stress élevé, est significativement associé à une moindre adoption de comportements en santé liés à ces même facteurs ($p<0.01$).

Discussion : Nos résultats soulignent l'intérêt pour les politiques de santé publique de ne pas considérer uniquement les risques perçus de cancers toutes causes confondues mais aussi ceux liés aux facteurs environnementaux notamment lorsque ceux-ci sont analysés en lien avec l'adoption de comportements en santé.

Poster # 113

IARC Handbook of Cancer Prevention Vol. 17 – Colorectal Cancer Screening

Nadia VILAHUR and Beatrice LAUBY-SECRETAN, on behalf of the IARC Handbooks Programme

IARC, International Agency for Research on Cancer
Contact: Vilahurn@iarc.fr

Keywords: prevention, screening, colorectal cancer, effectiveness, evaluatione

The WHO/IARC Handbooks on Cancer prevention program conducts evidence-based expert evaluations of the cancer preventive effects of chemopreventive agents and of primary and secondary interventions. According to Globocan data, colorectal cancer (CRC) is the third most common cancer in men and the second most common in women. In November 2017, 23 experts from 15 countries met at the Agency in Lyon to evaluate different methods of screening for CRC, by assessing the benefits in reducing mortality and incidence, and the net benefit-harm ratio, taking into account medical and psychological adverse effects. Evaluations were conducted for the stool-based blood tests (guaiac faecal occult blood test, gFOBT, and immunochemical fecal test, FIT), endoscopic techniques (colonoscopy and sigmoidoscopy) and the computed tomographic colonography (CTC), an imaging method based on scanning technology The published evidence from randomized controlled trials, observational studies and modelling studies, was critically reviewed and evaluations were formulated by consensus. The Handbook also covered other relevant topics including worldwide availability of CRC screening, participation to screening, emerging CRC screening techniques and screening in high-risk groups. The results of the evaluation have been submitted for publication, and will be disclosed by the time of the CLARA meeting.

Poster # 114

Sentiment d'efficacité personnelle et consommation chronique d'alcool et de tabac chez les étudiants de 1er cycle universitaire

Laura RATENET, Julien MASSON, Laurent GERBAUD, Veronique REGNIER

Centre Hygée
Contact: laura.ratenet@etu.univ-lyon1.fr

Le sentiment d'efficacité personnelle est une théorie motivationnelle issue des travaux A. Bandura (2007). Il peut se définir comme « la croyance en sa propre capacité à organiser et exécuter une série d'actions nécessaires pour parvenir à une situation visée » (Bandura, 1997, p3). Le SEP constitue par ailleurs un prédicteur solide de nombreux comportements en santé, or les étudiants de premier cycle constituent une population particulièrement à risque aussi bien pour la consommation d'alcool et de tabac (par ex. Vaysse et al., 2016) que pour les troubles de l'anxiété générés par leur nouvelle vie d'étudiant (Bruffaerts et al., 2017). Il apparaît dès lors intéressant d'essayer de mieux comprendre, dans un premier temps, quel est le sentiment d'efficacité personnelle de ces étudiants à faire face aux difficultés inhérentes à l'arrivée à l'université.

La méthodologie employée serait ici quantitative puisqu'il s'agirait de mesurer le SEP universitaire des étudiants de 1er cycle avec une échelle validée (type Likert), de le caractériser et d'évaluer dans le même temps leur consommation d'alcool et de tabac via un questionnaire en ligne.

Dans un second temps, nous nous appuierons sur des outils statistiques afin de calculer des corrélations entre ces différentes variables (SEP, consommation de tabac et d'alcool).

Nous faisons l'hypothèse que les étudiants ayant un SEP universitaire faible sont plus enclins à consommer de l'alcool et du tabac pour palier leurs difficultés.

RESEARCH2BUSINESS ONCOLOGY MEETING : Pitchs de projets collaboratifs

Bioactive Coatings of Multiple-Well Culture Plates

Catherine PICART, Institut National Polytechnique de Grenoble (INPG)
Contact : catherine.picart@grenoble-inp.fr

DESCRIPTION DE L'ACTIVITE
Biomedical engineering, Tissue engineering
Engineering of very thin surface coating of biopolymers and bioactive proteins and peptides (thickness in the nanometer and micrometer range), which play the role of biomimetic environments for cells to grow and form mini-tissues
Controlling the composition (polymer type), the stiffness and the bioacctivity (nature of the biomolecules trapped in the biomimetic film) of the biomimetic films
Automated process to deposit the biomimetic films in multiple-well cell culture plates has been patented
The film-coated microlates can be analysed at high content using conventional techniques (optical microscopies, microplate readers...)

PARTENARIAT RECHERCHE
Pharmaceutical company to provide and test their bioactive molecules (proteins or drugs) (of GMP grade)
Companies workiing on stem cell therapies: the biomimetic coatings can be used to prepare and specific stem cells in view of future therapies
Companies producing GMP-grade extracellular matrix proteins, polysaccharides and polypeptides
Academic labs who want to study specific cellular responses

DESCRIPTION DU PROJET
Cell culture is widely used for growing living cells artificially outside their natural environment under controlled physical conditions: to study cellular structures and functions, stem cell differntiation, to do molecular and genetic engineering as well as drug screening, commercial production of drugs and biologics.

To date, cell culture in vitro is performed in plates, flasks, dishes of different sizes that are made of stiff and synthetic materials (glass, polystyrene), which may bias the experimental results. In vivo, the cellular behavior is strongly influenced by the mechanical and biochemical properties of their microenvironment, namely their extra-cellular matrix (ECM). This soft ECM network is made of proteins and polysaccharides confining bioactive molecules, such as growth factors that provide biochemical signals modulating cellular functions. The challenge is to mimic this natural environment in vitro and to present these biochemical signals from softer substrates in order to control and study cellular processes.

We developed an innovative surface-coating of multi-well plates with advanced physico-chemical and biochemical functionalities. This surface-coating is made by self-assembly of biopolymers that mimics the natural extracellular matrix (ECM), providing a soft environment and biochemical signals (proteins, peptides, growth factors). Advantageously, our technology is flexible in terms of chemical composition, mechanical properties and bioactivity, compatible with automated liquid handling systems and microscopic analysis, high throughput thanks to multiple-well plate format.
Our innovative process will broaden the applications of coated plates in research and industry

MOTS-CLES
nanomedicine, health technologies, tissue engineering, biomimetisms, surface coating

MECACHIPS

Camille MIGDAL, Mecachips
Contact : camille.migdal@cea.fr

DESCRIPTION DE L'ACTIVITE
Mecachips develop culture plates for in vitro 2D cell culture that mimic the in vivo chemo-mechanical properties of almost all our tissues. Indeed, the Mecachips innovative and patented technology allows the elaboration of a soft and flat layer made of polyacrylamide hydrogel that can exhibits uniform or patterned elastic properties. Mecachips culture plates are pre-coated with proteins of the extracellular matrix and supports long time cell cultures without degradation nor modification of its mechanical and chemical properties. MecaChips culture plates are very easy to handle and ready-to-use, similar to plastic culture plates and are being developed in standard size and format. Mecachips culture plates are dedicated to (1) cell culture and cancer research, with the aim of offering cell culture conditions with mechanical features as close as possible to the pathophysiological features of animal or human tissues, (2) stem cells differentiation, to promote the emergence of physiologically relevant phenotypes and (3) drug discovery, in order to screen drugs in more physiological conditions so to raise the relevance of the hits and uncover new molecules more efficient in clinic. Indeed, studies reveal that responses derived from current assays are biased by the lack of mechanical physiological relevance of the in vitro culture device. Thus Mecachips culture plates will provide a new and more physiological microenvironment for cell culture and tests.

PARTENARIAT RECHERCHE
We are looking for a partnership with a Biotech or a CRO company able to drive a drug screening assay on Mecachips Culture Plates.

DESCRIPTION DU PROJET
Our organs are "soft", with rigidities span between few Pa and few tens of kPa. However, up to now, cell culture and cell tests performed in cancer research laboratories, pharmaceutical industries or screening platforms are mostly operated on plastic (or glass) dishes, which rigidities are about gigapascal (GPa), thus more than 1 6 times stiffer than our organs. This lack of in vivo relevance and mechanical physiology of the standard culture plates is a true limitation, as many studies have proved that the mechanical properties of the micro-environment deeply impacts almost every aspect of cell behavior (e.g. adhesion, spreading, migration, proliferation, differentiation) for a vast number of cell types. The Mecachips project fills this gap by developing a completely new generation of cellular culture plates that offer soft and biomechanical substrates for in vitro 2D cell culture and tests. The MecaChips technology combines an unprecedented micron scale control of the plate mechanical properties with an independent control of the surface chemistry thus assuming the chemo-mechanical robustness of the culture environment. Unique is the ability of MecaChips culture plates to mimic physiological mechanical heterogeneities of the extracellular matrix on a single plate!
Mecachips is currently in incubation with the SATT Grenoble Linksium and currently located at the Laboratoire des Technologies de la Microélectronique, in the Minatec campus (CEA Grenoble).

MOTS-CLES
in vitro cell biology, elastic culture plates, physiological in vitro cell culture

Development of In Vivo Tumor Models Resistant to Treatments

Elsa KRESS, Antineo
Contact : elsa.kress@antineo.fr

DESCRIPTION DE L'ACTIVITE

Antineo accelerates and optimizes preclinical development of anticancer agents. We carry out Proof-of-Concept studies to reveal the antitumor efficacy of your compounds. We provide the best preliminary in vitro and ex vivo data to refine in vivo experimental designs.
Our scientific team is able to advice you on:

- the best choice of indication
- the best model
- the reference treatment to use as comparison
- the reference treatment to combine with your compound

Our clients benefit from animal facilities and personnel fully and immediately authorized for PK, toxicity and antitumor efficacy studies on mice and rats.
Our most sought-after activities are:

- our expertise in the development of therapeutic antibodies: deciphering of the mechanistic action in vitro, ex vivo (ADCC, ADCP, CDC etc) and in vivo (ADCC, CDC, test of bispecific antibodies without the costly use of humanized mice).
- our fully characterized models of acquired resistance to reference treatment (anti-CD2 , ADC anti-Her2, anti-CD38, anti-PD1/PDL1 etc). Such models allow to test in vivo innovative therapeutics designed for resistant tumors, in a clinically relevant context.
- Antineo also develops bespoke resistant models upon request.

With its expertise and reactivity, Antineo will accelerate the development of your anticancer agents

PARTENARIAT RECHERCHE

We would like to integrate and offer our expertise within public funded projects such as PoC, EuroStars or FUI call for projects, for co-development with R&D teams developing new cancer treatments, either in combination or in competition with reference drugs. Antineo's partners will benefit from high-end model development technology, years of experience and top-level expertise in several oncology diseases for the development and the use of relevant and reliable pre-clinical resistance models.

DESCRIPTION DU PROJET

A large number of cancer patients will initially respond to medical therapy before suffering relapse with resistant disease. In order to develop novel active and original therapies it is therefore necessary to test novel agents in clinically relevant resistance models.
Our models are developed to be resistant to gold standard therapies, which reflect the clinical situation in which novel agents will be analyzed in the scope of phase II clinical trials. Importantly we perform molecular and phenotypic characterization of our resistance models in comparison to the parental sensitive models. While all preclinical models suffer from limitations, our approach provides our customers with a unique opportunity to evaluate their agents in models which are closely related to clinical situations of resistance.
So far, Antineo has obtained models resistant to chemotherapy and/or immunotherapy. Those models, CDX or syngeneic, are representative of various indications. We therefore have the know-how to develop, in the frame of a consortium agreement, a variety of resistant models

MOTS-CLES

oncology, resistance, immuno-oncology

CellenONE™ X1, the Single Cell Dispenser

François MONJARET, Cellenion
Contact : f.monjaret@cellenion.com

DESCRIPTION DE L'ACTIVITE

Cellenion has developed a new tool, CellenONE™ X1, for single cell isolation based on deterministic delivery of ultra-low volume via automated image analysis. CellenONE™ X1 can be compared to an automated liquid handler producing picodrops (each drop is a few hundreds of picoliters), able to monitor live if the next drop formed will contain a single cell and dispense only those drops containing single cell onto a define target. Thus, about 1 cells can be isolated in less than 4 minutes, a 384wp can be filled in ~15minutes. The rigorous control of the presence of one and only one cell per drop allows our deterministic (as opposed to statistic for most competing technologies), high throughput tool to be the only one on the market to deliver 1 % of single isolated cell in customer defined labware.

Major competitive advantages of CellenONE™ X1 are numerous:

1. Developed as an open platform: any type of sample (cells, particles, biologicals) and any labware/consumable can be used as source and target.
2. Ideally suited for isolation of single cells from rare samples given that isolation can be undertaken from just a few µL of sample with outstanding recovery rates up to >95%.
3. Allow isolation of cells within tiny droplets hence limiting background signals in single cell analysis.
4. The expertise developed at Cellenion is broad: clonal selection of transformed/transfected cells, isolation of cells from human samples, rare sample enrichment, NGS applied to single cells...

PARTENARIAT RECHERCHE

We are looking to partner with:

1. Research and medical teams specialized in cancers (new therapeutic target, mechanisms of drug resistance, companion test, cell therapy development, monitoring of patients, ...)
2. Teams or companies working in the field of NGS for technical development and miniaturization on specific technologies (scChIP-Seq, G&T-Seq, MALBAC, DR-Seq, SUPeR-Seq, Quartz-Seq, CEL-Seq, FRISCR Sequencing, scATAC-Seq, scBS/scWGBS, scM&T-Seq, scRRBS, Hi-C/3C-Seq, …)

DESCRIPTION DU PROJET

The single cell is the fundamental operative unit of a cancer. Single cells are genetically and epigenetically different depending on their environment (proliferating or quiescent, in the primary tumor mass or disseminated elsewhere, vascularized or not…). Most of current studies on cancer cells look at averages over cell populations, typically limiting observations to small variations. Single-cell analyses provide the ultimate level of resolution in the quest for a fundamental understanding of cellular processes such as cancer. Historically, this quest has been hampered by technological shortcomings that we hope address.

Our aim at Cellenion is to participate in the development of single-cell studies. By introducing CellenONE™ X1 on the market, we make single-cell isolation easier and more reliable. Using Cellenion's R&D and engineering resources together with this technology we would like to support the development of advanced methods in the field of oncology and precision medicine. One way we could contribute to a collaboration could be by offering the use of our single cell technology for proof of concept studies or by participating in the preparation of complex projects involving challenging technological developments.

MOTS-CLES

single cell, oncology, precision medicine, immunology, immunotherapies, personalized medicine, transcriptomics, genomics, big data, sequencing, RNAseq, bioinformatics

Infiltrative Glioma Detected by Fast Field Cycling NMR: A Nuclear Magnetic Resonance Technology of Low and Variable Magnetic Fields

Hana LAHRECH, Brain Tech Lab, Inserm
Contact : hana.lahrech@univ-grenoble-alpes.fr

DESCRIPTION DE L'ACTIVITE

My research consists on the development of MRI methods for neuroscience applications in preclinic and in clinic in particular for brain tumors, but other pathologies and animal models are occasionally studied. It consists in establishing the relations between the multi-parametric NMR signal and the molecular and cellular characteristics of the biological tissue, its physiology and pathophysiology processes. It relies on the understanding of the NMR signal and its interaction at micro and nanometer scale. The methods use endogenous NMR parameters but also take advantage on the use of paramagnetic and super-paramagnetic probes. Methodological developments also concern NMR signal simulations (such Monte Carlo simulation of water diffusion on numerical models of brain microstructure) and mathematical NMR signal modelling (such the pharmacokinetics of contrast agents in tumors). Innovative MRI techniques for diagnostics and treatment monitoring are developed to study and characterize the microstructure and the microvasculature of brain tumors during their development. Most MRI methods using the properties of contrast agents for quantitative perfusion and methods using microscopic diffusion tensor for imaging white matter alteration and tumor cell migration are well established. I focus on new developments, like: molecular MRI for pH mapping, cellular MRI for tumor therapy and Fast-Fields Cycling NMR and MRI (FFC-NMR/MRI) for molecular dynamic characteristics

PARTENARIAT RECHERCHE

Clinicians, scientist and physicians specialists in breast cancer, brain cancer and cancer in general

DESCRIPTION DU PROJET

Fast Field Cycling Nuclear Magnetic Resonance (FFC-NMR), which measures relaxation times T1 at different magnetic fields (T1-dispersion profiles) in low regime (< 1T) is used in physics and chemistry to characterize the molecular dynamics of materials. Here in this project, our aim is to highlight the role of FFC-NMR in medicine. This project is a part of the European H2 2 project (IDentIFY: Improving Diagnosis by Fast Field Cycling MRI) that includes the development of basic theory which will improve our knowledge of Nuclear Magnetic Resonance relaxation phenomena and will provide quantitative and precise data analyses, in turn providing FFC "biomarkers" that will be directly useable by clinicians. Our first aim is to perform FFC-NMR experiments on human tissue samples, obtained from tissue banks and during surgical procedures and to carry out FFC-MRI studies on patients. Only by performing measurements on human tissues can the robustness of the FFC disease biomarkers be determined. This is a vital first step in validating the clinical effectiveness of FFC-MRI after completion of the technical upgrades above compared to existing diagnostic techniques.Purpose

MOTS-CLES

fast-field-cycling NMR, fast-field-cycling-MRI, relaxometry, cancer, glioma, T1-dispersion curve, power model, quadrupolar peaks

Development of New RF Sensor for Early Diagnosis of Breast Cancer

Latifa BOUCHET, INSA de Lyon/ UCB Lyon1
Contact : latifa.fakri-bouchet@insa-lyon.fr

DESCRIPTION DE L'ACTIVITE

Dr. Latifa Fakri-Bouchet received her B.S., M.S., and her Ph.D. degrees (1996) in engineering physics, specialized in electronics and RF instrumentation, from the University Claude Bernard Lyon 1, Lyon, France.
From 2 to 2 14, she was Associate Professor at the University Claude Bernard Lyon1. Since 2 15, she is currently Associate Professor (Hors Classe) at INSA of Lyon and affiliated with the ISA Laboratory (Institute of Analytical Sciences – UMR 528), Villeurbanne, France.
Her expertise is within Electronic, RF instrumentation: coil and microcoil for NMR (MRI and MRS) biomedical applications (Alzheimer Disease) and RF sensors for RF/Microwave Interaction with Biological Tissues and application for Early Diagnosis of Breast Cancer.

PARTENARIAT RECHERCHE

To find academic partners with expertise in algorithmic field, signal processing and imaging reconstruction, same as private partners for technological transfer, industrial scholarship (CIFRE). Also to find different partners to apply for national or European project calls.

DESCRIPTION DU PROJET

Our project focuses on the development of the RF sensors, and more particularly on the development of the RF sensor array configuration that plays an important role in MI systems. Our RF sensor array system is chosen in order to improve resolution and to enhance the sensitivity and selectivity with new innovative and flexible microstrip antennas that might allow one of the first possible underwear-integrated, optimal signal, low cost, and easy-use prototypes.Breast cancer is the most commonly diagnosed cancer among women [1] According to the American Cancer Society, approximately 252,71 breast cancer deaths are expected in 2 17 in the United States [2].
An early diagnosis will increase the survival chance among patients and they will require less expensive treatment [3]. Many breast imaging techniques were been studied and are commonly used for diagnosing early-stage breast cancer, like Mammography, Contrast-enhanced (CE) digital mammography MRI, ultrasonography, PET, CT and biopsy. However all these techniques are expensive methods that require trained people and have respective limitations [4] that imply complementary investigation.
Over the past years, several Breast Cancer Non-Invasive Detection Techniques have been started to develop using different equipment and materials, confirming that one of the most efficient ones is Microwave Imaging (MI).
MI techniques can be grouped as passive and active approaches. Passive MI uses radiometry to measure the temperature differences between normal and malignant tissues Active one concerns microwave tomographic and radar-based MI. It measures the dielectric properties (DPs) contrast between healthy tissue and malignant tissue in the high-MHz to low-GHz regime. Active MI is an emerging mammography technique for diagnosing breast cancer.

[1] Mohebian, M.R. et al. Comput. Struct. Biotechnol. J. 2 17.
[2] www.breastcancer.org
[3] Migowski, A.et al. Cienc. Saude Coletiva, 2 15.
[4] Abel, E.J. et al. BJU Int. 2 13.

MOTS-CLES
breast cancer; radio frequency sensor, microwave-sensing, microwave imaging.

Accélérer la recherche grâce à une plateforme de recherche collaborative: Seintinelles.

Laura SABLONE, Seintinelles
Contact : contact@seintinelles.com

DESCRIPTION DE L'ACTIVITE

Au-delà des besoins financiers, les chercheurs ont des besoins fondamentaux en ressources humaines pour trouver des volontaires susceptibles de participer à leurs études. Bien souvent, l'inclusion de volontaires est laborieuse ce qui peut mettre en péril la faisabilité de certaines recherches. La mission de Seintinelles consiste à accélérer le temps du processus de recherche grâce à une collaboration plus étroite entre citoyens et chercheurs via la 1ère plateforme de recherche collaborative dédiée à tous les cancers en France. Le recrutement de volontaires se fait sur www.seintinelles.com. L'animation de la communauté, principalement par email et via les réseaux sociaux, la création d'outils facilitateurs de la collaboration volontaires-chercheurs de même que l'administration de questionnaires en ligne, de modules de sciences participatives et de conférences sont organisés par les Seintinelles pour renforcer ce lien. Les projets mis en ligne sur seintinelles.com sont toujours validés au préalable par les autorités législatives classiques (CCTIRS, CNIL, CPP si nécessaire). Chaque projet est également soumis au comité scientifique des Seintinelles, dont le rôle est d'une part d'évaluer la pertinence scientifique de l'étude ainsi que sa faisabilité dans le cadre de la plateforme.

PARTENARIAT RECHERCHE

Dans une logique de promotion de la recherche communautaire et d'une forme de démocratie sanitaire, l'association Seintinelles vise d'une part à **impliquer davantage les citoyens dans la recherche** dès la conception même des études, et leur faire bénéficier plus rapidement de ses avancées. L'association et les chercheurs partenaires s'engagent en effet à communiquer les résultats obtenus à l'ensemble de la base de données. D'autre part, l'objectif de l'association est de **mettre à disposition des chercheurs des outils innovants permettant d'optimiser leurs processus de recherche**: le système informatique permettant d'encoder des questionnaires sur mesure, une base de données de plus de 20 000 citoyens volontaires, des communications régulières par newsletters et sur les réseaux sociaux, une responsable communication dont la mission est de donner de la visibilité aux projets de recherche, autant auprès de la base de données qu'auprès d'un réseau de partenaires et des médias. Un projet d'application mobile est également en préparation, afin d'avoir accès à des données jusqu'ici impossible à collecter à grande échelle.

DESCRIPTION DU PROJET

Quatre ans après le lancement du site, 21 000 citoyens (hommes et femmes, malades ou non) se sont déjà inscrits sur Seintinelles. Une vingtaine d'études ont été menées dont certaines sont toujours en cours, parmi lesquelles : Prédisposition à la douleur après une mastectomie, Entourage de personnes malades, Effets secondaires des traitements du cancer du sein, Etude sur le cancer de la prostate, Impact du cancer sur les conjoints, Etude sur les implants PIP.

Les recrutements (de quelques dizaines à plusieurs milliers de volontaires) peuvent s'effectuer en quelques heures ou quelques jours seulement : 1000 volontaires en 24h pour un questionnaire sur le dépistage et la prévention, 20 personnes pour des entretiens qualitatifs en 48h là où on aurait mis plusieurs mois avec des processus classiques de recrutement.

L'objectif global vise à recruter et animer une communauté de 50 000 citoyens d'ici 3 ans, et de mettre en œuvre une quinzaine d'études par an. Le processus même de mise en place de la plateforme Seintinelles, sa démarche et ses questionnements scientifiques, éthiques et épistémologiques animent le conseil scientifique des Seintinelles et donneront lieu à une production scientifique parallèle.

ADDomer: A New Technology for the Immunotherapy of Cancer

Pascal FENDER, CNRS-IBS
Email : pascal.fender@ibs.fr

DESCRIPTION DE L'ACTIVITE
We address the challenge of a prophylactic vaccine to combat cancer such as melanoma. We have developped a novel synthetic protein scaffold, ADDomer, that we recently patented. ADDomer is a bio-similar based on a dodecahedral superstructure derived from human adenovirus penton base protein. ADDomer is uniquely suited for displaying up to 180 copies of peptide or protein epitopes and provides for adjuvant-free vaccination. Moreover, ADDomer can be produced in very large quantities, is ultrastable and has no cold-chain requirements.

PARTENARIAT RECHERCHE
We are seeking for academic or industrial partners having expertise in the immunotherapy field. Our goal would be to validate our ADDomer vaccine technology in animal models bearing cancer. Tumour Associated Antigens (TAAs) or neoantigens could be inserted in the ADDomer. Ideally, both the immune response triggers by our platform against the antigens and the prophylactic response would be studied by animal challenges.

DESCRIPTION DU PROJET
We have recently brought the ADDomer proof of concept in another topic. Indeed, a Chikungunya virus epitope displayed on ADDomer was able to trigger a strong immune response against this epitope, in absence of adjuvant, thus validating our versatile technology. We would like now to broaden the applications of ADDomer by adressing immunotherapy of cancer. For this, TAAs will be inserted in the ADDomer scaffold (preliminary data were obtained with OVA system) and we are seeking for partners to assess the efficiency of the immune response and the therapeutic effects in cancer models.

MOTS-CLÉS
vaccine, immunotherapy, TAAs, nanoparticle, patented