FORUM
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BOOK DES COMMUNICATIONS ORALES ET POSTERS

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Environnement, nutrition et épidémiologie

#1

Risk of breast cancer associated with long-term exposure to Benzo[a]pyrene (BaP) air pollution: Evidence from the French E3N cohort study

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Keywords : *airborne benzo(a)pyrene, breast cancer, residential history, hormone receptor status, differentiation grade*

Background: Benzo(a)pyrene (BaP) is an endocrine-disrupting pollutant formed during incomplete combustion of organic material. It has been recognized as a reproductive and developmental toxicant, however its role in the risk of breast cancer (BC) is limited. Thus, we used data from the French E3N cohort study to evaluate the association between BaP air pollution and risk of BC, overall, according to hormone receptor status (estrogen receptor negative/positive (ER-/ER+) and progesterone receptor negative/ positive (PR-/PR+)), stage and grade of differentiation of BC.

Methods: Within a nested case-control study of 5,224 incident breast cases, and 5,224 matched controls, annual estimates of BaP exposure were estimated using a CHIMERE model and then were assigned to the geocoded residential addresses of participants during the 1990-2011 follow-up period. Multivariable conditional logistic regression models were used to compute odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Overall, cumulative airborne BaP were significantly associated with the overall risk of BC, for each one interquartile range (IQR) increase in the levels of BaP, OR = 1.15 (95% CI: 1.04-1.27). By menopausal status, the positive association appeared statistically significant only in postmenopausal women (OR per 1 IQR = 1.15; 95% CI: 1.03-1.28, P for interaction = 0.009). By hormone receptor status, positive associations were observed for ER+, PR+ and ER+PR+ BC, with ORs = 1.18 (95% CI: 1.04-1.33), 1.16 (95% CI: 1.01-1.33), and 1.18 (95% CI: 1.02-1.36) per 1 IQR, respectively. We also found a suggested positive association between BaP and grade 3 BC.

Conclusions: We provide evidence of an increased risk of BC associated with BaP air pollution, which varied according to menopausal status, hormone receptor status, and grade of differentiation of BC. Our results add further epidemiological evidence to the previous experimental studies suggesting the adverse effects of BaP exposure.

#2

Food additive E171 promotes colonic tumorigenesis and induces changes in gut microbiota composition in APCmin/+ murine model

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Keywords : *Cancer colorectal, microbiote intestinal, nanoparticules de dioxyde de titane, inflammation*

Contaminant molecules could play a key role in the initiation and/or promotion of colorectal cancer (CRC). Titanium dioxide (TiO2) is a white natural metal oxide and is one of the most widely used engineered nanomaterials in daily consumer products, including food. TiO2 nanoparticles (NPs) were classify as a possible carcinogen by inhalation for humans by IARC. The gastro-intestinal tract may be an important absorption route for TiO2 NPs. The food additive TiO2, referred to as E171 in the European Union, which is commonly used as a whitening and brightening agent in sugar-based foods and pastries, could be involved in the CRC etiology. Thus, this project aims to assess the impact of chronic exposure of E171 (10 mg/kg of body weight (BW)) in CRC development using APCmin/+ mouse model, which spontaneously develop intestinal tumors. Because intestinal microbiota play a role in colorectal carcinogenesis, carcinogenic properties of TiO2 will be evaluated in association with microbiota dysbiosis. The E171 compound, which was characterized by X-ray diffraction (XRD) and thermogravimetric analysis, was purely mineral and the size of NPs administrated to mice in this study did not exceed 28 nm. No significant body weight loss was observed between mouse groups suggesting no toxicity in our experimental conditions. Macroscopic and histological observations showed a more advanced tumor development in mice receiving the E171 compared to control animals, which was associated with increased level of fecal lipocalin-2 concentration. Mice with adenocarcinoma within this group also exhibited an increase of Bacteroides and Akkermansia as well as a higher prevalence of Escherichia coli and a decrease of Bifidobacterium as analyzed by quantitative PCR. Additive food E171 promotes colonic tumorigenesis and induces changes in gut microbiota composition. Investigations of underlying carcinogenic mechanisms focusing on microbiota dysbiosis implication are in progress.

#3

Utilisation d'antiagrégants plaquettaires et risque de cancer du sein dans une cohorte prospective de femmes ménopausées.

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Keywords : *Pharmaco-épidémiologie, cancer du sein, antiagrégants plaquettaires, aspirine, clopidogrel*

Les antiagrégants plaquettaires, dont l'aspirine faible dose (AFD) et le clopidogrel, sont supposés jouer un rôle préventif dans l'apparition du cancer du sein (CS). L'objectif de cette étude était d'évaluer les associations entre utilisation d'AFD ou de clopidogrel et risque de CS dans l'Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale (cohorte E3N). La cohorte E3N inclut 98 995 femmes volontaires françaises, adhérentes à la Mutuelle Générale de l'Education Nationale (MGEN) et suivies depuis 1990. Des informations personnelles et relatives au mode de vie ont été recueillies tous les deux à trois ans par auto-questionnaires. Depuis 2004, les données de remboursement de médicaments issues de la MGEN sont aussi disponibles. Pour chaque médicament considéré, les femmes ayant au moins deux remboursements dans une période de trois mois ont été définies comme exposées. Des modèles de Cox multivariés ont été utilisés pour estimer les Hazard Ratios (HRs) de CS associés aux antiagrégants plaquettaires. Durant un suivi moyen de 9 ans, 2887 CS ont été identifiés chez les 62,390 femmes ménopausées suivies (âge moyen au début du suivi: 63 ans). Durant le suivi, 17% ont été exposées à l'AFD et 3% au clopidogrel. L'AFD était associée au risque de CS uniquement pour les femmes ayant une durée d'utilisation cumulée de plus de quatre ans [HR = 0,68 (0,47 – 0,98)]. Le clopidogrel était associée à une augmentation du risque de CS [HR = 1,31 (1,01 – 1,69)], indépendamment de la durée d'utilisation et plus particulièrement pour les CS n'exprimant pas les récepteurs hormonaux à l'œstrogène (ER-) [HRER+= 1,12 (0,81– 1,56), HRER-= 3,17 (1,69 – 5,92), P hétérogénéité=0.02]. En conclusion, l'utilisation d'AFD sur une durée cumulée de plus de quatre ans était associée à une diminution de risque de CS tandis que le clopidogrel était associé à une augmentation du risque de CS ER-, indépendamment de la durée d'utilisation.

#4

Long-term atmospheric exposure to PCB153 and breast cancer risk in a case-control study nested in the French E3N cohort from 1990 to 2011

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***Keywords** : polychlorinated biphenyls, air pollution, breast cancer, nested case control, E3N*

Background: Although the genetic and hormonal factors of breast cancer are well identified, they cannot fully explain the occurrence of all cases. Epidemiological and experimental studies have suggested that exposure to environmental pollutants, especially those with potential estrogenic properties, may have a role in the development of breast cancer.

Objectives: We aimed to estimate the association between cumulative atmospheric exposure to polychlorinated biphenyl congener 153 (PCB153) and breast cancer risk.

Methods: We conducted a case-control study of 5,224 cases and 5,224 matched controls nested within the French E3N cohort from 1990 to 2011. Atmospheric PCB153 concentrations were estimated based on concentration simulated by a chemistry-transport model (CHIMERE) and were assigned to subjects using their geocoded residential history. Their cumulative PCB153 exposure was calculated for each subject from their inclusion to their index date (case diagnosis date). Breast cancer odds ratios (ORs) associated with cumulative PCB153 exposure and their 95% confidence intervals (95% CI) were estimated using multivariate conditional logistic regression models.

Results: Overall, our results showed a statistically significant linear increase in breast cancer risk related to cumulative atmospheric exposure to PCB153 as a continuous variable (adjusted OR = 1.19; 95% CI, 1.08-1.31 for an increment of 55 pg/m3). After analyses by hormone receptors status, the positive association remained statistically significant only for ER positive breast cancer (adjusted OR = 1.18; 95% CI: 1.05-1.33). No statistically significant associations were observed when studying PCB153 exposure in quintiles.

Discussion: This study is the first to have estimated the impact of atmospheric exposure to PCB153 on breast cancer risk. Our results showed a statistically significant increase in breast cancer risk, which may vary by hormone receptor status. However, further studies are needed to confirm them.

#5

Implication des bisphénols dans la tumorigénèse des cellules souches mammaires via une interaction entre les signalisations ERα36 et BMP2.

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Keywords : *Bisphénols, Recepteur à l'oestrogene alpha ER36, Bone morphogenetic protein BMP2, Cellules souches mammaires, Microenvironnement*

Stem cells are regulated by several cues from their microenvironment and it is becoming increasingly clear that perturbations of these signals can participate to transformation. Previously, our lab showed that BMP2 (B2) was able to induce the transformation of breast epithelial stem cells. We found that a potential source of B2 over-expression by the mammary gland microenvironment was the exposure to Oestrogen (E2)-mimetic environmental pollutants such as BPA, BPS and BPF which raises concerns about their effect on breast cancer (BC) development. In clinic, the main criteria used to guide BC therapeutic choices is the expression of the classical oestrogen receptor alpha isoform (ERα66). However, the existence of others non-detected isoforms such as ERα36 can also mediate an alternative E2 signalling. Preliminaries results and data from literature suggest the existence of a crosstalk between the BMP and ERα36 signalling pathways. Alternatives bisphenols, such as BPS and BPF, are considered as a safer alternative to BPA due to their lower affinity for ERα66, but the possibility that they can be potent activator of ERα36 has been suggested.

The goal of my work was to characterize and to study the role of the interaction between ERα36 and BMP2 signalling pathways. For that, in one hand, we followed the impact of chronical exposure to B2, E2, BPA, BPS and BPF, alone or in combination, on the stem cell activity and transformation on an ERα66 negative but ERα36 positive immature human mammary epithelial cell line (MCF10A), and in other hand, we determine the actors of ERα36 and BMP2 signalling pathways involved in this crosstalk.

Our results shed light on the relation between two important pathways, independently involved in breast cancers development. Linking ERα36-mediated oestrogen signalling and BMP2 pathway will allow to better understand how hormonal signals participate to stem cell transformation.

#6

Mycotoxins and cancer: experimental and epidemiology investigations of causal links

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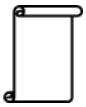
Keywords : *mycotoxins, carcinogen, epidemiology, mutational signatures, HepG2 cells, HT-29 cells, Hupki MEF, cytotoxicity, genotoxicity*

Given the global ubiquitous nature of mycotoxin exposure, there exists an urgent need for a profound mechanistic understanding of the contribution of these toxins to tumorigenesis, extended epidemiological evidence and a coordinated international response to the problem of dietary multi-mycotoxin contamination. (De Ruyck et al., 2020). Using experimental in vitro and in vivo exposure models, we provide proof-of-principle for the genome-scale analysis of characteristic mycotoxin-induced mutation patterns. Aflatoxin B1 induced mutation spectra (Huang et al., 2017), while ochratoxin A exposure resulted in oxidative stress. Chronic multi-mycotoxin exposure was recently hypothesized to be associated with an increased risk of developing cancer (Claeys et al., 2020), one of the aims of this study was to assess effects of single and multiple mycotoxin exposures in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. The results revealed an association of deoxynivalenol (DON) and patulin (PAT) with liver cancer risk, while DON, PAT and Fusarium toxins' exposure increased colorectal cancer risk. Multi-mycotoxin exposures were associated with both, liver and colorectal cancer (Huybrechts et al., 2020). Experimental work revealed DON- and PAT-induced cytotoxicity and genotoxicity in human liver & colon cancer cell lines and mouse embryonic fibroblasts (MEF), suggesting potential mutagenic effects. Ongoing cell-based DNA adductomics analyses as well as chronic single and multi-mycotoxin exposures, followed by clonal expansion and genome-scale sequencing, will allow the identification of DNA damage and mutational signatures, for comparison with signatures from human primary tumors extracted from cancer genome sequencing data.



#7

Digital Phenotyping of Lifestyle and Environmental Factors in Breast Cancer Survivors

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Keywords : *physical activity, diet, pollution, eHealth*

Background: In France, 41% of cancers are linked to our lifestyle and environment. Among the main causes of preventable cancers, several concern environmental and lifestyle factors, including nutrition, physical activity and environmental pollution. The main objective is to leverage and combine various sources of digital data generated by women with a history of breast cancer and apply digital phenotyping approaches to better understand how lifestyle, environmental and contextual factors play a role in the health evolution after a cancer. Methods: The study is a prospective, 12-month e-cohort study. Three hundred Seintinelles participants with a history of breast cancer will be recruited throughout the already existing Seintinelles smartphone app. The following data (clinical, psychological, nutrition, physical activity) will be collected using the Seintinelles mobile. For the clustering analysis, descriptive statistics will be performed to describe the distribution of the different lifestyle factors included in the clustering. We will use k-means and hierarchical clustering on a selected set of variables to clusterize the population and then use other clinical, psychological (assessed with questionnaires) and sociodemographic factors to describe the groups. Expected outcomes: This study will provide a better understanding on the lifestyle changes over a one-year period in patients with a personal history of breast cancer, and will help future prevention programs and intervention studies to target subgroups of individuals of interest. The digital phenotyping offers the possibility to stratify prevention strategies and identify patients with an increased risk of deteriorate lifestyle, which is an increased risk factor for recurrence.

#8

Incidence du cancer broncho-pulmonaire dans la wilaya d'Annaba : Période 2007 à 2017

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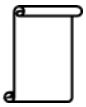
***Keywords** : Cancer-épidémiologie-poumon- incidence*

IntroductionDans le monde, le cancer du poumon est responsable du plus grand nombre de décès soit 1,8 million de décès, soit 18,4 % du total, en raison de son mauvais pronostic. En Algérie, il reste toujours parmi les cancers les plus fréquents chez l'homme. Objectif : Déterminer l'incidence du cancer broncho-pulmonaire dans la wilaya d'Annaba au cours de la période 2007 à 2017.Etudier les caractéristiques démographiques et pathologiques de ces cancers. Matériel et Méthode : Les données ont été extraites du registre du cancer de la wilaya d'Annaba pour la période 2007-2017. La wilaya d'Annaba comptait au milieu de la période en 2013, 638 847 habitants .La localisation retenue était selon la CIM-10 codée entre C33-C34.Résultats :Avec 765 nouveaux cas survenus pendant la période d'étude, les cancers du poumon représentent 9% de tous les cancers chez les 2 sexes.Chez l'homme, il représente le premier cancer une fréquence 16,5%. Chez la femme, sa fréquence est de 2,2%.Les taux d'incidence brute et standardisé sur l'âge (TSA) étaient respectivement chez l'homme 18,1 cas et 20,8 cas pour 105 hommes. Chez la femme, ils étaient respectivement de 2,7 et 3,0 cas pour 105 femmes. L'âge moyen de survenue de ce cancer était de 61,2 ±11 ans chez l'homme et de 60,8 ±14 ans chez la femme. Les taux spécifiques d'âge les plus élevés étaient observés dans les tranches d'âge 70-75 ans chez l'homme avec un taux de 142 cas pour 105 hommes et chez la femme dans la tranche d'âge 65-70 ans soit un taux de 23 cas pour 105 femmes.Les adénocarcinomes, sont les types histologiques les plus fréquents et représentent 60% de tous les types histologiques observés.Conclusion:Devant la persistance des facteurs de risque et particulièrement le tabagisme avec une prévalence de consommation actuelle en Algérie de 32% chez l'homme, avec l'association d'autres facteurs de risque qui restent méconnus en Algérie, la politique de prévention doit être renforcée davantage



#9

Inflammatory biomarkers and breast cancer risk: results from the EPIC study

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Keywords : *Inflammation, breast cancer, adiposity, cytokines, epidemiololgy*

Inflammation is suspected to play a role in breast carcinogenesis.

In a case-control study nested within the European Prospective Investigation into Cancer and Nutrition cohort, prediagnostic concentrations of 11 cytokines and adipokines (TNF-α, IFN-γ, IL-6, IL-8, IL-10, IL-13, IL-17D, IL-1RA, CRP, leptin and adiponectin) were measured in samples from 1,618 case-control pairs. Conditional logistic regression models were used to estimate the associations between breast cancer (BC) risk and biomarkers, before and after adjustment for adiposity. Preliminary results showed no significant associations with BC risk overall. However, in postmenopausal women (870 cases), TNF-α was associated with breast cancer risk (OR for 1 SD increment =1.33, 95% CI 1.04-1.70), while leptin was associated with BC risk only in non-hormone users (OR for 1 SD increment = 1.21, 95% CI = 1.01–1.45). Adjustment for adiposity attenuated these estimates. These results suggest that BC development in postmenopausal women may be linked to specific inflammatory components

#10

Implementation of a program based on adapted physical activity and recommendations for second cancers prevention for adolescents and young adults with cancer: PREVAPAJA study

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Background/Objectives: About 1,000,000 new cases of cancer in Adolescent and Young Adults (AYAs) are diagnosed annually worldwide. . While their long term survival is about 80%, they are six times more likely to develop a second primary cancer (SPC) compared to their peers. This risk is multifactorial and depends on the type of first cancer, treatment received and prevalence of risk factors. PREVAPAJA aimed to implement a clinical program based on physical activity (PA) and cancer prevention recommendations for AYAs with cancer at Centre Léon Bérard-AYAs Department. Methods: The study was conducted at Leon Berard Comprehensive Cancer Centre among patients aged 15-25 years. AYAs attended PA sessions during the active treatment period and were individually informed on SPC risk prevention. PA, sedentary, anthropometrics, quality of life and fatigue were assessed at baseline (T1) and at the end of treatment (T2). PA level and intention of changes in health behaviors were assessed by phone 1 year after T1. Results: 68 AYAs (median age=19 years) were enrolled in 2016-2017). The results showed an improvement in PA level during and at distance of the intervention, with also a reduction of sitting time. Fatigue decreased between T1 and T2 (=<0.003) and overall quality of life improved significantly between T1 and T2 ($p<0.001$). Conclusions: This study showed the feasibility of implementing a clinical program based on PA intervention and cancer prevention recommendations for AYAs with cancer. It responded to AYAs' needs for support and discussions regarding PA recommendations and ways to prevent SPC. Beneficial outcomes of this program should encourage to systematically proposing PA intervention in combination with information exchanges with AYAs with cancer.

#11

Améliorer la prise en charge nutritionnelle des patients en surpoids/obésité atteints de cancer

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***Keywords** : Nutrition, Activité physique,Obésité,Cancer, Surpoids Pluridisciplinaire*

Plus de 50 % des patients atteints de cancer sont en surpoids au diagnostic. Les patients en surpoids ont un risque plus élevé de mortalité mais également de développer un second cancer ou une autre pathologie chronique. La prise en charge nutritionnelle de ces patients est désormais au cœur des politiques ; la promotion de l'activité physique et des comportements nutritionnels adaptés est une mesure du dernier plan Cancer. L'objectif de ce projet est de mettre en place un parcours pour les patients permettant une prise en charge nutritionnelle interdisciplinaire et adaptée à leurs besoins pour réduire la prise de poids pendant les traitements. Un espace dédié à la prise en charge nutritionnelle et physique des patients atteints de cancer a ouvert au Centre Léon Bérard en septembre 2018, avec des enseignants en APA, des diététiciens et du personnel soignant en charge d'un programme d'éducation thérapeutique (ETP). Un hôpital de jour a été mis en place en juillet 2019 avec un bilan en 3 étapes auprès d'un enseignant en APA, un diététicien et un médecin. Depuis l'ouverture de l'espace, le nombre de patients ayant participé au programme d'APA a augmenté de 152%. Les diététiciens ont réalisé 120 consultations individuelles. Concernant l'ETP, 81 patients ont bénéficié du programme d'APA en 2019 et 90 patients du programme nutrition (+22%). L'hôpital de jour a débuté en juillet 2019, permettant d'inclure 33 patients. L'approche pluridisciplinaire auprès des patients permet de mieux suivre les patients puisque 43% des patients ont été vus plusieurs fois depuis l'ouverture de l'espace contre 39% l'année précédente. Au total, 85% des patients suivis depuis septembre 2018 ont perdu/stabilisé leur poids contre 81% l'année précédente.

#12

Design and methods of a national, multicenter, randomized controlled trial to assess the efficacy of a physical activity program to improve quality of life and reduce fatigue in women with metastatic breast cancer: the ABLE02 trial

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***Keywords** : Metastatic breast cancer, Physical activity, Connected devices, Quality of life, Fatigue*

INTRODUCTION: Patients with a metastatic breast cancer suffer from a deteriorated quality of life and numerous symptoms such as pain, severe fatigue and a decrease of their physical fitness. As the feasibility of a physical activity program has been demonstrated in this population, ABLE02 aims to assess the efficacy of a 6 month-physical activity program based on connected devices to improve health-related quality of life and to reduce fatigue in women with metastatic breast cancer. METHODS/ANALYSIS: ABLE02 is a prospective, multicenter, randomized, controlled and, open-label study. 244 patients with a metastatic breast cancer, at least one positive hormone receptor and a first-line chemotherapy planned will be randomly assigned (1:1 ratio) to: (i) the intervention arm to receive physical activity recommendations, an activity tracker to wear 24 hours a day during the whole intervention (6 months) with at least three walking sessions weekly and quizzes to answer each week on physical activity and nutrition (ii) the control arm to receive physical activity recommendations only. Quality of life will be assessed every 6 weeks (EORTC QLQ-C30) for the primary endpoint. Assessments will be conducted at baseline, M3, M6, M12 and M18 to evaluate the clinical, physical, biological and psychological parameters and survival of participants. All questionnaires will be completed on a dedicated application. DISCUSSION: An activity program based on smartphone application linked to an activity tracker may help to improve quality of life and reduce fatigue of patients with a metastatic breast cancer. The growth of connected health offers the opportunity to get real-time data as well as improving patient empowerment in order to change long-term behaviors.

Sciences humaines et sociales, prévention

#13

iDEFCO :

Implémentation d'un outil de repérage des fragilités sociales dans le parcours de soins en cancérologie

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PREDUCAN - CIC 1408

***Keywords** : Fragilités sociales, cancer, Implémentation, Dépistage, Machine learning*

Contexte : Afin de repérer le plus tôt possible les fragilités sociales des patients traités en cancérologie et d'en tenir compte tout au long du parcours de soins, un outil de dépistage systématique des fragilités sociales (l'outil DEFCO) a été créé. Cet outil est un auto-questionnaire sur tablette, relié à un réseau neuronal. Développé dans un établissement spécialisé en cancérologie, cet outil doit faire la preuve de sa transférabilité et de ses possibilités d'implémentation dans d'autres structures. Il est aussi nécessaire de l'évaluer en termes d'impact notamment sur la fluidité des parcours de soins et sur les conséquences sociales de la maladie.

Méthode : l'outil DEFCO a été mis en place dans 4 centres de la région Auvergne-Rhône-Alpes ayant des organisations différentes. Pour évaluer l'implémentation de l'outil, le design utilisé est celui d'une méthode mixte d'une intervention complexe, alliant les méthodes qualitatives et quantitatives. L'objectif de l'étude est d'évaluer l'atteinte de la population cible, l'adaptation de l'outil à son contexte, l'impact de l'outil ainsi que se durabilité. Cet outil est ainsi proposé à tout patient nouvellement diagnostiqué de cancer, au début de sa prise en charge. Chaque patient est ensuite suivi pendant 1 an dans le cadre de l'étude. Cette étude est en cours de réalisation : les résultats de l'étude seront disponibles en 2022.

#14

Jeûne et chimiothérapie - Représentations et pratiques dans un centre de soins en cancérologie

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Keywords : *Jeûne thérapeutique, régime cétogène, chimiothérapie*

Un courant de pensée américain, véhicule l'idée d'un jeûne thérapeutique aux vertus détoxifiantes, voire curatives, pour les patients atteints de cancer. Cette pratique est contrindiquée en France. L'étude vise à améliorer la connaissance de cette pratique pendant la chimiothérapie et à établir des recommandations pour faciliter les échanges entre médecins et patients sur le jeûne. Méthodologie Des patients suivant un traitement par chimiothérapie ont rempli un auto-questionnaire concernant l'alimentation, le jeûne thérapeutique et les médecines alternatives. Un sous-échantillon de patients ayant l'intention d'avoir des restrictions alimentaires ou de faire un jeûne pendant leur chimiothérapie a participé à un entretien semi-directif. Résultats Parmi les 133 patients ayant complété l'auto-questionnaire 21 avaient l'intention d'avoir des restrictions alimentaires ou de faire un jeûne pendant leur chimiothérapie. Il s'agissait principalement de femmes, d'une moyenne d'âge de 56 ans, soignées pour un cancer du sein, connectées, ayant recours à des médications alternatives. Ils avaient peu d'échanges avec l'équipe de soin mais auraient souhaité en avoir davantage avec leur oncologue. Neuf patients ont été vus en entretien. Ils avaient testé le jeûne partiel et/ou avaient adopté un régime cétogène dans l'objectif d'améliorer l'efficacité du traitement, d'atténuer les effets secondaire et/ou afin d'avoir plus de maîtrise sur la prise en charge de la maladie. Ils n'osent pas en parler avec l'oncologue et regrettent cette absence de dialogue. Ils sont souvent conseillés par des naturopathes et ont testé l'homéopathie pour accompagner leur chimiothérapie. Conclusion Les patients justifient leur choix comme voulant mettre toutes les chances de leur côté. Ils souhaiteraient que des temps d'échanges (ateliers, débats) soient proposées sur la thématique par le corps médical, le silence étant perçu par les patients comme potentiellement délétère.

#15

Caractéristiques anatomopathologique et épidémiologique des carcinomes ovariens (séreux/mucineux) dans l'Ouest Algérien.

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Keywords : *Cancer de l`ovaire, dépistage, diagnostic précoce, sensibilisation.*

Le cancer de l`ovaire est l`un des cancers gynécologiques les plus fréquents après le cancer du sein et la deuxième cause de mortalité par cancer chez la femme. Ce problème de santé public devient de plus en plus important du fait de l`augmentation de la durée de vie. Le diagnostic précoce de toutes tumeurs ovariennes et la sensibilisation des femmes en vers ses tumeurs est importante vu que la situation profonde de l`ovaire et les signes non spécifiques expliquent souvent un diagnostic tardif, par ailleurs, à ce jour, aucun impact favorable du dépistage sur la mortalité imputable au cancer de l'ovaire n'a été démontré. Notre travail a été réalisé au niveau du service d'anatomo-pathologie de l'établissement hospitalier universitaire d'Oran. L'objectif de notre travail était de réaliser une étude épidémiologique et anatomopathologique pour déceler les facteurs de risques les plus courants chez les sujets présentant le cancer de l'ovaire sur une période d'une année. Les résultats de notre étude ont montré que l'apparition du cancer de l'ovaire augmente proportionnellement avec l'âge. La fréquence la plus élevé a été observé pour des femmes entre 45 et 59 ans. Ce qui coïncide avec la ménopause. 80% des femmes malades sont mariées, dont la majorité ont eu leur première grossesse à un âge tardif (après 25 à 30 ans) ou sont hypofertiles. Les tumeurs épithéliales (mucineux/séreux) sont les plus fréquents. Actuellement, il n'existe aucun test spécifique permettant de dépister le cancer ovarien à un stade précoce à cause de la localisation profonde et intrinsèque de l'ovaire. En perspective à cette étude, il faudrait envisager un dépistage précoce afin d`éviter un diagnostic tardif des tumeurs ovariennes malignes ou bénignes, primitifs ou secondaires pour assurer une prise en charge adéquate.

#16

PAPRICA : une formation participative pour les médecins généralistes sur la vaccination HPV

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***Keywords** : médecins généralistes, vaccination HPV, formation, conflit socio-cognitif*

Contexte : en France, la couverture vaccinale contre les papillomavirus humains (HPV) n'a pas dépassé 30% depuis l'introduction du vaccin en 2007. Ce sont les médecins généralistes qui sont chargés de conseiller et de vacciner les adolescentes âgées entre 11 et 14 ans. Une formation, fondée sur le concept de conflit sociocognitif, a donc été mise en œuvre à leur intention. Les représentations professionnelles des généralistes au sujet de la vaccination HPV ont été investiguées, et l'efficacité de la formation a été mesurée.

Méthodes : quinze généralistes ont participé à la phase pilote de la formation. Des méthodes mixtes (questionnaire pré-post formation, enregistrement des discours et recueil des supports co-construits) ont été utilisées.

Résultats : l'analyse des données met en évidence que les patients ne sont pas considérés comme une barrière à la recommandation vaccinale HPV par les généralistes. Cependant, ces derniers considèrent aussi que leur rôle est fondamental pour lutter contre la désinformation des patients. Pour cela, ils réclament davantage d'informations claires et transparentes sur la vaccination HPV. Enfin, la formation a été efficace pour augmenter leur capacité perçue à informer les patients sur la sécurité et l'utilité de la vaccination HPV.

Conclusions : PAPRICA s'appuie sur un cadre théorique solide, le conflit sociocognitif, pour fournir des informations relatives à la vaccination HPV aux généralistes. Les résultats de la phase pilote appellent à une mise en œuvre à plus grande échelle de cette intervention éducative pour améliorer la couverture vaccinale HPV, en France comme à l'étranger.

#17

Enjeux éthiques de la médecine prédictive en oncologie

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***Keywords** : Cancer. Médecine prédictive. Tests génétiques. Ethique.*

Les progrès accomplis en génétique médicale ces dernières années ont permis la découverte d'un nombre de plus en plus important de gènes responsables de maladies génétiques notamment les cancers. Aujourd'hui, les tests génétiques ne relèvent pas d'une médecine de luxe, mais doivent faire partie intégrantes de la médecine. C'est un domaine ou les implications médicales, sociales, éthiques et l'égales sont considérables. Détecter chez un individu une prédisposition à un cancer du sein, afin de retarder, atténuer, voire prévenir son apparition : tels sont les objectifs de la médecine prédictive au sens strict.

En Algérie, le Plan National Cancer 2015-2019 est un projet national de tests moléculaires consistant à l'amélioration de la prévention, et du dépistage de certains cancers, la redynamisation du traitement et le renforcement des capacités de financement de la prise en charge. Ce projet s'intègre dans le domaine d'une prise en charge des maladies cancéreuses, prenant en compte les caractéristiques intrinsèques des tumeurs mais aussi les caractéristiques individuelles des patients dans le but de s'orienter vers une médecine personnalisée. Ainsi, il est devenu indispensable d'établir le statut mutationnel de chaque patient afin d'orienter le clinicien vers une médecine personnalisée selon la signature moléculaire.

Il s'agit donc de mettre à leur disposition des tests moléculaires afin d'établir le statut mutationnel de chaque patient. Seuls ceux possédant des mutations de ces gènes dits oncogènes, seront éligibles à un traitement par des thérapies ciblées, dite médecine personnalisée. Ceci va permettre d´éviter aux patients non éligibles, les effets secondaires des drogues et également, de réduire le coût d'achat des produits anti cancers exorbitant. En outre, il est nécessaire d'explorer le statut mutationnel des gènes héréditaires constitutionnels tels que les gènes BRCA1 et BRCA2 dans la population algérienne où le taux de consanguinité est très élevé. Ceci aura un impact de prévention étant donné que les personnes ayant des mutations de ces deux gènes pourront décider d'établir des mastectomies ou ovariectomies de prophylaxie afin de prévenir le cancer. Un « Comité National chargé du Suivi de la Lutte contre le Cancer» a été créé par arrêté Ministériel N°64 du 24 mars 2014. Selon son article 2, le comité a pour missions l'élaboration du Plan National de lutte contre le Cancer pour la période 2015-2019.

Faire un test génétique et découvrir une anomalie, c'est mettre au jour une donnée médicale définitive avec laquelle la personne concernée doit vivre désormais. En un sens, c'est conférer a la personne une nouvelle identité diagnostique, même s'il n'y a pas de symptômes présents et que leur survenue n'est pas certaine (toutes les femmes porteuses d'une anomalie du trait BRCA1 ou BRCA2 ne font pas un cancer du sein ou des ovaires) d'où les précautions dans le domaine de la médecine prédictive.

Ce domaine émergeant, malgré des opportunités prometteuses, les enjeux rattachés à ce domaine sont complexes, tant sur le plan scientifique que sur les plans social ou sanitaire. Sur le plan social, les individus devront être protégés contre toute discrimination liée à la médecine prédictive.

#18

Mise en œuvre de la méthode ABC pour l'estimation des coûts directs des maladies cancéreuses : Cas de cancer du sein au Centre hospitalier universitaire Hassan II de Fès-Maroc

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***Keywords** : Economie de la santé, Contrôle de gestion, Méthode ABC, Gouvernance publique, Structure hospitalière, Cancer de sein.*

L'objectif de cette étude est d'examiner la faisabilité de la démarche de calcul des coûts du cancer de sein au niveau du CHU Hassan II de Fès (Maroc). Au plan national, cette pathologie lourde représente 25 % des nouveaux cas annuels par rapport aux autres types de cancers pour les deux sexes. L'étude tentera de faire le point sur la part des dépenses relatives à la prise en charge du cancer de sein et d'estimer le coût réel global, pour enfin déterminer son impact sur le budget alloué à la pharmacie de l'établissement, et ce, pour les années 2014, 2015 et 2016.

A ce titre, nous avons ciblé particulièrement les coûts de produits pharmaceutiques qui connaissent une progression continue, sous l'effet notamment de la demande croissante de médicaments, impactant fortement les dépenses de l'établissement.

Matériels et méthodes : Il s'agit d'une étude descriptive à la fois rétrospective et prospective, qui a consisté à estimer, du point de vue de l'établissement hospitalier, les coûts directs de la consommation des produits pharmaceutiques pour la prise en charge du cancer du sein. Pour mener cette étude, nous avons collecté les données relatives à 2 600 patientes de 2010 jusqu'à 2016. L'échantillon a été choisi pour prendre en considération les patientes qui ont bénéficié du traitement durant les trois années 2014- 2015-2016, soit un total de : 2329 patientes.

#19

La médecine génomique de demain : pour une approche francophone et sociale de l'innovation santé

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Keywords : *Médecine génomique, focus group, santé publique, connaissance en santé, représentations et attitudes*

Aujourd'hui, la médecine génomique n'a plus vocation à étudier exclusivement les maladies rares. Elle étudie des maladies chroniques telles que le cancer, le diabète, ou les maladies cardiaques (Lea & al., 2011) permettant ainsi de dépister, prévenir, et adapter la prise en charge de la maladie, en fonction de ses susceptibilités génétiques. Conscientes de l'importance que représente la médecine génomique pour la santé des populations, plusieurs recherches d'outre-Atlantique ont étudié la perception de la médecine génomique auprès des populations dans le but de construire des programmes d'éducation, d'information et de sensibilisation auprès des populations afin, notamment, d'inciter au dépistage génétique. Or, aucune recherche similaire ne semble avoir été effectuée en France alors que le Plan France médecine génomique 2025 prévoit de « mettre en œuvre les adaptations nécessaires du plan tout au long de son développement en assurant l'information et l'implication du public, des usagers et des associations de malades » (p.7). En effet, la médecine génomique n'est plus une promesse, mais une réalité. Elle peut transformer la manière dont on prévient, diagnostique et soigne les maladies. Toutefois, le soutien et l'adhésion de la population sont essentiels à sa réalisation. Il semble donc nécessaire d'étudier les connaissances, les représentations sociales et l'acceptabilité des français face à la médecine génomique. Pour cela, il semble pertinent de reproduire l'étude Hahn et al. (2010), déjà reproduite par Génome Québec en français (un article est en cours de rédaction pour publication). Nous allons donc réaliser 5 focus group en utilisant la même grille d'entretien que nos collègues d'outre-Atlantique. Ces données permettront de créer des programmes d'informations et de sensibilisation avec un contenu spécifique et adapté à la population française afin de démocratiser la médecine génomique.

#20

Création d'un manuel d'analyse de contenu appliqué aux post diffusés sur les réseaux sociaux en ligne

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Keywords : *Adolescents - Réseaux Sociaux en Ligne - Analyse de contenu - Influence - Média*

Quotidiennement, en 2019, plus de 3 milliards de Snaps ont été envoyés et 4.2 milliards de Likes ont été distribués sur Instagram. Utilisés par plus d'un adolescent sur deux, les réseaux sociaux en ligne (RSL) permettent aux adolescents de communiquer avec leurs proches et de partager des informations associées à leur quotidien. Ces informations, diffusées sous la forme de post audio, photo, vidéo ou autre, ont un potentiel d'influence particulièrement important. De nombreuses études ont mis en avant l'influence des médias traditionnels (magasines, télévision, …) sur le comportement des populations, notamment en termes de santé. Une augmentation de la consommation de produits à risque pour la santé (aliments gras, sucrés, alcool, tabac, …) a ainsi été observée suite à la diffusion de messages promotionnels sur ces médias. Réciproquement, des messages de prévention intégrés au sein de ces mêmes médias ont montré une meilleure acceptabilité des comportements protecteurs pour la santé (dépistage, vaccination, …). Le pouvoir d'influence observé par ces médias traditionnels est considéré comme décuplé via l'utilisation d'internet et des réseaux sociaux. Cependant, peu de données existent sur la forme et le contenu des messages diffusés sur les RSL des adolescents. De plus, les techniques d'analyse de contenu permettant de décrire précisément ce type de message ne semblent pas encore être adaptées à ces formats de communication en constante évolution. Le poster que nous souhaitons présenter souhaite rendre compte de l'élaboration d'un manuel de codage créé spécifiquement pour répondre à ce type de problématique. Elaboré à partir d'une revue de littérature ciblée sur l'analyse de contenu des médias utilisés par les adolescents ; le manuel de codage entend mettre à disposition de la communauté, un outil favorisant l'analyse et la transcription des différentes forme et sources d'influences sur la santé qu'il est possible d'observer sur les réseaux sociaux en ligne.

#21

Déterminants de la santé et du cancer perçus par des enfants âgés de 6 à 11 ans : entre doutes et certitudes

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***Keywords** : Déterminants de la santé, Déterminants du cancer, Enfants, Doutes, Certitudes*

Contexte : Chez l'enfant, le développement psychoaffectif et cognitif est un processus complexe qui l'amène à se questionner sur son entourage et sur lui-même. Ce processus n'est pas linéaire et ne se résume pas à construire des réponses définitives. A cet âge de la vie, l'enfant a tendance à se positionner avec ambivalence, reflet des incertitudes et des doutes qu'il rencontre. Les travaux de recherche relatifs aux connaissances de l'enfant sur le cancer sont peu nombreux. Objectifs : Explorer ce phénomène de doute chez des enfants âgés de 6 à 11 ans en analysant les questions et les connaissances qu'ils formulent sur le cancer. Cela nous permettra d'identifier les interrogations récurrentes et les incertitudes exprimées pour adapter les modalités de prévention sur le cancer. Méthodologie : Elle s'inscrit dans un recueil multiphasé articulé autour de 4 outils : photo expression, « QC » (questions/connaissances), photo narration et groupe focal. Nous nous intéressons plus spécifiquement ici à l'outil QC qui consiste à demander aux enfants d'écrire 3 connaissances et 3 questions à propos du cancer. Résultats : 640 productions ont été recueillies pour la phase QC : 395 connaissances et 619 questions. On observe un déficit de connaissance chez les enfants sur la santé et le cancer. Les enfants rencontrés restent très centrés sur les symptômes et les conséquences et évoquent peu les causes, que ce soit dans les affirmations ou les questionnements. Ce faible niveau de connaissances montre la vigilance nécessaire pour tenir compte de ses questionnements récurrents afin de l'accompagner pour l'aider à stabiliser ses connaissances et lever ainsi certaines de ses incertitudes. Conclusion : Cette étude fournit des éléments de compréhension méthodologique pouvant contribuer au développement d'outils de prévention à destination des publics jeunes pour améliorer leur niveau de connaissance en santé et plus particulièrement sur le cancer, et réduire le phénomène lié au doute.

#22

Une analyse des pratiques et représentations liées au tabac chez les personnes immigré.es et descendantes d'immigré.s en régions Rhône-Alpes et Francilienne au prisme du genre.

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Keywords : *Tabac, immigrés, genre*

INTRODUCTION : Les migrations internationales augmentent sur le globe, et la France ne fait pas exception à cette situation. En 2015, un individu sur cinq soit environ 12 millions d'individus nés à l'étranger et ayant un ou deux parents nés à l'étranger résidaient en France. En dépit du recensement de cette population, leurs habitudes en termes de consommation de tabac, un des premiers facteurs de risque évitable, n'est pas renseignée. OBJECTIF : L'objectif de cet article est d'analyser les pratiques et les représentations liées au tabac chez les personnes immigrées et descendantes d'immigré·s au prisme du genre. MÉTHODE : Cette enquête est une étude qualitative, menée par des entretiens individuels et collectifs, se déroulant à Lyon, Paris et Saint-Etienne. L'échantillon est constitué de 67 personnes immigrées et descendantes d'immigré·s, et de 45 professionnel·les de santé et travailleur·euses sociaux·ales. RÉSULTATS : La variable immigration semble avoir une portée explicative faible dans la pratique tabagique, qui arrive bien après les variables d'âges, de milieux sociaux et enfin, de sexe. Il y a une essentialisation des pratiques tabagiques par l'argument de la fragilité du corps maternel, la ségrégation spatiale genrée des usages de la cigarette et les stigmates renvoyant à une sexualité débridée… CONCLUSION : Ces constats répondent à une logique induite par des rapports de genre à l'œuvre dans la population d'enquête, comme en population générale. Les comportements, les pratiques et les représentations détaillées dans cet article ne concernent pas seulement les femmes immigrées ou descendantes mais concernent avant tout les femmes.

#23

Vers une métropolisation des soins de cancer ? Analyse géographique de l'évolution des parcours de soins depuis le début des années 2000

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Keywords : *Inégalités territoriales, Centralisation, Survie, Qualité de vie, Mobilité*

Les progrès techniques et organisationnels en cancérologie depuis plusieurs décennies ont permis une amélioration significative de la survie des patients. Ces avancées se concrétisent par une centralisation accrue des soins de cancer au sein d'établissements spécialisés, en raison des moyens humains, techniques et financiers nécessaires à la mise en œuvre du traitement optimal. Cette dynamique peut indirectement alimenter un processus de métropolisation des soins de cancer en France métropolitaine. Nous avons mesuré l'évolution de l'accessibilité spatiale de la chirurgie carcinologique entre 2005 et 2018 ainsi que l'évolution de l'activité de chirurgie entre 2005 et 2012 entre les aires urbaines dotées de CHU et/ou CLCC et les autres territoires français. Alors que 150 communes ont perdu leur autorisation entre 2005 et 2018, le temps moyen pour accéder au centre de chirurgie carcinologique le plus proche a augmenté de 5 minutes. 20% de la population est concernée par une hausse du temps d'accès minimum, dont 2,1% par une hausse de plus de 30 minutes. Alors que l'activité de chirurgie des cancers entre 2005 et 2012 a augmenté de 9,1% dans les aires urbaines équipées d'un CHU ou CLCC, celle-ci a très légèrement diminué (-0,3%) dans les autres communes françaises. Ces résultats rapportent donc une forte dynamique de métropolisation de l'activité de chirurgie des cancers. Ce phénomène, favorable à la survie des patients, est d'autant plus intéressant qu'il semble assez peu lié aux retraits d'autorisation, puisque ces derniers ont eu un impact limité sur l'accessibilité de la chirurgie. Cette évolution fait néanmoins peser de nouvelles contraintes pour les patients ainsi que pour les différents acteurs du soin qu'il convient aussi d'évaluer et d'appréhender. A la fois vertueuse et contraignante pour les territoires périphériques, ces résultats illustrent bien la complexité des interactions engendrées par le processus de métropolisation.

#24

La prise en compte des antécédents familiaux permettrait de prévenir 8910 cancers colorectaux par an en France

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***Keywords** : cancer colo-rectal, prévention, antécédents famillliaux*

Le cancer colo-rectal (CCR) atteint 40 500 personnes par an en France, dont 22% avaient des antécédents familiaux de CCR. La recommandation pour les apparentés au premier degré en cas de CCR avant 65 ans, hors cause monogénique, est la coloscopie dès 45 ans, tous les 5 ans jusqu'à 74 ans. L'extension jusqu'au second degré pour tout âge du CCR est recommandée par les sociétés savantes françaises et américaines de gastro-entérologie.

L'objectif est d'évaluer les antécédents familiaux de CCR chez les patients atteints de CCR.

De février 2019 à janvier 2020 l'arbre généalogique avec antécédents familiaux a été recueilli chez les patients atteints de CCR pris en charge en Oncologie digestive.

Après exclusion de 6 formes monogéniques, 101 patients ont été inclus, 60 hommes et 41 femmes, atteints CCR entre 33 et 88 ans (diagnostic moyen (DM) 62,9 ans). Des antécédents familiaux de CCR ont été retrouvés pour 22 patients (22%), 11 hommes et 11 femmes (D 49-80 ans, M 64,1 ans) :

- 8 patients (8%, D 50-75 ans, M 64,9) avaient un apparenté au premier degré atteint avant 65 ans (D 53-65 ans, moy 60).

- 7 autres patients (7%, diag 53-80 ans, moy 63,8) avaient un apparenté au premier degré atteint après 65 ans (diag 68-94 ans, moy 79,4).

- 7 autres patients (7%, diag 49-77 ans, moy 61,1) avaient un apparenté au second degré atteint (diag 45-60 ans, moy 51,0).

Conclusion Pour ces 101 CCR de cause a priori multifactorielle, 22% étaient précédés par un antécédent familial de CCR. Le potentiel pour la prévention du CCR en suivant les recommandations actuelles est de 8%. En étendant ces recommandations jusqu'au au second degré pour tout âge de CCR, le potentiel est de 22% de CCR prévenus par an. En extrapolant à la population générale, pour un potentiel de 8 910 CCR prévenus par an. La mortalité du CCR à 5 ans étant estimée à 50% et 1/3 des CCR survenant avant 65 ans, 4 455 décès par CCR, dont 1 485 prématurés, pourraient être évités par an.

Progression et résistance tumorale, thérapies innovantes

#25

Design, synthesis and in vitro biological evaluation in breast cancer cell lines of a series of fluorescent PARP1 inhibitors

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Keywords : *PARP inhibitors, breast cancer, fluorescent probes synthesis, intracellular distribution, spheroids*

The nuclear enzyme Poly(ADP-ribose) polymerase (PARP), which plays a pivotal role in DNA repair, has recently emerged as a promising target in cancer therapy. Over the last decade, the clinical development of PARP inhibitors (PARPi) has resulted in the approval by both FDA and EMA of several drugs in breast and ovarian cancers, namely olaparib, talazoparib, niraparib and rucaparib. A series of fluorescent probes (FLUO-PARPi) which exhibit structural similarity and behavior akin clinically relevant PARPi was synthesized. Secondary amine functionalities distant from the heteroaromatic active moiety were thought to tolerate bulky substituents and were therefore chosen to introduce a fluorochrome through NHS-ester coupling reactions. Thus, the coupling of four PARPi to a variety of commercial fluorochromes with different physicochemical properties was performed. Coupling reactions occurred in moderate to good yield, after a short reaction time in acetonitrile or dimethylformamide. All FLUO-PARPi were isolated and purified by liquid chromatography and their identities were confirmed by full characterization (13C NMR, 1H NMR, HRMS, fluorescence spectroscopy). A PARP1 activity assay was then used to verify that all FLUO-PARPi retain target binding, before their cellular distribution was assessed in breast cancer cell lines (SUM1315, MDA-MB-231) cultured in both two and three dimensions. Such fluorescent cellular imaging agent allowed a better understanding of the PARP inhibitors molecular pharmacology, and particularly their intracellular distribution and cellular effects over time. This data would be of the utmost importance to predict the response to PARP inhibitor targeted chemotherapy in cancer patients.

#26

SMAD4 in CD8 T lymphocytes prevents intestinal chronic inflammation and tumor development

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***Keywords** : inflammation, immunologie, intestin, lymphocytes, SMAD4, TGF beta*

Inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn's disease are intestinal chronic inflammation resulting from exacerbated activation of the intestinal immune system. IBDs patients have an increased risk of developing gastrointestinal cancers. The increasing incidence of IBDs is considered by the WHO as a major health problem for the next decades. It is widely accepted that dysregulated intestinal epithelial cells (IECs) homeostasis and immune cell activation against the microbiota contribute greatly to the pathogenesis of IBDs. However, the cellular and molecular mechanisms that regulate the crosstalk between IECs and the immune system during IBDs remain elusive. Here, we propose that CD8 T lymphocytes act as a rheostat that tunes the threshold of IEC response to commensal bacteria and thereby, fueling chronic intestinal inflammation. Using a known mouse model for IBDs, in which T lymphocytes lack the molecule SMAD4 (SKO) important for immunosuppression, we show that CD8 T cells are the major contributor of colonic inflammation. SMAD4 deletion in CD8 T cells led to the intrinsic up-regulation of the integrin CD103, important for the interaction between lymphocytes and IECs. The accumulated CD8 cells in the colonic epithelium produced considerable amounts of cytotoxic and pro-inflammatory molecules in a microbiota-dependent manner. Using transcriptomic analysis, we found that, under inflammatory conditions, colonic IECs acquired immune functions associated with antigen processing and presentation by MHC-I and MHC-II. Either depletion of CD8 T cells, or the blockade of CD103, totally abrogated the immune features acquired by IECs under inflammatory conditions and recovered SKO mice from intestinal inflammation and tumor development. Altogether, these data contribute to our understanding of the mechanisms that govern gut inflammation and could open new clinical perspectives in term of IBDs diagnosis and treatment.

#27

OptiPASS® culture medium improves artificial tumors® survival and recovery after cold and anoxic conservation: a short-term alternative to cryoconservation

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Keywords : *Cryoconservation alternative, anoxic storage, short-term storage, cancer spheroids, artificial tumor, Triple Negative Breast Cancer*

The conservation of high added value biological samples represents today a big challenge for the Scientific community. Cryoconservation is formerly considered to be the gold-standard method to store biological samples ensuring their preservation for several decades. However, these classic methods often require cytotoxic cryoprotectants and are time-consuming. Among complex and valuable cellular models, the 3D cell cultures need adapted preservation conditions to ensure their complete recovery. Our research works are focused on the development of the more predictive in vitro models entitled artificial tumors® (cancer spheroids). In this context, these works were focused on the development of a new conservation concept for artificial tumors®, based on cold and anoxic storage conditions. For this, Triple Negative Breast Cancer MDA-MB-231 spheroids were maintained in different culture media (RPMI or OptiPASS®), temperatures (-80; 4 and 20°C) and normoxia or anoxia conditions. The analysis of -80°C stored spheroids showed a significant altered proliferation rate, cell viability/mortality (Live/Dead® test) and metabolic activity (resazurin test – survival = 55,25%), compared to non-stored/control spheroids. In the same way, spheroids kept at 4°C or 20°C in normoxia for 3 days presented decreased cell proliferation, survival and metabolic activity. However, for these conditions, all the measured parameters were higher for OptiPASS® cultured spheroids (survival = 22,6%) compared to RPMI medium (survival = 0%). Interestingly, the same OptiPASS® cultured spheroids placed under anoxia at 4°C for 3 to 7 days recovered very similar growth, viability and metabolic activity than controls (survival =100%). All these results allowed to develop an easier and short-term artificial tumors® preservation concept alternative to cryostorage.

#28

Identification of a metastatic relapse prognostic signature in triple negative breast cancer based on transcriptomic expression

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***Keywords** : Cancer du sein triple négatif, Rechute métastatique, Signature pronostique*

Triple negative breast cancer (TNBC) is a poor prognosis clinical subtype known for being aggressive with a high risk of distant recurrence. However, almost half of these cancers do not progress to metastases and a stratification of the patients would improve the health care pathway. Due to its complex heterogeneity, high metastatic ability and therapeutic escape, biomarkers predicting the recurrence of distant metastasis remain crucial for a better clinical outcome in TNBC. Gene expression metastatic prognostic signatures have been systematically evaluated in several breast cancer subtypes while no such analyses have been successfully applied to TNBC. Our study was designed to bring out such a signature in this pejorative breast cancer.

Inclusion criteria for this study were as follow:

a. Confirmation of all triple negative cases by a single pathologist

b. Availability of a five-years follow-up post diagnosis

c. Availability of tumor samples

d. Successful transcriptomic sequencing data

e. Metastasis-free state at diagnosis

Data of Whole Transcriptome Sequencing for 64 patients were stratified into two groups: metastatic TNBC within 5 years (mTNBC) and non-metastatic TNBC (non-mTNBC). We constructed a logistic regression model to explain the metastatic prognosis from the gene expressions. This approach yielded an eight-gene metastasis-associated prognostic signature. All the metastasis relapses of the combined cohort were explained with our eight-gene signature (sensitivity=100%; specificity=100%). The association between the signature risk score and relapse-free survival was measured using Kaplan-Meier survival curves. A validation assay of the eight-gene metastasis-associated prognostic signature is ongoing on an external set of samples.

Overall, we constructed the first TNBC metastasis-associated signature providing a set of valuable prognostic biomarkers. Although further validation is required, preliminary results exhibit great prognostic discrimination for TNBC evolving or not to metastatic disease.

#29

Evaluation of the role played by chemokines in shaping the immune microenvironment in neuroblastoma associated with opsoclonus-myoclonus

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***Keywords** : neuroblastome; réponse immune; chimiokines*

In neuroblastoma (NB), MYCN amplification is associated with a T cell-poor immune microenvironment. Some MYCN non-amplified NB are associated with Opsoclonus Myoclonus Syndrome (OMS), a neurological disorder linked with autoimmunity. We designed a study to describe and understand the role of chemokines (CHK) in shaping the immune microenvironment in NB associated with OMS.

We analyzed CHK secretion by 4 NB cell lines and fresh tumor samples obtained from 2 patients with or without OMS. CHK arrays (38 CHK), and transwell migration experiments were performed to analyze immune cell migration driven by NB supernatants, with quantification of antigen presenting cells (myeloid and plasmacytoid dendritic cells, monocytes and B lymphocytes), T lymphocytes (CD4+, CD8+, CD56+ T cells), and innate effector cells (NK cells , □□ T lymphocytes and iNKT).

NB cell lines without MYCN amplification secrete higher level of CCL2 compared to MYCN-amplified NB cell lines and induced active migration of myeloid dendritic cells (mDCs), that was dependent on CCR2/CCL2 axis.

The analysis of immune cell infiltration in 2 fresh tumor samples showed an enrichment of mDCs in tumors compared to blood samples, associated with CCL2 secretion. Interestingly, OMS patient's tumor had higher numbers of effector cells (CD3+CD8+ and γδT lymphocytes), compared to patient's blood and the non-OMS patient's tumor. The CHK responsible for this preferential recruitment are under investigation, and migration experiments are being performed to decipher the mechanisms involved.

We provide here a characterization of CHK expression and immune cell infiltration in NB, highlighting the major role of CCR2/CCL2 in the preferential recruitment of mDCs by MYCN non-amplified NB tumors. We also demonstrate that tumor from patient with OMS is infiltrated by higher numbers of effector cells compared to non-OMS patient, which might be directly related to the autoimmune activation leading to OMS symptoms. #3

#30

Impact de l'homéostasie du fer sur la méthylation de l'ADN dans des lignées leucémiques humaines

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***Keywords** : Epigénétique ; Méthylation ; LAM ; Fer ; 5-méthylcytosine ; 5-hydroxyméthylcytosine*

Les leucémies aigües myéloblastiques (LAM) sont des hémopathies malignes de la cellule souche hématopoïétique avec un taux de survie à 5 ans de 30%. L'identification des anomalies génétiques dans les LAM montre que des mutations apparaissent souvent dans les gènes impliqués dans la régulation de la méthylation de l'ADN notamment DNMT3A, TET2 et IDH, et que ces mutations influencent le pronostic des patients. Par ailleurs, le fer est indispensable à la prolifération cellulaire et est présent dans la structure des enzymes TET suggérant que les altérations de l'homéostasie du fer puissent impacter la progression tumorale à travers le contrôle épigénétique de l'expression de certains gènes.

Pour évaluer l'impact du fer sur la méthylation de l'ADN, nous avons mesuré les taux de 5-méthylcytosine (5mC) et de 5-hydroxyméthylcytosine (5hmC) dans 5 lignées leucémiques représentatives de différents sous types cytologiques et moléculaires de LAM (KG1, HL60, K562, OCI-AML3 et HEL), à l'état basal, puis, après privation en fer par chélation avec la déféroxamine. Nous avons également mesuré ces taux après re-supplémentation en fer par ajout de transferrine saturée en fer. Les mesures de 5mC et 5hmC ont été réalisées par spectrométrie de masse en tandem avec utilisation d'un standard interne isotopique.

A l'état basal nous avons observés des différences significatives pour les taux de 5mC (de 1.6% à 4.6%) et de 5hmC (de 0.009% à 0.023%) entre les lignées. La privation en fer par des doses de déféroxamine capable de bloquer le cycle cellulaire en phase G2/M dans chacune des lignées, induit une augmentation des taux de 5mC sans variation des taux de 5hmC. Par contre, nous n'avons pas observé d'impact de la re-supplémentation en fer sur les taux de méthylation.

Ces résultats montrent un lien entre les niveaux de méthylation de l'ADN et le statut génétique des LAM ainsi qu'un rôle de l'homéostasie du fer sur la régulation de ces niveaux de méthylation. Ces mécanismes seront notamment intéressants à explorer pour mieux cerner le passage des états pré-leucémiques aux LAM, ainsi que la réponse à certaines approches thérapeutiques telles que les agents hypométhylants.

#31

Rôle of Prokineticin 1 and its receptors in the development and progression of ovarian cancer.

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***Keywords** : HGSC, high grade serous carcinoma; PROK1, prokineticin 1; PROKR1, prokineticin receptor 1; PROKR2, prokineticin receptor 2*

High-grade serous ovarian cancer (HGSOC) is the most frequent and deadliest cancer among all gynecological cancers. It is diagnosed at advanced stages and is associated with significant drug-resistance. Hence, there is an urgent need for novel approaches to improve clinical outcomes. We have recently demonstrated that prokineticin1 (PROK1), the canonical member of a new family of inflammatory and angiogenic factors is highly expressed in human ovaries and is involved in the development and progression of choriocarcinoma. PROK1 acts via two GPCR receptors, PROKR1 and PROKR2. In the case of HGSOC, the role of PROK1 and it receptors remains unclear and controversial. Here, we conducted i) a clinical study to compare in non-tumor and in HGSOC patients, circulating levels of PROK1 as well as the ovarian expression of its receptors ii) an in vitro study to determine the levels of PROKR1 and PROKR2 in two cell lines, the SKOV3 and OVCAR8, and test the effect of PROK1 on the phosphorylation of AKT, Src and MAPkinases, three proteins involved in tumorigenesis. The effect of PROK1 on the proliferation, migration and invasion of these tumors cell lines was also investigated. Our results demonstrate that i) circulating PROK1 were increased in HGSOC patients, ii) the in situ expression of both the ligand and receptors was increased in infiltrating immune cells including, macrophages, neutrophils and lymphocytes; iii) tumor cell lines secreted low levels of PROK1, express similar levels of PROKR1 and PROKR2 proteins and exhibited increased AKT, Src and MAPkinases phosphorylations in response to PROK1. No significant effect of PROK1 was observed on the proliferation, migration and invasion of tumor cells. Altogether, these results bring new insights into the role of PROK1 and its receptors in ovarian tumorigenesis and suggest that the prokineticin system might play a central role in the cross talk between OC cells and their microenvironment.

#32

Recherche de nouvelles cibles moléculaires pour le traitement de la douleur osseuse du cancer de prostate

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***Keywords** : cancer de la prostate, métastases osseuses, douleur, riluzole*

Les signes cliniques du cancer de la prostate (CaP) ne sont perceptibles que tardivement dans la chronologie de la maladie et témoignent généralement d'un cancer localement avancé ou métastatique (ganglions et os). A ce stade, la qualité de vie des patients est fortement réduite notamment à cause de douleurs osseuses très invalidantes et mal contrôlées par les antalgiques de références (1). Le riluzole, une molécule antiglutamatergique, possède à la fois un potentiel antalgique dans divers modèles de douleur et a également montré un effet antiprolifératif sur plusieurs lignées de cellules cancéreuses (2). Le but de notre étude a été d'évaluer l'effet du riluzole sur la douleur osseuse du cancer de prostate (CaP) in vivo et sur la prolifération de cellules humaines du CaP in vitro et in vivo. Nous avons utilisé un modèle de douleur osseuse induite par l'injection unilatérale de cellules humaines PC3 dans le tibia de souris SCID mâles (3) chez lequel le riluzole (60µg/ml dans l'eau de boisson) a démontré un effet antalgique. De plus, les données obtenues in vitro suggérant un effet antiprolifératif du riluzole sur les cellules PC3 a été confirmé in vivo grâce à un suivi longitudinal de la prolifération de ces cellules (transfectées avec le gène codant la luciférase). L'ensemble de ces données suggère l'intérêt de l'utilisation de molécules antiglutamatergiques pour la prise en charge de la douleur du CaP et ouvre des perspectives d'identification de nouvelles cibles moléculaires dans ce contexte.

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#33

Functional Exploration & Inhibition of BET Proteins in Refractory Agressive B-Cell Lymphoma

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***Keywords** : Epigenetics, Cancer, EpiDrugs, Chromatin, BET proteins*

Diffuse large cell B-Cell lymphoma (DLBCL) represents the most common form of non-Hodgkin's B lymphomas. Current DLBCL standard of care consists in an immunochemotherapy regimen. Even if this treatment benefits from a high response, 30% of patients present a refractory state. Among refractory cases, double and triple hit (DH and TH) DLBCL represent a highly aggressive subtype for which no alternative treatment is available. DH/TH DLBCL is characterized by chromosomal rearrangements involving the oncogenes c-MYC, BLC2 and/or BCL6. It has been recently demonstrated that these proteins can be targeted by a new generation of epidrugs, BET inhibitors (BETi). These small compounds target BET proteins (BRD2, BRD3, BRD4 and BRDT) that are chromatin readers that play key roles in controlling oncogenes expression, but also proteins involved in cell cycle control, apoptosis and anti-tumor immune response. While BET are general transcription regulators, pharmacological inhibition of BET shows therapeutic activity in solid and hematological cancers. Their effects have been attributed to specific subsets of target genes (including MYC and BCL2 in B-cell lymphoma) whose expression would be "hypersensitive" to BETi in a cell-specific context. But clinical potential of BETi is impeded by severe side effects related to lack of selectivity. Here, we propose to explore mechanisms and evaluate clinical potential of BET inhibition in DH/TH DLBCL. This is being done by testing BETi of different chemical scaffolds and selectivity on model cell lines. Preliminary results have shown different patterns of sensitivity among DH/TH lymphoma cell lines for the 4 BETi tested. We are currently investigating BETi treatment impact on gene expression profiles and BRD-dependent interactome. This set of data should provide a deeper understanding of BET molecular targets and allow to rationalize their clinical use as single agents or in combination therapies and improve DH/TH DLBCL clinical outcome.

#34

MRP7 and P--glycoprotein chemoresistance proteins expression in MDA--MB--231 and SUM1315 spheroids following Olaparib treatment.

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Keywords : *Triple--Negative Breast Cancer, TNBC, Olaparib, Anti--PARP, Multi Drug Resistance protein,*

MRP7, P--gp, 3D cell culture

Among the multiple breast cancer subtypes, the Triple-Negative tumours (TNBC) are particularly aggressive and difficult to treat, leading to very poor prognosis. In order to optimize patient outcome, Poly-ADP-ribose Polymerase inhibitors (anti-˘PARP) targeted therapies were developed, such as the anti-˘PARP1 Olaparib. Although promising results in preclinical and clinical studies, some resistances to Olaparib were highlighted at the molecular or cellular level. Among them, the overexpression of Multi Drug Resistance (MDR) efflux pumps targeting anti-PARP and notably Olaparib, is a major obstacle for the treatments efficacy. Thereby, these works aimed to analyze the co-˘expression of MRP7 and P-gp, in two TNBC cell lines, MDA-MB-231 and SUM1315, cultured in 2D and 3D with Olaparib treatment. In MDA-MB-231 2D cell culture experiments, 5 and 50 µM Olaparib treatment induced a relay-expression of MRP7 and P-gp proteins, at short-term (4h). In both spheroid models, after 5 µM Olaparib treatment at long-term (8 to 10 days), P-gp expression increased whereas no MRP7 increase was detected. These results showed clearly the implication of these two major MDR proteins in TNBC cell lines resistance against Olaparib, suggesting the persistence of selected-resistant cells in spheroids after treatment.

#35

Adjuvant therapeutic potential of hypothermia: an in vitro study on glioblastoma cell growth

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Keywords : *Brain tumor, glioblastoma, hypothermia, cell proliferation, cell migration, cell cycle*

Glioblastoma is a particularly aggressive and infiltrative brain tumor with an annual incidence of three per 100,000 adults worldwide. Despite multimodal treatments associating surgical resection with combined radiotherapy and temozolomide-based chemotherapy, prognosis remains poor. Median survival is only 15 months because of tumor recurring in the resection margins in over 90% of patients, due to the activation of residual glioblastoma cells. To handle this issue, we propose therapeutic hypothermia – a promising approach in various medical applications – as an adjuvant treatment. In fact, the aim is to place tumor cells at the resection margin in a dormant state by using moderate hypothermia. In this study, we performed in vitro experiments on four glioblastoma cell lines with different p53 status and various growth rates. We investigated the influence of moderate hypothermia on two key processes involved in tumor growth: glioblastoma cell proliferation and migration, and performed cell cycle analysis using flow cytometry. Results were similar for all glioblastoma cell lines, demonstrating a consistent effect of hypothermia and a high sensitivity of cells to this treatment. We showed that moderate hypothermia induced a strong reduction of glioblastoma cell migration, and a long-lasting and near-total inhibition of proliferation. We also demonstrated an accumulation of glioblastoma cells in the G2/M phase of the cell cycle, which could explain proliferation arrest. If in vivo preclinical studies demonstrate the same inhibitory effects, moderate hypothermia applied at the resection margin could delay tumor recurrence after surgical resection, combined with current treatments. Thus, these results support a therapeutic role for hypothermia as an adjuvant therapy for patients with glioblastoma.

#36

Le récepteur FXRα comme nouvel acteur de la biologie des tumeurs germinales du testicule

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***Keywords** : tumeurs germinales du testicule, biologie tumorale, récepteur nucléaire FXRalpha,*

Les tumeurs germinales du testicule (TGTs) représentent près d'un tiers des cancers de l'homme jeune avec une incidence en constante augmentation ces 30 dernières années. Ces tumeurs dérivent majoritairement des cellules germinales et sont classées en tumeurs germinales séminomateuses (TGS) et non-séminomateuses (TGNS) qui se distinguent selon leur prise en charge thérapeutique et leur pronostic. L'histoire naturelle de la maladie reste incertaine bien qu'elle plaide pour des composantes fœtales et hormonales du fait que : 1- les lésions précurseurs appelées néoplasies germinales in situ (NGIS, Germ Cell Neoplasia In Situ) partagent des caractères communs avec les gonocytes fœtaux, puis que 2- ces lésions pré-invasives n'évoluent qu'à partir de la puberté pour former un carcinome. Nos travaux sur la fonction du récepteur nucléaire des acides biliaires FXRα montrent que son abondance est réduite dans les tumeurs germinales du testicule (TGT) chez l'homme en comparaison avec le testicule sain alors que les gènes de la pluripotence sont augmentés. De plus, la perte d'activité et/ou de son expression augmente de façon anormale le nombre de cellules germinales souches (CGS) indifférenciées chez la souris pour générer des altérations semblables aux lésions précurseurs des TGT. L'analyse de l'expression de FXRα dans des lignées tumorales testiculaires et hépatiques nous a permis d'identifier un nouveau variant de FXRα, FXRαΔE5 dont la fonction n'est pas encore décrite. Nos études montrent que ce variant est exprimé dans différentes lignées cellulaires tumorales ainsi que dans plusieurs tissus murins. Ces données interrogent sur la participation de ce récepteur et de son nouveau variant à l'étiologie de la maladie. L'objectif de nos travaux vise à définir comment ils interviennent pour contrôler la physiologie des CGS en lien avec le développement et la progression des TGT. Ce travail est soutenu par une aide de la FRM (code dossier FRM : FDM20170839110).

#37

Altered splicing of ATG16-L1 contributes to acquired resistance of non-small cell lung cancer to EGFR-TKI through autophagy inhibition

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Keywords : *Lung Cancer, EGFR-TKI, Resistance, Autophagy, Alternative splicing*

Management of Non-small cell lung cancer (NSCLC) patients with secondary resistance to EGFR-TKI is still a great challenge that requires alternative strategies to maximize patients benefit. Alternative splicing of transcripts is an essential step in regulating gene expression. While differential splicing patterns of genes have been associated with NSCLC progression, their role in drug resistance remains scarce. The aim of this study was to investigate whether deregulation of alternative splicing may play a role in acquired resistance to EGFR-TKI. NSCLC clones with acquired resistance to EGFR-TKI were generated by chronic exposure of sensitive PC9 lung adenocarcinoma cells to gefitinib. In resistant clones, we observed aberrant accumulation of the splicing factor SRSF2, and showed that SRSF1 or SRSF2 knock-down induced apoptosis in response to gefitinib. Using high throughput RNA sequencing, we identified a splicing switch of the autophagic gene ATG16-L1, in favor of a splicing variant containing exon 8 (ATG16-L1 Ex8), which was redirected back when resistant cells were resensitized to gefitinib through SRSF1/2 depletion. Importantly, accumulation of the ATG16-L1 Ex8 splice variant was observed in tumors from 3 of 11 NSCLC patients with acquired resistance to EGFR-TKI. Autophagy activation was blocked in resistant cells treated with gefitinib. Neutralization of ATG16-L1 Ex8 restored autophagy induction, promoted apoptosis, and limited the growth of tumor xenografts in response to gefitinib. Inhibition of autophagy by Bafilomycin A1 rescued gefitinib resistance by preventing apoptosis in ATG16-L1 Ex8-depleted cells. These results highlight autophagy inhibition as a mechanism of acquired resistance to EGFR-TKI, and offer a rationale for the use of RNA-based therapeutic strategies to correct ATG16-L1 splicing in those NSCLC patients who accumulate the ATG16-L1 Ex8 isoform at relapse.

#38

The apoptosis inhibitor Bcl-xL controls breast cancer cell migration through mitochondria-dependent Reactive Oxygen Species production

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Keywords : *Bcl-x, breast cancer, migration, calcium, apoptosis, VDAC, mitochondria*

The Bcl-xL apoptosis inhibitor plays a major role in vertebrate development. In addition to its effect on apoptosis, Bcl-xL is also involved in cell migration and mitochondrial metabolism. These effects may favor the onset and dissemination of metastasis. However, the underlying molecular mechanisms remain to be fully understood. We focused on the control of cell migration by Bcl-xL in the context of breast cancer cells. We show that Bcl-xL silencing led to migration defects in Hs578T and BT20 cells. These defects were rescued by re-expressing mitochondria-addressed, but not endoplasmic reticulum-addressed, Bcl-xL. The use of BH3 mimetics, such as ABT-737 and WEHI-539 confirmed that the effect of Bcl-xL on migration did not depend on interactions with BH3 containing death accelerators such as Bax or BH3 only proteins. In contrast, the use of a BH4 peptide that disrupts the Bcl-xL/VDAC1 complex supports that Bcl-xL by acting on VDAC1 permeability contributes to cell migration through the promotion of reactive oxygen species production by the electron transport chain. Collectively our data highlight the key role of Bcl-xL at the interface between cell metabolism, cell death and cell migration, thus exposing the VDAC1/Bcl-xL interaction as a promising target for anti-tumour therapy in the context of metastatic breast cancer

#39

Analysis of genomic and non-genomic signalling of oestrogen receptor in breast cancers PDX treated by the PI3KCA inhibitor BYL719 combined to fulvestrant

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Keywords : *Breast cancer, oestrogen receptor, PI3KCA inhibitor*

Endocrine therapies targeting oestrogen signalling have significantly improved the survival of breast cancer (BC) patients, although 30% of ERα-positive breast cancers do not respond to those therapies. Besides to genomic signalling, estrogen triggers also non-genomic pathway by forming a complex containing methylERα/Src/PI3K, a hallmark of aggressiveness as well as resistance to tamoxifen treatment. We aimed to investigate whether targeting this complex in vivo could improve tumor response. We first studied the expression of ERα/Src and ERα/PI3K by proximity ligation assay (PLA) in a new cohort of 440 BC. Next, we treated different models of patient's derived xenografts with fulvestrant or PI3KCA inhibitor BYL719 alone or in combination. We then analyzed their efficacy to inhibit tumor growth as well as their effects on estrogen genomic and non genomic signaling. First, we confirmed that ERα/Src and ERα/PI3K expression is associated with a decrease in patient's survival, ERα/PI3K being the most significant. In ERα-positive tumors, we found that fulvestrant was fully efficient to inhibit tumor growth when both pathways were inhibited, however, when only one pathway was abolished, the inhibition was partial. However, BYL719 was not efficient to target non genomic signaling in vivo, thus it could be useful to find molecules able to disrupt this interaction. Also, we showed that targeting estrogen non-genomic complex in ERα-negative models has an impact on tumor growth. Taking together, our results demonstrated that ERα/PI3K could constitute a new prognostic marker as well as a new target in BC to target specifically estrogen non genomic pathway in both ERα-positive and ERα-negative BC.

#40

Two antagonistic microtubule targeting drugs act synergistically to kill cancer cells

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***Keywords** : Cancer therapy, microtubules, drug synergy*

Paclitaxel is a microtubule stabilizing agent and a successful drug for cancer chemotherapy inducing, however, adverse effects. To reduce the effective dose of paclitaxel, we searched for drugs which could potentiate its therapeutic effect. We have screened a chemical library and selected Carba1, a carbazolone, which exerts synergistic cytotoxic effects on tumor cells grown in vitro, when co-administrated with a low dose of paclitaxel. Carba1 targets the colchicine binding-site of tubulin and is a microtubule-destabilizing agent. The Carba1-induced modulation of microtubule dynamics increases the accumulation of fluorescent paclitaxel inside microtubules, providing a mechanistic explanation of the observed synergy between Carba1 and paclitaxel. The synergistic effect of Carba1 with paclitaxel on tumor cell viability was also observed in vivo in xenografted mice. Thus, a new mechanism favoring paclitaxel accumulation in microtubules can be transposed to in vivo mouse cancer treatments, paving the way for new therapeutic strategies combining low doses of microtubule targeting agents with opposite mechanisms of action.

#41

Integrin avb8-mediated TGF-beta activation by Foxp3+ Treg cells leads to tumor progression

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Keywords : *Tregs, Integrin avb8, cancer, CD8, anti-tumor immune response*

A large part of solid tumors express high amounts of Transforming Growth Factor beta (TGF-b), known as a potent suppressor of the immune system. However, TGF-b is secreted under its inactive form and how TGF-b produced by the tumor is activated remains totally unknown. Here, we demonstrated that tumor-produced TGF-b is activated by the avb8 integrin (Itgb8) expressed at the surface of Foxp3 regulatory T cells (Tregs). The selective deletion of Itgb8 in Tregs impairs TGF-b signaling in tumor infiltrating T cells. Subsequently, the cytotoxic program of effector T cells is activated, leading to efficient tumor cell-apoptosis and control of the tumor burden. The relevance of our data found in mice was confirmed in the human pathology. Thus, our study reveals that Tregs and tumor cells work together to allow the suppressive effect of the TGF-b on effector T cells, which consequently impacts tumor progression.

#42

Treatment and prevention of afatinib resistance in preclinical models of NRG1-driven tumors

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Keywords : *NRG1- Fusions-ERBB2-ERBB3-Afatinib*

Background: NRG1 fusions were recently described as an oncogenic event in solid tumors. NRG1 protein contains an EGF-like motif that binds and activates receptor-tyrosine kinases in the ErbB family. NRG1 fusion leads to extracellular overexpression of the EGF-like domain of NRG1. ERBB3 binds to the EGF-like domain and forms heterodimers with ERBB2 which subsequently signals through the PI3K/AKT and MAPK pathways, promoting a pro-tumorigenic signaling. Afatinib, an ERBB2 tyrosine kinase inhibitor, is effective in some NRG1-positive patients as supported by clinical cases, but shows also transient response and progression in the majority of patients.

Hypothesis: Our hypothesis is that afatinib resistance can be overcome and prevent with a combination of afatinib with anti-ERBB2/ERBB3 or MEK/PI3K inhibitors in NRG1-driven preclinical models.

Material and Methods: We propose to create NRG1 fusion-driven models with acquired resistance to afatinib. NRG1 fusion-positive breast cancer cell line MDA-MB-175-VII and NRG1-overexpressing lung cancer cell line HCC-95 are exposed to increasing concentrations of afatinib until a discrete colony of resistant cells will be visible and capable of proliferating. The colony will be then isolated and expanded for characterization. We will evaluate the effects of the combination of afatinib with anti-ERBB2/ERBB3 or MEK/PI3K inhibitors in our afatinib-resistant NRG1 fusion-driven models. Tumor xenograft studies will be performed by grafting afatinib-resistant clones subcutaneously in anesthetized athymic nu/nu mice. Mice will be randomized and treated with afatinib and combination of anti-ERBB2/ERBB3 and MEK/PI3K inhibitors.

Significance: Data generated will help to understand the molecular mechanisms underlying the heterogeneity of clinical benefit with afatinib in NRG1-positive patients. We aim to identify a rational combination of afatinib and a candidate drug that will be able to treat and prevent resistance to afatinib in clinic.

#43

Loss of Tenascin-X expression during tumor progression: a new pan-cancer marker.

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Keywords : *Tenascin-X, Cancers, Meta-analysis, Tumor progression, Prognosis marker*

Tenascins (TNs) are a family of 4 glycoproteins (TNC, TNR, TNW and TNX) of the extracellular matrix, sharing a common modular structure, but having specific expression patterns. While TNC and TNW involvement in different cancers has been extensively studied, the status of TNR and TNX remains to be clarified. For the TNX notably, the few available studies are focused on cancers with low incidence and mortality worldwide, and the results remain controversial. Herein, we thus determined the status of TNX in different cancers comprising the 6 cancers with the highest incidence and mortality worldwide, and the 7 cancers for which TNX status had already been described in the literature. To do so, we studied TNX expression in human tumors, (1) at the mRNA level, by the analysis of microarray datasets obtained from GEO and TCGA databases; and (2) at the protein level by immunohistochemistry on human Tissue MicroArrays. Finally, in order to study TNX potential to be a prognosis marker, we studied the survival rate of patients depending on TNX level in their tumors. At the mRNA level, we revealed a significant decrease of TNXB gene expression in the 6 most incident cancers and in most of the previously studied cancers, except brain tumors. Most of these results were confirmed at the protein level. Additionally, TNX regulation was inversely correlated with tumor progression, and through deeper GEO dataset analysis, we highlighted that high TNXB mRNA expression in breast and lung carcinomas was correlated with a good survival prognosis. This work, in press in Matrix Biology Plus, shows that TNX is a new pan cancer marker. In order to determine the therapeutic potential of a reintroduction of TNX in tumors, its precise role during carcinogenesis (and more particularly pancreatic carcinogenesis) is under study, using mouse and in vitro 3D models. Ultimately, this protein could be considered as a new therapeutic tool.

#44

SMYD3 oncogenic lysine methylation signaling in small cell lung carcinoma

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***Keywords** : Lysine methylation, protein lysine methyltransferases, KMT, cancer*

Development and progression of many types of cancer are under the epigenetic and cell signaling control of gene expression through post-translational modifications (PTMs) of proteins, dysregulation of which often occurs in human pathologies. Lysine methylation signaling is a dynamic and reversible PTM, regulating biological functions through specific activities of methyltransferases and demethylases enzymes. SMYD3 is a methyltransferase overexpressed in at least 15 types of cancer. Its first clear oncogenic activity was found in RAS-driven lung and pancreatic adenocarcinomas. Loss of SMYD3 in KRAS-induced mouse model reduces tumor progression thereby implying its therapeutic potential. However, SMYD3 also participates in the progression of RAS-independent cancers. Therefore, identifying further signaling of SMYD3 can offer promising targets for lung cancer subtypes.

By crossing a SMYD3 conditional knock-out mouse model with a small cell lung carcinoma (SCLC) mouse model, a lung cancer subtype where RAS oncogenic signaling is not relevant, we demonstrated the implication of SMYD3 in SCLC progression. By performing methylation assay on a protoarray with more than 9500 candidates, we discovered a new substrate of SMYD3, and validated and characterized this new methylation event in vitro and in cell. In addition, we identified a crosstalk mechanism between methylation and phosphorylation linked to the activity of this new substrate, and its role in DNA damage repair. Therefore, we hypothesize that SMYD3 can participate in DNA damage repair in cancer cells through this newly identified signaling, and our preliminary results tend to demonstrate that SCLC cells overexpressing SMYD3 and its substrate are more resistant to DNA damage than other SCLC cells. A better understanding of this new signaling will be extremely helpful for further translational studies in cancers, especially those with high resistance to actual therapy or without valid therapeutic option.

#45

Biophysical properties of intermediate states of EMT outperform both epithelial and mesenchymal states

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Keywords : *Epithelial to mesenchymal transition, micropatterning, Triple Negative Breast Carcinoma, Chemoresistance*

The epithelial to mesenchymal transition (EMT) allows mammary breast cancer cells to dissociate from the primary tumour and initiate the formation of metastases. Recent works have revealed that cells in intermediate states of EMT have acquired augmented capacity to invade surrounding tissues and transdifferentiate into several cell types and are therefore specifically responsible for tumour dissemination. These states have been characterized by surface markers but the structural features and the cellular mechanisms that underlie the acquisition of their scattering and invasive properties are still unknown. Here we induced the expression of ZEB1, a transcription factor responsible for EMT initiation, to generate intermediate stages of EMT in human mamary epithelial cells and stimulation with TGFß to push further the transition to the mesenchymal state. We measured and compared the architecture, internal organisation and mechanical properties of each state. We found that the lack of inter-cellular cohesiveness in intermediate and later stages of EMT can be detected early by microtubule destabilisation and the repositioning of the centrosome from the cell junction to the cell center. Consistent with their high migration velocities, we found that cells in intermediate state of EMT were in a low tensional state compared to epithelial and mesenchymal cells. The high contractility of mesenchymal cells powered a retrograde flow pushing the nucleus away from cell adhesion to the extra-cellular matrix (ECM). These measures revealed how defined structural and mechanical rearrangement in intermediate stages of EMT confered them specific dissociation and migration properties that distinguish them from epithelial and mesenchymal states.

#46

Identification of PKA-dependent signaling pathways in the migration and metastatic behavior of breast cancer cells.

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Keywords : *Migration, Adhesion, PKA, mechanobiology, breast cancer, network biology*

Metastasis is responsible for the majority of breast cancer deaths. The aggressive behavior of cancer cells depends on the epithelial-to-mesenchymal transition (EMT). EMT is characterized by the loss of the mechanical equilibrium thus helping cancer cells to migrate and to invade the surrounding tissue. This cell mechanic is coordinated by the cross-talk between cell-cell and cell-matrix contacts organizing the actin cytoskeleton important for cell tensional homeostasis. In breast cancer, the protein kinase A (PKA) has a controversial role promoting both EMT and MET. The role of PKA in regulating cell contractility remains unclear. In order to understand the role of PKA in the signaling pathways associated with cell migration, we have developed a network biology approach. Based on a computational approach using data from the literature, we have defined a protein-protein interaction network between actin and adhesive machineries, PKA isoforms, and regulators of cell contractility. An additional computational prediction of specific PKA phosphorylation sites allowed to identify nine potential targets in the control of PKA dependent cell migration. The PKA phosphorylation of three of these nine targets was confirmed in the triple-negative breast cancer model cells (MDA-MB-231 cells). We are focusing on one of these novel PKA substrates which is a metastatic marker involved in chemotherapy resistance in triple-negative breast cancer. We are investigating its role in the acto-adhesive signaling pathways. In parallel, we have developed a computational approach based on drug repositioning to identify new drugs fighting chemotherapy resistance. We have identified 27 drugs already FDA approved as potential blockers of cell progression and migration in triple-negative breast cancer cells. We are combining isolated and collective migration tests (in 2D) and morphogenesis tests in mammospheres (in 3D) to test their efficiency in cells expressing PKA dependent chemoresistance markers.


#47

Etude des rôles du récepteur membranaire des acides biliaires TGR5 dans la chimio-sensibilité des cellules germinales saines ou tumorales.

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***Keywords** : Acides biliaires, Fertilité, Cancer, Chimiothérapie, Signalisation*

Actuellement, les traitements de chimiothérapies entraînent des effets indésirables dont l'un des majeurs sur le long terme concerne l'altération de la fertilité. Les mécanismes mis en jeux ne sont pas complètement définis. De manière intéressante, des liens ont été mis en évidence entre les chimiothérapies et des altérations hépatiques, elles même associées à des altérations de la fertilité. Mon projet vise donc à mieux comprendre les liens entre chimiothérapie, hépato-toxicité et repro-toxicité. Chez la souris les liens entre troubles hépatiques et fertilité résultent en partie de l'augmentation des taux d'acides biliaires qui survient lors d'une pathologie hépatique. En effet, il a été montré que les modèles murins reproduisant une pathologie hépatique (cholestase) induite par un régime riche en acides biliaires présentaient des troubles de la fertilité associés à une diminution du nombre de spermatozoïdes. Ces effets sont dépendants du récepteur membranaire des acides biliaires TGR5. Ainsi, notre étude a pour objectif de définir l'implication potentielle du récepteur TGR5 dans les liens entre chimiothérapie, hépato-toxicité et repro-toxicité. Pour cela, des souris sauvages ou invalidées pour le gène codant Tgr5 ont été utilisées et la spermatogenèse a été étudiée par l'analyse de différents marqueurs germinaux et du nombre de spermatozoïdes. Ces travaux soulignent le rôle de TGR5 dans la cinétique de la spermatogenèse en réponse à une chimiothérapie. De plus, une analyse RNA-seq sur un modèle cellulaire de spermatogonies a mis en évidence les voies de signalisation impliquées. Nos travaux montrent que la modulation de TGR5 joue un rôle clé dans la chimio-sensibilité des cellules germinales. TGR5 pourrait donc être une cible pour préserver les cellules germinales saines lors d'une chimiothérapie, et il pourrait également être un marqueur de diagnostic/pronostic voire une cible thérapeutique des tumeurs chimio-résistantes.

#48

Dual disruption of aldehyde dehydrogenases 1 and 3 promotes functional changes in the glutathione redox system and enhances chemosensitivity in non-small cell lung cancer

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Keywords *: Non-small cell lung cancer; cisplatin; aldehyde dehydrogenase; gluthation metabolism; oxidative stress*

Aldehyde dehydrogenases (ALDHs) are multifunctional enzymes that oxidize diverse endogenous and exogenous aldehydes. We conducted a meta-analysis based on The Cancer Genome Atlas and Gene Expression Omnibus data and detected genetic alterations in ALDH1A1, ALDH1A3 or ALDH3A1, 86% of which were gene amplification or mRNA upregulation, in 31% of non-small cell lung cancers (NSCLCs). The expression of these isoenzymes impacted chemoresistance and shortened survival times in patients. We hypothesized that these enzymes provide an oxidative advantage for the persistence of NSCLC. To test this hypothesis, we used genetic and pharmacological approaches with DIMATE, an irreversible inhibitor of ALDH1/3. DIMATE showed cytotoxicity in 73% of NSCLC cell lines tested and demonstrated antitumor activity in orthotopic xenografts via hydroxynonenal-protein adduct accumulation, GSTO1-mediated depletion of glutathione and increased H2O2. Consistent with this result, ALDH1/3 disruption synergized with ROS-inducing agents or glutathione synthesis inhibitors to trigger cell death. In lung cancer xenografts with high to moderate cisplatin resistance, combination treatment with DIMATE promoted strong synergistic responses with tumor regression. These results indicate that NSCLCs with increased expression of ALDH1A1, ALDH1A3 or ALDH3A1 may be targeted by strategies involving inhibitors of these isoenzymes as monotherapy or in combination with chemotherapy to overcome patient-specific drug resistance.

#49

Synthesis and antitumoral activity of C-meso substituted alditolporphyrin conjugates

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Keywords : *Porphyrins, Glycoporphyrins, photodynamic therapy, cancer.*

Porphyrins are macrocycles commonly utilized as photosensitizers in photodynamic therapy due to their capacity in generating reactive oxygen species under light irradiation. Carbohydrates are molecules usually identified by specific recognition proteins (lectins) related with cancer-associated biochemical pathways. Glycoporphyrin (molecules that combine both carbohydrate an porphyrin structures) synthesis has become of interest, generating conjugated compounds with specific-target action against cancer cells. The present work is focused on the synthesis and biological evaluation of two porphyrin-galactose conjugates. The synthetic process was initiated by generating acetylated and deacetylated galactose derivatives for dipyrromethane obtention. The C-alditolporhyrin macrocycles were formed via dipyrromethane-benzaldehyde condensation using BF3OEt2 and SeO2 as oxidizing system. The antitumoral activity of the molecules was evaluated on UM-MC-3 cells (bladder cancer cells). Uptake assays indicated cell internalization after 4 hours. Cell-viability assays showed no toxicity in the absence of light. After light irradiation period, the deacetylated molecule exhibited decrease of cell viability by 20% at 0,5 µM versus an 80% of cell viability at the same concentration for the acetylated derivative. These preliminary tests suggest promising phototoxicity properties for the deacetylated conjugate that could be used in PDT.

#50

Glucocorticoid Receptor signaling via the coregulator complex G9a/GLP/HP1g/AURKB in Estrogen receptor negative Breast cancer

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Keywords : *Glucocorticoid Receptor, Breast Cancer, Transcriptional Regulation , Coregulators, Lysine Methylation*

Breast cancer (BC) is a cause of high mortality in women worldwide. It was recently shown that the activity of the Glucocorticoid receptor (GR) could be involved in BC, leading to chemotherapy resistance and metastasis formation. GR is a transcription factor whose activity is regulated by ligand binding (glucocorticoid (GC)) and different coregulatory proteins. Coregulators remodel chromatin structure and promote or inhibit the recruitment and activation of RNA polymerase II. For instance, the histone methyltransferase G9a acts as coactivator or corepressor in a gene-specific manner. Our previous work demonstrated that the coactivator function requires the self-methylation of G9a to provide a binding site for HP1g, which facilitates the recruitment of RNA polymerase II. In contrast, phosphorylation of the adjacent threonine by Aurora kinase B (AURKB) opposes this effect. This molecular switch regulates migration of the lung cancer cells and GC-induced cell death in leukemia.

Targeting GR activity in BC is not an option because of its pleiotropic activity. Since GR regulates many physiological pathways through different GR coregulator activities, its coregulators, as G9a/HP1g/AURKB, may therefore be useful targets in BC for modulating the specific pathways regulated by GR in order to target its adverse side effects in BC, without affecting its beneficial ones.

In a cohort of ERα-negative BC patients, we found that high AURKB expression is associated with prolonged survival, whereas high expression of GR, G9a and HP1g is a signature of shorter survival. In addition, we observed this complex formation in different ERα-negative BC through assessing (i) G9a methylation and (ii) the interaction between GR, G9a and HP1g. Additionally, we are examining the impact of G9a and HP1g on the dex-regulated target genes. The project aims to decipher the impact of the G9a/HP1g/AURKB regulatory axis of GR signaling in ERα-negative BC in order to identify new therapeutic targets.

#51

Impact of Glucocorticoid Receptor methylation by PRMT5 on its transcriptional activity in Breast Cancer.

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Keywords : *PRMT5, Estrogen receptor (ERα), Glucocorticoid Receptor (GR), GR methylation*

Breast cancer (BC) is the most common invasive cancer in women. One of the factors leading to BC is the presence of steroid hormone receptors, among which estrogen signaling is a major contributor because 75% of BC express estrogen receptor (ERα). Besides ERα, glucocorticoid receptor (GR) is also involved in breast tumorigenesis. Function of steroid hormone receptors is widely described to be regulated by post-translational modifications. Among them, we demonstrated that the protein arginine methyltransferase 5 (PRMT5) methylates GR in its DNA binding domain. PRMT5 is the major type II methyltransferase depositing the symmetric dimethylarginine mark within proteins in order to regulate different cellular processes, such as DNA repair, signal transduction or transcriptional regulation. Dysregulated PRMT5 expression has been described in a variety of cancers. The objective of our research is to understand the role of PRMT5 in GR signaling pathway in BC. We demonstrated that PRMT5 methylates GR in the nucleus of ERα-positive and ERα-negative cell lines. This methylation event is induced by the dexamethasone (Dex), a synthetic glucocorticoid. Moreover, GR methylation is observed in human breast tissues showing the relevance of this event in BC. Our results indicate that PRMT5 impacts the transcriptional activity of GR on some specific GR-target genes and more specifically through a change in GR recruitment on the chromatin. Additional works are in progress to determine which GR signaling pathway is regulated by PRMT5 and its methylation. Complementary analyses are focusing on the identification of the methylated residue of GR modified by PRMT5. The overall goal of this study is to delineate the roles for PRMT5 on GR signaling activity in order to determine if PRMT5 could constitute new prognostic/predictive markers of response to treatment or a new potential therapeutic target.

#52

Neuroendocrine differentitation, a novel paracrine effect of cellular senescence

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Keywords : *Senescence, breast carcinomas, neuroendocrine differentiation, SASP*

After various stresses cells can enter a program called senescence resulting in a stable cell cycle arrest accompanied by a senescence-associated secretory phenotype SASP, including among others pro-inflammatory cytokines. Senescent cells, largely in part through their SASP, display different, sometimes opposite biological effects. It blocks proliferation and induces immune-mediated clearance of senescent cells presenting risk of transformation whereas accumulation of senescent cells and their SASP can exert pro-tumoral effects. The initial aim of this project is to investigate the role and impact of SASP on different breast cancer cells. Surprisingly, we observe induction of a neuroendocrine (NE)-like phenotype in luminal breast cancer cells, MCF-7, upon SASP treatment. This NE differentiation (NED) is also observed in LNCaP, prostate cancer cells known to undergo this differentiation in some contexts. My results demonstrate that pro-inflammatory molecules from SASP, through NF-κB activation, are necessary to induce this phenotype and that calcium signalling seems to participate in it. We also investigated the relevance of our observations using the breast cancer database METABRIC where we classified about 2% of breast tumors as NE breast carcinomas (NBC), all positive for estrogen receptor and preferentially p53 WT, in accordance with models used for functional data (MCF-7 and LNCaP). Interestingly, patients with NBC are older suggesting that accumulation of senescent cells and their SASP during aging can promote NED. In vivo, in mammary gland from old mice present increase of NE markers, compared to young mice, suggesting that aging and neuroendocrine differentiation are link. In conclusion, we are deciphering a novel paracrine effect of SASP, neuroendocrine differentiation that affect breast and prostate cancer characteristic and behaviour.

#53

Development of a novel anti-cancer strategy for Adrenocortical Carcinoma by nanovectorisation of microRNAs via Lipidots®

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Keywords : *Cancer corticosurrénalien, microARN, Lipidots, thérapies ciblées*

Adrenocortical carcinoma (ACC) is a rare endocrine malignancy associated with poor prognosis and unmet clinical needs. Although high-throughput molecular profiling has improved our knowledge of ACC genetics and driver genes, the disease pathogenesis is still unclear. Analysis of ACC microRNA (miRs) landscape revealed an aberrant microRNA expression in both tumors and patient serum. MicroRNAs are small non-coding RNAs of about twenty nucleotides that repress gene expression at the post-transcriptional level. Besides tumor-associated miR signatures, circulating miRs have emerged as promising diagnostic and prognostic biomarkers. We have previously demonstrated that overexpression of two miRs, miR-483-5p and miR-139-5p is involved in ACC aggressiveness. Our aims are (1) to identify the oncogenic pathways activated by miR-483-5p and miR-139-5p in ACC, and (2) to evaluate both miRs as therapeutic targets for ACC. Using PCR arrays and Antibody arrays dedicated to cancer hallmarks, we established that miR-483-5p and miR-139-5p activate MAP kinase p38 and and Akt/mTOR signaling pathways. Moreover, both miRs induce expression of key players in epithelial-mesenchymal transition (EMT) process and extracellular matrix remodeling. Thus, our data suggest that miR-483-5p and miR-139-5p are potential therapeutic targets to prevent ACC invasion. To test this hypothesis, we are using the lipid nanoparticles "Lipidots®" patented by the CEA LETI, to vectorize inhibitors of our candidate miRs in pre-clinical ACC models. The physico-chemical properties of Lipidots® as well as their biocompatibility and their particular tropism for the adrenal cortex suggest that they could be relevant vectors for our cancer model. We have generated miR Inhibitors-Lipidots® nanoparticles and started to investigate their effects on the aggressive phenotype of ACC cell lines. This nanoparticle-mediated delivery of miR-inhibitors or miR-mimics could be extended to other cancers featuring miR deregulations.

#54

Involvement of LIM Kinases in the regulation of microtubule dynamics

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***Keywords** : LIM Kinases, mitotic spindle, microtubules,actin, Crisp-Cas9*

The LIM Kinases 1 and 2 (LIMK1 and LIMK2) are central regulators of the cytoskeleton. They play a crucial role for the stability of actin filaments through the phosphorylation and inactivation of cofilin, an actin-depolymerizing factor. They are also involved in regulating mitotic spindle formation and chromosome segregation during cell division. We and others have previously shown that specific inhibitory compounds targeting LIMKs increase microtubule (MT) stability. However, the molecular mechanism of how LIMK actions influence microtubule dynamics is still unexplored. To investigate the role of LIMKs in MT dynamics, we generated HeLa cell lines deficient in LIMK1 or LIMK2 or both kinases by a Crispr-Cas9 approach. A significant decrease of phospho-cofilin and a modification of the actin network confirmed the reduced/absent LIMK activity in the three Crispr-Cas9 modified HeLa cell lines. Abnormal mitosis was observed when LIMK1 or LIMK2 or both kinases were deficient. By measuring the size of EB1 comets, we observed that EB1 comets were smaller in LIMK deficient-HeLa cells, suggesting an impairment of MTs dynamics. In a pharmacological assay of microtubule stability MTs appeared, indeed, to be more stable when LIMK activity is diminished. Our results confirm that LIMK contribute to the stability of the MT network. These single deficient-LIMK1 or -LIMK2 and double deficient-LIMKs HeLa cells are valuable tools to identify the molecular link between LIMK and MT dynamics and to decipher the respective functions of LIMK1 and LIMK2.

#55

CCM deficient endothelial cells undergo a mechanically induced reprogramming into a senescence associated with a secretory phenotype

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Keywords : *endothelial tumor cell, mechano-transcription, extra-cellular matrix remodelling, Senescence-associated with secretory phenotype.*

Cerebral Cavernous Malformations (CCM) are vascular lesions leading to potentially hemorrhagic strokes. The onset of CCM lesions is comparable to tumor angiogenesis and several points from transcriptional program to cell behaviors are matching with tumor endothelial cell features. The CCM lesions appear upon the endothelial loss-of-function mutation in ccm genes that code for the CCM protein complex. This complex maintains a tensional homeostasis by coordinating the dialog between ß1-integrin at the extracellular matrix (ECM)-cell interphase and VE-cadherin at the cell-cell junctions. We previously showed that within this dialog, the CCM complex coordinates ROCK1 and ROCK2 activities to control the architecture of the endothelial cell in response to its microenvironment. Depletion of CCM complex is sufficient to produce an exaggerated ROCK-dependent cell contractility which increases ß1-integrin dependent adhesion and destabilizes VE-cadherin-dependent cell-cell junctions. At the transcriptional level, the CCM complex is involved in the maintenance of the endothelial cell identity as the loss of CCM complex sets up an endothelial to mesenchymal transition. We did a transcriptomic analysis by RNA-seq in order to study the role of the ROCKs-dependent intra-cellular contractility on this gene expression reprogramming. This technique allowed us to discover the set-up of a mechano-sensitive gene expression program named Senescence Associated with a Secretory Phenotype (SASP) occurring upon CCM depletion. The SASP is known to set up a pro-tumorigenic stroma and to promote cancer cell invasiveness. In CCM model, we found that this SASP reprogramming gives new functions to the endothelial cells in a ROCK-dependent manner. We found that CCM-depleted HUVECs acquire mesenchymal characteristics such as invasiveness through the proteolytical and mechanical remodelling of the ECM. Moreover, they acquire the ability to chemo-attract wild-type endothelial and immune cells.

#56

Biological markers predictive of the risk of progression from hepatitis B virus infection to hepatocellular carcinoma in Senegal

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***Keywords** : HBV, HCC, Biological markers, Senegal*

Among the 257 million hepatitis B virus (HBV) carriers worldwide, approximately 70 million live in Africa. The feared complications of the infection are cirrhosis and hepatocellular carcinoma (HCC). In Senegal, the prevalence of HBV is estimated at 11% and HCCs are often diagnosed at an advanced stage. Various factors appear to influence liver carcinogenesis, including viral genotype, expression of micro-RNAs (mi-RNAs) and exposure to aflatoxin B1 (AFB1). This work aims to identify predictive markers of progression from hepatitis B to HCC. A retrospective collaborative study on samples collected between 2013 and 2016 was conducted. Samples of 340 HBV chronic carriers and HCC patients recruited as part of the Prolifica Project are currently analyzed to identify the genotypes / subgenotypes of HBV by sequencing (Sanger / Next Generation Sequencing (NGS)), to explore the mi-RNAs by Nanostring's nCounter and to detect the TP53 mutation by NGS. Among 24 samples sequenced to date, nine (37,5%) are genotype A and fifteen (62,5%) genotype E. Among 34 samples with more than 800 mi-RNAs explored, 28 mi-RNAs of interest were identified: 11 overexpressed and 17 under expressed in HCC, including miR-122-5p. Fifteen mi-RNAs shared strong interactions in the regulatory pathways of different genes and 5 mi-RNAs, let-7g-5p, miR-185-5p, miR-26a-5p, miR-503-5p and miR-126-3p, were significantly linked ($p < 0.05$) in the cancer, hepatitis B, p53 and viral carcinogenesis pathways. The detection of the TP53 R249S mutation is underway to confirm the recent results obtained in Gambian patients. The preliminary results of this study will allow us to finely define the genetic variability of HBV viral strains in Senegal and to characterize biological markers in order to understand the molecular mechanisms of HBV-related HCC in this country, in which HBV infection is endemic.

#57

Cholesterol and sex steroids bioavailability affect early tumorigenesis of prostate-like drosophila accessory gland.

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Keywords : *Prostate, Cholesterol, Drosophila, Sex steroids, Cancer*

Several studies indicated a probable implication of cholesterol and its derivatives, and particularly sex steroid hormones, in prostate cancer progression. However, whether the same molecules are important for early tumorigenesis remains uncertain.

Drosophila accessory gland is a functional equivalent of human prostate. In this organ, we have defined the conditions to induce early tumorigenesis in a reproducible manner, from initiation to basal extrusion, the first step of invasion.

Drosophila tumors formed outside the epithelial compartment accumulate lipids, as in human late carcinogenesis. High cholesterol diet increases the risk to develop such tumors, as downregulating intratumoral cholesterol metabolism blocks this phenomenon.

Ecdysone is the steroid hormone that sustains accessory gland reproductive function. Downregulating ecdysone receptor, or ecdysone intratumoral synthesis, specifically in the tumor cells, alters tumorigenesis.

We conclude that early tumorigenesis relies both on cholesterol and ecdysone. We furthermore show that this is an intratumoral hormone synthesis which is necessary for tumors to leave the epithelial compartment, a phenomenon that is reminiscent of the suspected mechanisms of resistance to androgen deprivation therapy.

Our aim is now to understand what molecular mechanisms are promoted by cholesterol and ecdysone to induce early tumorigenesis, and to evaluate their relevance for human pathology.

#58

Porphyrin derivatives: converting substrates into specific inhibitors of the breast cancer resistance protein

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Keywords *: Cancer, Multidrug Resistance, ABCG2 transporter, Porphyrins, Inhibitors, Substrates*

Multidrug resistance (MDR) is a challenge in cancer treatment. Among the 48 protein ABC on human genome, three are mostly involved on MDR: P-gp, MRP1 and ABCG2. The treatment of MDR faces the lack of approved drugs for clinical uses. In addition, the inhibitors currently in clinical trials are specific for P-gp, ABCG2 is far from having an approved inhibitor. ABCG2 can transport compounds with unrelated structures; but one of them, Pheophorbide a (porphyrin related compound), is a specific substrate of ABCG2, a rare phenomenon since the ABC transporters share the capacity of efflux the same drugs. The heme group can also interact specifically with ABCG2, showing the relevance of the porphyrinic scaffold. We tested 26 porphyrins as ABCG2 substrates or inhibitors and one inhibited the ABCG2 activity, an effect unknown for porphyrinic derivatives. The inhibition was selective for ABCG2, the maximum inhibition was around 80% at 10μM, and the IC50 value was 1.6μM. The co-treatment with chemoterapeutic and the porphyrin successfully chemosensitized the resistant cells overexpressing ABCG2, exhibiting a similar cell death to the parental cell line. The porphyrin interaction triggers protein conformation changes, increasing the 5D3 antibody binding at the extracellular loop ECL3. The ATPase activity was inhibited, classifying the porphyrin as a truly ABCG2 inhibitor. The inhibition mechanism is mixed, the inhibitor can binds in presence or absence of the substrate. Docking using Pheophorbide a showed a good fit on the upper part of the protein. However, the porphyrinic inhibitor binds in the lower part, suggesting different binding sites between porphyrinic compounds that act as inhibitors or substrates. Also, the porphyrin pocket is symmetric, it can interact simultaneously with both ABCG2 chains. In summary, we describe the first porphyrin as a specific ABCG2 inhibitor, showing exclusive inhibition features and binding sites that can be explored on further studies.

#59

Dynamic Cross-talk between Mutagenesis and the Regulatory Genome during Carcinogen-induced Cell Immortalization

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Keywords : *Carcinogen, Mutation,Chromatin, experimental cell model, multiomics, gene expression*

Exposure to carcinogens is a well-established risk factor for tumor development. Carcinogens can act directly on the DNA, and chromatin topography changes have emerged as another mechanism linking carcinogen exposures to DNA repair and gene expression changes, which can ultimately lead to cancer driver alterations and tumorigenesis. However, the relationship between genetic alterations, chromatin structure and the regulatory genome is still not fully understood. Using carcinogen exposure-mediated mammalian cell immortalization that involves senescence bypass, we obtained a panel of recurrently mutated genes. In addition to oncogenes and tumor suppressor genes, key regulators of cancer-related pathways were mutated. We observe that the mutations in the subunits of BAF and TIP60 complexes were mutually exclusive, signifying that destabilization of a single subunit is enough to modify the activity of the complex. Ongoing work is addressing the contribution of inactivation of a chromatin remodeling factor, linked to genomic stability, to the mutation landscape using the same experimental model. In human mammary epithelial cells exposed to B[a]P we observe increased mutation frequencies associated with repressive chromatin, paralleling observations in tumors. ATAC-seq and DNA methylome analyses showed transformation-specific changes in chromatin accessibility, primarily in enhancer regions, which were frequently accompanied by changes in DNA methylation. We observe an overlap of mutations in regions of differential chromatin accessibility with enhancer regions, raising the possibility of a functional contribution of the mutations to changes in the regulatory landscape. Our work highlights the suitability of these experimental cell models in not only recapitulating cancer events, but also in revealing putative drivers through their suitability for functional studies.

#60

Human Heterochromatin dynamics through the Heat Stress Response. What impact on genome integrity ?

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Keywords : *Heterochromatin · Heat Stress · Long non-coding RNAs. Genome Stability*

In eukaryotes, Pericentric Heterochromatin (PHC) is formed of DNA repetitive sequences, named Satellite III (sat III) and organized as tandem repeats. PHC plays an essential role in genome stability and gene expression. It maintains the cohesion of sister chromatids during mitosis and forms repressive hubs for transcription. Alterations of PHC structure are involved in chromosomes instability (CIN) in tumor cells.

The formation and transcriptional silencing of PHC occurs during early development, which makes these events difficult to analyze.

Surprisingly, it has be shown that upon heat stress, PHC is activated by the transcription factor Heat shock Factor 1 (HSF1), triggering an accumulation of pericentric long non-coding satellite III transcripts.

Heat stress is a powerful model to understand the mechanisms involved in the transcriptional activation of PHC and in its (re)formation. Indeed, while PHC is transcriptionally activated upon stress, transcriptional silencing of PHC is observed during the recovery period from stress.

My objective is to characterize the implication of actors (proteins, histone modifications, RNA) associated with the transcriptional silencing of PHC regions during the recovery period from stress. In particular I focused on the role of sat III transcripts in PHC (re)formation following stress to determine if these transcripts play a role in the recruitment of two main actors of PHC : Heterochromatin Protein 1 (HP1) and H3K9me3. In parallel, I am also undergoing a comprehensive study to analyze how sat III RNAs accumulation or knock down impair cycle cell and genome stability. To achieve this, I am performing microscopy-based and In Situ analysis to detect CIN (chromosome lagging or micronucleus formation) on living cells and fixed cells, in cancerous and non-cancerous cell line.

#61

Mechanisms of actions of BET bromodomain inhibitors in inflammation-induced hepatocellular carcinoma.

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Keywords :

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths. It is a multifactorial disease that is derived from a sustained liver inflammation. Although various therapeutic strategies were designed to extend survival of HCC patients, none of them are currently effective. Sorafenib remains the sole first-in-line treatment with an extended survival of 3 months only. Therefore, the prevention of HCC development by reducing chronic liver inflammation could represent a promising therapeutic strategy to decrease incidence and mortality rate of HCC. Henceforth, the introduction of a novel therapeutic strategy, using 'EpiDrugs' to target epigenetic factors -which are known to be involved in gene expression dysregulation in complex diseases - could be interesting. More specifically, BET bromodomain inhibitors (iBETs) have a strong potential for HCC prevention, since these small molecules inhibitors have recently showed promising results as both anti-inflammatory and anti-tumor agents. However, the molecular properties of iBETs have not been sufficiently studied and their mechanism of action remain unclear. Thus, this project aims at identifying and defining the molecular targets of iBETs of various chemical scaffold and selectivity in immune cells and their impact on gene expression and pro-inflammatory secretory functions in context of HCC Preliminary data obtained using stimulated macrophages (J774 cell line) showed that several iBETs are capable of significantly reducing IL-6 and TNF-alpha secretion without affecting immune cell viability. These results provided a first set of information about iBETs' anti-inflammatory properties, which are being further extended using patients PBMC (Peripheral Blood Mononuclear Cells) and finally preclinically tested in a rat model of chronic inflammation-induced HCC.

#62

Unexpected microtubule stabilizing activity of certain kinase inhibitors, clinically approved or in the process of approval

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Keywords :

Agents able to modify microtubule dynamics are important anticancer drugs. The absence of microtubules resulting from drug-induced depolymerization is easy to detect. However the detection of a stabilized microtubule network needs specific assays since there is not a significant visual difference between normal and stabilized microtubule networks. We describe a quantitative cell-based assay which allows the detection of stabilized microtubules without the need of microscopic examination. Using this assay to screen a kinase inhibitor library allowed the selection of seven known kinase inhibitors. The yet undescribed ability of these inhibitors to stabilize cellular microtubules was confirmed using additional markers of stable microtubules and time-lapse video-microscopy to track individual microtubules in living cells. None of the compounds interacted, however, directly with tubulin. We demonstrated that, depending on the compounds, their microtubule stabilizing activity resulted either from the inhibition of a kinase that regulates the microtubule cytoskeleton, never described before, or from their effect on a target not yet identified. Many of these inhibitors are clinically approved or currently assayed in phase 2 or phase 3 clinical trials. Their microtubule-stabilizing effect may account for their therapeutic effect as well as for some of their adverse side effects. These results indicate also a possible repurposing of some of these drugs. #

#63

Controlling macrophage invasion by modulation of SRC activity through optogenetic

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Keywords :

Src, a member of an 8 non-receptor tyrosine kinase family, is a key regulator of podosomes. These organelles are found in physiological cells, such as macrophage, but could be assembled in invasive cancer cell in which they are called invadosomes. In both cases, they are composed of an actin core surrounded by a signaling hub of regulatory and adapter proteins whose are connected to trans-membrane proteins adhering and sensing extra cellular matrix (ECM). Such acto-adhesive machinery is also involving local recruitment and activation of metalloproteases responsible for degradation of ECM. Interestingly, during the few minutes of podosomes life, the SRC activity is implicated both in the birth and in its disassembly. How a same kinase is able to drive two antagonistic events remains an unclear phenomenon. To investigate this paradigm, the laboratory hypothesized that the spatio-temporal control of SRC activity allows to take different signaling decisions leading to different cellular responses. To test it, our group engineered a photo-sensitive SRC kinase (OptoSRC) by combination with the optogenetic system CRY2, allowing induction of an OptoSRC activity inside the cell at the second scale. By controlling SRC activation, I aimed that it is possible to control macrophage invasion by controlling the functions of its podosomes. In macrophages, it appears that activated OptoSRC increases de novo podosome formation by 20 points coupled with an increase of their auto-organization into large rings. Futhermore, activation of OptoSRC induces also a decrease of podosome life-span from 10 to 4 minutes. This change of podosome dynamics is also associated with an increase of their ECM degradation capability. Taken together, our data suggest that controlling OptoSRC activity is sufficient to control podosome dynamics and functions. This is a new way to control macrophage functions in order to regulate its invasion of tumors.

#64

SMYD2 Lysine Methylation Signaling meets Actin Cytoskeleton in Breast Cancer

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Keywords :

Post-translational modifications are a key biological mechanism increasing functional diversity of proteins, therefore participating in cell adaption to environmental changes. Lysine methylation signaling is a highly specific and dynamic process catalysed by lysine methyltransferases, well known to impact chromatin regulation through histones methylation, as well as cell signaling pathways through non-histone proteins methylation. Importantly, deregulation of lysine methylation signaling is involved in human diseases, such as cancer. SMYD2 is a methyltransferase overexpressed in 30 % of invasive breast cancer patients, and has been linked to regulation of cell motility and invasiveness of breast cancer cells. However, how SMYD2 impacts migration and invasion is still elusive. Using a conditional knockout Smyd2 mice model of breast cancer we showed a significant delay of tumour progression, suggesting important downstream signaling of SMYD2. Through proteomics approach, we found that SMYD2 mono-methylates a protein known to be crucial for breast cancer cell migration, and we confirmed this event both in vitro and in breast cancer cells. Since methylated lysines act as a docking site for other proteins, we performed a SILAC-Peptide Pulldown and identified through proteomics approach that this methylated protein can bind to a family of proteins known to polymerize and remodel actin cytoskeleton. Using engineered breast cancer cell lines we showed that this new signaling is important for actin organisation in lamellipodia, a specific cytoskeletal structure allowing cell migration. We are now in the process of characterizing this pathway, which directly impacts motility of cells, and we will highlight the consequences of its deregulation in the aggressiveness of breast cancer. This new axis could represent a major pathway whereby breast cancer cells acquire invasive properties to metastasize, and could therefore be an important therapeutic target.

Nanomédecine & technologies pour la santé

#65

Tissue Imprint Technology to improve molecular deciphering of brain tumors

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Medimprint

***Keywords** : Glioblastoma, Tissue Imprint, Genome driven therapy, Silicon, Medical Device*

Progress in precision medicine shows that genomic and transcriptomic characterization of tumors have improved therapy recommendations and patient outcome, and expands personalized cancer treatment. Several successes have been reported using genome-targeted or immune-targeted therapies with drugs affecting the abnormal molecular pathways.

Unfortunately, not all malignancies have benefited from these molecular-driven therapies. Glioblastoma (GBM) remains an incurable disease, despite the extensive molecular deciphering. Most targeted therapy trials were negative from bevacizumab to check point inhibitor immunotherapy. Moreover, several basket trials targeting druggable mutations did not increased survival, questioning genomic informed precision medicine. GBM is a paradigmatic example of the bottlenecks explaining these failures: tumor heterogeneity, molecular adaptation when single pathway targeting is initiated or the missing of remote tumor drivers such as the peritumoral area.

Considering the lack of medical technologies enabling safe and surgically-compatible tissue sampling to explore uncharted tumor and peritumoral heterogeneity, Medimprint has developed a breakthrough concept, the non-lesional brain tissue imprint. This device is based on the development of an innovative mesoporous silicon surface to collect biological material by spontaneous adhesion with no functional lesions in the explored region. This innovation is perfectly compatible with NextGen Sequencing approaches that have substantially improved the ability to identify known actionable alterations in patients and led to the discovery of new potentially druggable alterations.

We envision that Medimprint technology could significantly participates to the current trend for cancer therapy that has clearly established that better management of cancer patients has to integrate extensive tumoral (and peritumoral) profiling.

#66

Verteporfin-loaded lipid nanoparticles improve ovarian cancer photodynamic therapy in vitro and in vivo

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Keywords *: photodynamic therapy; lipid nanoparticles, ovarian cancer, drug delivery system, verteporfin*

Advanced ovarian cancer is the most lethal gynecological cancer, with a high rate of chemoresistance and relapse. Photodynamic therapy offers new prospects for ovarian cancer treatment, but current photosensitizers lack tumor specificity, resulting in low efficacy and significant side-effects. In the present work, the clinically approved photosensitizer verteporfin was encapsulated within nanostructured lipid carriers (NLC) for targeted photodynamic therapy of ovarian cancer. Cellular uptake and phototoxicity of free verteporfin and NLC-verteporfin were studied in vitro in human ovarian cancer cell lines cultured in 2D and 3D-spheroids, and biodistribution and photodynamic therapy were evaluated in vivo in mice. Both molecules were internalized in ovarian cancer cells and strongly inhibited tumor cells viability when exposed to laser light only. In vivo biodistribution and pharmacokinetic studies evidenced a long circulation time of NLC associated with efficient tumor uptake. Administration of 2 mg.kg-1 free verteporfin induced severe phototoxic adverse effects leading to the death of 5 out of 8 mice. In contrast, laser light exposure of tumors after intravenous administration of NLC-verteporfin (8 mg.kg-1) significantly inhibited tumor growth without visible toxicity. NLC-verteporfin thus led to efficient verteporfin vectorization to the tumor site and protection from side-effects, providing promising therapeutic prospects for photodynamic therapy of cancer.

#67

Caractérisation de tumeurs par spectroscopie ultrasonore : étude préliminaire

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Keywords : *spectroscopie ultrasonore, caractérisation tissulaire, classification*

Actuellement, l'examen de référence permettant de caractériser une tumeur est la biopsie. Cependant, cet examen est invasif, local ainsi qu'une source de stress pour le patient. Il y a donc un besoin de développer de nouvelles techniques non-invasives et plus globales pour caractériser les tumeurs. Celles-ci présentent des différences dans leur microstructure tissulaire avec les tissus sains et entre elles : différences de propriétés mécaniques cellulaires, différences morphologiques (acini, lobules), et structurelles (répartition plus compacte et désordonnée des cellules). Des biomarqueurs de la microstructure tissulaire, évalués par spectroscopie ultrasonore quantitative, pourraient donc porter des informations sur la nature d'une tumeur et son type. Afin d'évaluer des biomarqueurs tant à l'échelle cellulaire qu'à plus grande échelle, il faudrait utiliser une excitation ultrasonore couvrant une très large bande de fréquences (quelques MHz à quelques dizaines de MHz). L'objectif de cette étude préliminaire est de déterminer s'il est possible de différentier différents types de tumeurs avec des informations, à l'échelle cellulaire seulement, sur des biofantômes de cellules et des tumeurs murines ex vivo. Pour cela, différents paramètres sont extraits des mesures du coefficient de rétrodiffusion ultrasonore moyen (les paramètres de Lizzi-Feleppa, des paramètres quantitatifs en utilisant les modèles gaussien et facteurs de structure, l'atténuation et des informations sur les maxima). La classification de biofantômes de 4T1 (carcinome mammaire murin), JC (adénocarcinome mammaire), MAT (adénocarcinome mammaire) et DSL (carcinome pancréatique) et de tumeurs ex vivo de 4T1, JC et MAT est réalisée en utilisant un arbre de décision (Classification Learner sous Matlab). Les différents types cellulaires sont classés avec une sensibilité > 0.76 (respectivement 0.78) et une spécificité > 0.88 (respectivement 0.85) pour les biofantômes (pour les tumeurs ex vivo).

#68

Microwave Imaging System using Artificial Intelligence (AI) for Diagnosis of Breast Cancer

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Keywords : *Artificial Intelligence, Breast-Cancer, Microstrip-Patch-Antenna, Microwave-Imaging, and Non-Ionizing.*

Breast Cancer deaths in 2020 are estimated to be around 42,690 for USA [ACS] and ~93,571 for Europe. [Carioli 2017]. Today is known that early diagnosis increases the survival chances among patients, and they will require less extensive treatments [Migowski 2015]. Traditional breast imaging tests like X-ray mammograms, Ultrasound, CE-MRI, PET, CT, and Biopsy had been used. [Abel 2013] However, newer imaging systems are being studied today to achieve similar and more efficient ways to make a diagnosis of breast cancer. Several are Molecular-Breast-Imaging (MBI), Optical Imaging Tests, Electrical Impedance Imaging (EIT), Elastography and Microwave Imaging (MWI). [ACS] In this study a novel Microwave Imaging System (MWI) for breast cancer detection is proposed. Recently MWI Systems had been confirmed to be the most efficient non-invasive cost-effective easy-to-use technique. [Wang 2018] MWI systems have an accuracy of 80-90 %. [Rahman 2018] Our contribution is to develop an active Radar MWI system with flexible cost-effective Microstrip Patch Antennas as Array RF sensors working in the unlicensed spectrum defined by the FCC (at USA) and ETSI (at Europe). The system benefits will be the enhanced Gain and Directivity of our sensors with the use of Electromagnetic-Band Gap (EBG) structures, and Artificial Intelligence methods to make data treatment and detect accurate Breast Cancer Tumors.

#69

Multi-physics system for breast cancer diagnosis

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Keywords : *UlraSound Transducers, US Imaging, Artificial Intelligence.*

Breast cancer is the second leading cause of death among women worldwide. Several detection techniques are common in the healthcare field. In this paper a novel breast cancer diagnostic system is proposed. This system is composed by a set of ultrasonic transducers mounded on a flexible support. The transducers measure the Speed of Sound (SoS) from the density and rigidity of the tissues. Indeed, the sound passes on average 3% faster through malignant tumors than surrounding healthy tissue, and 1.5% faster than benign tumors [1]. Using this property, the proposed system can accurately detect the nature of the breast tumor form the measure of the Speed of sound in tissues. To ensure the reliability and the accuracy of the measurement, the proposed system will also measure the local temperature of the tissue based on the spectral components of the same ultrasonic transducers. Thus, the proposed system is a multi-physical system with flexible appearance. Therefore, it is possible to apply it to several parts of the human body.

#70

Specific targeting of cancer cells through modulations of the liposomal membrane fluidity

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Keywords : *Liposomes, Biotechnology, Membrane fluidity, Drug delivery, Targeted therapy*

In the field of cancer, current chemotherapy relies on carriers to reach their cellular targets. Between the different drug carriers available, liposomes distinguish themselves due to their biocompatibility, biodegradability and overall innocuity. Conventional liposome drug delivery relies on membrane composition modifications to target a specific cell type with ligand-receptor interactions and liposomes grafted with antibodies or ligands recognizing a specific protein overexpressed in the targeted cells. Specific drug delivery never used extensively lipid membrane composition, even though lipid composition is one of the key parameters that defines membrane properties such as membrane fluidity. In this study, we modulated the lipid composition of PC/DOPE fluorescent liposomes to create a range of membrane fluidity. Assessing their interaction with four prostate cancer cell lines showed that the interaction of liposomes with cell membranes hinges on the fluidity of both membranes. Liposomes with a fluid-state membrane target metastatic cells (which were shown to have a fluid membrane), while rigid-state liposomes preferentially interact with the control cells, which have a more rigid membrane when compared with tumor cells. Moreover, investigating the interaction patterns of liposomes containing two different fluorophores, one hydrophobic incorporated in the liposome membrane and one hydrophilic encapsulated in the liposome aqueous core, we determined that the mechanism of this interaction is based on membrane fusion. From a drug delivery point of view, this shows a great potential to overcome the usual limits of conventional strategies that revolve around endocytosis internalization pathways, as membrane fusion allows the liposome contents to be directly released inside the cell. These results suggest that fine-tuning the liposome membrane fluidity to target a specific cell type is a promising alternative to current targeting strategies based on covalent grafting.

#71

Magnetic isolation of Circulating Tumor Cells in a microfluidic device

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Keywords : *Circulating tumor cells, Negative selection, Immunomagnetic separation, Micro-magnets, Microfluidic devices*

During the past years, the use of circulating tumor cells (CTCs) directly isolated from blood as a real-time liquid biopsy has received attention since CTCs could provide clinical information on cancer diagnosis, prognosis, and treatment monitoring, paving the way for personalized medicine. However, the recovery of CTCs from blood samples is challenging given their low abundance in blood and their heterogeneous phenotype due to the epithelial-to-mesenchymal transition (EMT). To meet these challenges, microfluidic devices are great tools given the precise cell manipulation at the microscale and the flexible integration of several functions in a single chip. Moreover, these devices offer cost reduction, portability, automation, and single-cell study. Among the existing approaches to isolate CTCs, immunomagnetic-based microsystems combine benefits from microfluidic format for rare cell handling and a highly selective sorting method based on magnetic forces. However, integrating micro-magnets in microfluidic devices requires a complex and costly fabrication process. Here we propose a novel technology based on the microstructure engineering of polymer composites to obtain arrays of efficient magnetic micro-traps integrated into microfluidic devices. The traps were obtained through the self-organization of NdFeB particles in a polydimethylsiloxane (PDMS) under a magnetic field, during PDMS curing. These traps of 4 to 11 µm in diameter were used for the capture of WBCs that were magnetically labeled with magnetic nanoparticles conjugated to anti-CD45 and anti-CD15 antibodies. We demonstrated WBCs capture in the microsystem and we determined its efficiency under various flow rates, as well as the recovery efficiency of spiked PC3 cells. Therefore, we report a new magnetic separation system that is low cost and with a simple fabrication process, breaking with standard microfabrication approaches.

#72

Multi-physics system for breast cancer diagnosis

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Keywords : *UlraSound Transducers, US Imaging, Artificial Intelligence.*

Breast cancer is the second leading cause of death among women worldwide. Several detection techniques are common in the healthcare field. In this paper a novel breast cancer diagnostic system is proposed. This system is composed by set of ultrasonic transducers mounded on a flexible support. The transducers measure the Speed of Sound (SoS) from the density and rigidity of the tissues. Indeed, the sound passes on average 3% faster through malignant tumors than surrounding healthy tissue, and 1.5% faster than benign tumors [1]. Using this property, the proposed system can accurately detect the nature of the breast tumor form the measure of the Speed of sound in tissues. The speed of sound in tissues depends on the temperature. To ensure the reliability and the accuracy of the measurement, the proposed system will also measure the local temperature of the tissue based on the spectral components of the same ultrasonic transducers. Thus, the proposed system is a multi-physical system with flexible appearance. Therefore, it is possible to apply it to several parts of the human body.

#73

Intracellular Water Lifetime: a new in vivo biomarker of glioma cell invasion/migration by FFC-NMR relaxometry and AQP4 implications

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Keywords : *RMN, FFC-NMR, relaxometry, cancer, brain tumors, glioma, tumor microenvirinment, tumor cell invasion/migration*

Fast Field-Cycling Nuclear Magnetic Resonance (FFC-NMR) is an emerging technology that probes water dynamics. Compared to standard NMR, FFC-NMR operates at low and variable magnetic fields < 1T. In our previous ex vivo work1, using 3 mouse models: U87 (characterized as solid glioma) and Glio6 and Glio96 (2 experimental models of glioma cell invasion/migration2), we showed that FFC-NMR can discriminate invasive/migrating glioma cells from solid glioma. Indeed at low fields, tissues with invasive/migrating glioma cells have longer T1 relaxation time. T1 is especially dependent on the extra/intracellular water content and on water exchanges across cell membranes. In a recent study on 3 breast cancer mouse models carried out in vivo, we demonstrated that it is possible to determine the intracellular water lifetime (□in) by fitting the biexponential magnetisation recovery, acquired at different magnetic fields, using 2SX model3,4. Data showed a significant correlation of □in decrease and tumor agressiveness4. Here, the same in vivo experiment was performed on the glioma models: U87, Glio6 and Glio96. As expected, Glio6 and Glio96□□in, compared to those of U87 and healthy tissues were found shorter. So, our aim here is to understand « why do tumor cells display rapid water exchanges for invasion/migrating glioma cells?» and to identify the Warburg effect mechanisms that promote rapid water exchanges across cell membranes.

For this purpose, HE histology and Immunohistochemistry of AQP4 and 1; Glut1; CAIX; NaK ATPase; NHE1were used. In particular, we focused on deciphering the link between invasion/migrating and glioma cells and AQP4 role in controlling water exchanges.

Our first FFC-NMR results show that (i) □in represents a hallmark of glioma cell invasion/migration and (ii) shorter □in of Glio6/Glio96 models are unequivocally correlated to the AQP4 expression, indicating a major role of AQP4 in controlling water exchanges in tissues of invasion/migrating glioma cells.

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#74

Solubility enhancement of a new inhibitor of the Ser/Thr kinase CK2 by inclusion complexation with ß-cyclodextrins: A joint experimental and theoretical investigation

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Keywords : *Small molecule, kinase inhibitor, Solubility, cyclodextrins, in silico studies, complexation*

The present investigation was aimed to optimize the solubility and the biological efficiency of a new small-molecule called NB4 having a marked inhibitory activity on the Ser/Thr kinase CK2 (IC50 = 16 nM). NB4 also demonstrated an anti-leukemic activity on multidrug-resistant lines (IPC, Bcl-2) despite its poor water-solubility (<< 0.002 mg/mL). Thus, there is a need to increase its hydrosolubility using a pharmaceutical carrier like cyclodextrins (e.g. ß-CD, hydroxypropyl-ß-CD) (1). The MM-GBSA, DMol3 and extra-precision flexible docking methods were used in various stages of the formulation development, including the selection of the most stable inclusion complex, the determination of intermolecular energy contributions, the prediction of hydrophilic surface and the measure of dielectric (solvation) energy (2). The use of two cyclodextrins (ß-CD and hydroxypropyl-ß-CD) in different molar ratios was virtually studied, indicating NB4–hydroxypropyl-ß-CD (HP-ß-CD) as the most stable and thermodynamically favored system. Based on the molecular modelling studies, the solid-state NB4–HP-ß-CD system was prepared by the co-evaporation method (3). Then, the mechanism of inclusion interaction of guest and host was established through 1H-NMR experiments. The dissolution study showed significantly improved dissolution profiles of NB4–HP-ß-CD compared to the pure NB4. The theoretical model was successfully validated, with a good correlation between experimental and in silico data. The theoretical and experimental results will be detailed and explained in this communication poster. References: 1) Nacereddine A, et al. Self-assembled supramolecular nanoparticles improve the cytotoxic efficacy of CK2 inhibitor THN7. Pharmaceuticals (Basel). 2018. 2) Quevedo, M.A, et al. Current trends in molecular modeling methods applied to the study of cyclodextrin complexes. J. Incl. Phenom. Macro. 2018. 3) Kontogiannidou E, et al. In vitro and ex vivo evaluation of tablets containing piroxicam-cyclodextrin complexes for buccal delivery. Pharmaceuticals (Basel). 2019.

#75

Ultrasound-Mediated Cavitation To Enhance The Delivery Of Liposomal Formulations For Targeted Radionucleide Therapy

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Keywords : *Ultrasound, liposomes, radiopharmaceutical.*

Introduction: Nanoparticles are powerful tools in cancer treatment but their low tumours penetration can hinder their efficacy. In this study, we used ultrasound (US) and microbubbles to improve the intratumoural delivery of liposomes (LPs) carrying radiolabelled epidermal growth factor (111-In-DTPA-EGF). The EGF receptor is over-expressed in many cancers providing selective targeting. After binding, 111-In-DTPA-EGF is shuttled to the cell nucleus and induces radiation therapy thanks to Auger electrons emission.

Methods: LPs were developed by encapsulation of DTPA-EGF inside a cavitation-sensitive LP (LP-inside) or by functionalising the surface of a cavitation-stable LP (LP-outside). This was followed by 111-In radiolabelling. MDA-MB-468 (overexpressing-EGFR) and MCF7 (low-EGFR expressing) cells were used in vitro. SonoVue® was used as cavitation agent. The pharmacokinetics and biodistribution of 111-In-LPs were studied after intravenous administration to mice bearing MDA-MB-468 xenografts.

Results: US-mediated cavitation induced the release of 111-In-DTPA-EGF from LP-inside which was not the case when US was not applied. Clonogenic assays demonstrated selective cytotoxicity of LP-inside in MDA-MB-468 with over 99% reduction in colony survival when US-mediated cavitation was applied compared to controls. LP-outside were internalized in a dose-dependent manner with greater uptake in MDA-MB-468 than in MCF7 cells. More radioactivity was detected in the nuclei of MDA-MB-468 than MCF7 cells which confirmed the ability of 111-In-DTPA-EGF to reach its target is not prevented by its grafting to LP-outside. In vivo, the blood half-life of the radiopharmaceutical was increased by its encapsulation into LP-inside. This was not the case for LP-oustide probably due to direct EGFR targeting to the liver. In both cases, application of US to the tumour and SonoVue® administration significantly increased the tumour uptake (by 135% and 66% for LP-inside and LP-outside respectively).

#76

Application of a new large scale protein protein interaction screening method to the Onco-proteins PER2 and cMYC and two cMYC potential inhibitors

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Keywords : *Inhibitory molecules, Onco-protein, Onco-Signature*

Proteins are not working alone but in the context of intricate regulatory networks within the cell. These networks result from hundreds of protein-protein interactions, also called interactomes, which will change from cell-to-cell. Any protein function is therefore dictated by cell-specific interactomes, and many mutations affecting the activity of major regulatory proteins are supposed to affect the integrity of those interactomes. Capturing interactomes in the appropriate cell context is a longstanding challenge that requires developing new experimental approaches.

Our laboratory has developed an experimental strategy that allows screening human interactomes at the large-scale level in human living cells. The approach relies on the Bimolecular Fluorescence Complementation (BiFC) technology and has been recently patented. More particularly, I will present how our tools were used to reveal the transcriptional interactome of two proteins, c-MYC and PER-2. C-MYC is a well-characterized regulator of cell homeostasis and is involved in a number of cancers in human. PER-2 is a master regulator of biological rhythm and identified as a negative prognostic marker in several cancers.

Our screen against more than 1,000 transcription factors revealed common cofactors, underlying a common cancer signature composed of well-known onco-proteins such as P53 and MAPK14, but also other more specific candidates of c-MYC or PER-2, such as SOX14 and PIN1.

Finally, our tools are also compatible for the screening of inhibitory molecules. I will present results obtained with two c-MYC inhibitors, F4 and Omomyc, showing their range of activity with regard to the c-MYC transcriptional interactome.

#77

Identification par ENDOscopie SWIR des marges tumorales dans les Cancers des Voies Aériennes et Digestives Supérieures.

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Keywords :

Le Cancer des Voies Aériennes et Digestives Supérieures (VADS) est classé au 6ème rang des cancers. Les principaux traitements sont la chirurgie, la radiothérapie et la chimiothérapie.

Actuellement lors de l'exérèse chirurgicale, les marges tumorales sont définies par l'appréciation du chirurgien, complétée de l'analyse histologique extemporanée des recoupes tumorales.

L'exérèse complète du tissu tumoral, la détection des ganglions métastatiques et la préservation des tissus sains, sont des paramètres influençant considérablement le pronostic des patients.

L'étude menée à l'Institut pour les Avancées en Biosciences (IAB) propose d'étudier l'apport d'un système d'imagerie optique innovant fonctionnant dans le domaine du court infra-rouge (SWIR) pour la définition précise des marges tumorales per-opératoire. Ce système a pour but à terme de différencier le tissu sain du tissu pathologique en temps réel.

Nous comparerons les profils obtenus ex-vivo et in-vivo sur les différents tissus de souris et de tumeurs implantées en orthotopique avec l'aide de l'imagerie optique SWIR » afin de démontrer notre capacité à identifier la présence des tumeurs en imagerie per-opétatoire.

Nous souhaitons montrer que l'utilisation de l'imagerie optique SWIR lors de la résection chirurgicale des cancers des VADS permet d'obtenir des marges de qualité et une analyse du lit opératoire fiables, ainsi qu'une réduction du taux de récidive sans utiliser d'agent de contraste.

Recherche clinique, Bio-informatique, modélisation

#78

An Open smart digital platform to monitor multidimensional aspects of health status and quality of life after cancer immunotherapy, the QUALITOP project

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***Keywords** : Big Data; artificial intelligence; cancer immunotherapy; health status; quality of life; immune related adverse events*

Cancer immunotherapy brought about significant progress in cancer treatment. Nevertheless, two main challenges still impede improving cancer patients' health status and quality of life (QoL) after immunotherapy initiation: 1) a crucial need for 'predictive markers' of occurrence of immunotherapy-related adverse events (IR-AEs) to predict and improve patients' health status and promote their QoL; and, 2) the lack of knowledge on patients' QoL after start of immunotherapy outside randomised controlled trials.

The QUALITOP project aims at developing and implementing an IT-based European immunotherapy platform and using big data analysis, artificial intelligence, and simulation modelling approaches to collect and aggregate efficiently and effectively real-world QoL data, monitor patients' health status, conduct causal inference analyses, create harm-reduction recommendations for patients and other stakeholders, and disseminate the findings.

An open-access smart digital platform and a medical data lake will be developed to enable exchanging and sharing trusted and secure data with automated and robust controls based on FAIR (Findable, Accessible, Interoperable, Reusable) principles combining security and privacy-preservation of data. Heterogeneous data from different sources will be collected to conduct causal statistical analyses. Using machine learning approaches, nearly 'real-time' recommendations depending on the patient's profile and feedback on the platform will be drawn.

A wide panel of experts (clinicians, psychologists and sociologists who can integrate complementary dimensions of quality of life; professionals familiar with pharmacovigilance and pharmacists who can assess the incidence of adverse effects; and epidemiologists, data scientists, and economists) will collaborate to collect, gather and analyse data and produce endpoints regarding health status and quality of life after immunotherapy important to multiple interested stakeholders.

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#79

Primary phases of a framework to reconstruct a TP53 signaling network in the context of lung adenocarcinoma

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Keywords :

Background. Lung adenocarcinoma (LADK) is the most frequent form of non-small cell lung cancer [Herbst et al. Nature. 2018;553(7689):446-454]. Although smoking is the main cause of lung cancer, LADK is more common in never-smokers [Sun et al. Nat Rev Cancer. 2007;7(10):778-90]. Mutations in TP53, a tumor suppressor showing the highest mutation rate in cancer, occur in nearly half of LUAD [Hainaut et al. CSHP Med. 2016;6(11): a026179]. TP53 is involved in numerous biological processes (BP), and alterations in its function, caused by events such as mutations, up- or down-regulation by instance, trigger adverse effects. An exhaustive literature-based reconstruction of a robust and comprehensive TP53 signaling network lacks to fully assess the impact of such events in cell fate.

Methods. We selected LADK datasets from Gene Expression Omnibus and retrieved clinical and gene expression data on R environment. Batch effect was assessed with sva. Differential expression between LADK and controls retrieved significance (Benjamini-Hochberg False Discovery Rate, FDR) and fold change (FC) of genes with limma. We mined the Gene Ontology base for BP terms that include TP53 and less than 500 other genes, and retrieved the genes shared by at least 50 GOBP terms.

Results. Primary results of our pilot phase identified 5 LADK datasets that were merged and successfully adjusted for batch effect. A total of 832 genes were differentially expressed in LADK (FC>2 and FDR<5%) and 385 in controls. We found 475 GO terms involving TP53, and an overall total of 99 genes shared in 50 terms at least.

Conclusion. The pilot phase addressed several statistical and mining issues and provided encouraging insights to further consolidate a literature-based TP53 network with highlighted hotspots. Ongoing development will allow bridging of extensive clinical, expression, and drug datasets to unveil therapeutic opportunities in TP53 network.

#80

Prévalence à long terme de la neuropathie périphérique induite par l'oxaliplatine après une chimiothérapie adjuvante FOLFOX: étude transversale multicentrique

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***Keywords** : neuropathie périphérique chimio-induite ; cancer colorectal ; oxaliplatine*

L'oxaliplatine induit une neuropathie périphérique (OIPN) chez plus de 30% des patients, mais peu d'études décrivent la prévalence à long terme de cette OIPN. L'objectif fut d'évaluer la prévalence à long terme de l'OIPN chez des patients en rémission d'un cancer colorectal. Une étude transversale multicentrique a été conduite (16 centres) pour évaluer la prévalence de l'OIPN (QLQ-CIPN20) jusqu'à 5 après la fin d'une chimiothérapie adjuvante FOLFOX. La douleur neuropathique, l'anxiété et la dépression, et la qualité de vie ont été évaluées. Parmi les 409 patients inclus, 31.3% (IC95% [26.8 ; 36.0]) avaient une neuropathie de grade ≥2, et 26.6% durant la 5ème année. Parmi ces patients neuropathiques, 36.5% rapportaient des douleurs neuropathiques. Aucun n'était traité par duloxétine et seulement 3.2%, 1.6% et 1.6% étaient traités par prégabaline, gabapentine et amitriptyline. Les scores de neuropathies étaient corrélés négativement avec ceux de qualité de vie ($p<0.05$). Les proportions d'anxiété et de dépression étaient plus élevés chez les patients neuropathiques ($p<0.001$ et $p<0.01$). Au-delà de la prévalence élevée à long terme, l'étude a souligné la détresse psychologique

des patients neuropathiques et un manque de prise en charge de ces patients. Des efforts devraient être faits pour traiter ces neuropathies dans la 3ème population de survivants du cancer.

#81

Melanocytic tumors with MAP3K8 fusions: report of 33 cases with morphological-genetic correlations

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Keywords : *melanoma, spitz, MAP3K8*

The list of driver anomalies in cutaneous melanocytic tumors is currently expanding with the opportunity of performing mass genomic screening techniques on FFPE material. We report here a series of 33 skin lesions harboring gene fusions of the serine/threonin MAP3K8 kinase, which conserve an intact kinase domain but remove the C-terminal regulatory domain of MAP3K8. The great majority (31) of lesions were of spitzoid morphology, covering the full spectrum ranging from benign Spitz or Reed nevus morphology to malignant Spitz tumors including intermediate atypical stages. Atypical and malignant cases more commonly occurred in younger patients. In 13 (46%) of the sequenced cases, the 3' fusion partner was SVIL, a gene coding for supervillin, a very large protein, with both plasma membrane and actin cytoskeleton binding capacities. Interestingly, MAP3K8-SVIL cases are characterized by unusual morphologic features, namely an epidermal ulceration and a dermal component with giant multinucleated cells and focal dermal pigmented clones. Moreover, gene expression analysis revealed that MAP3K8 expression levels were significantly elevated compared to a control group of 57 Spitz lesions harboring other known tyrosine kinase fusions. Since these melanocytic tumors could present a metastatic potential and given that MAP3K8 fusions were also found in other tumor types with a more aggressive clinical behavior, a better understanding of the molecular mechanisms that underline the development of such tumors would be crucial to consider specific therapeutic agents of the MEK pathway.

#82

Corrélation entre les éléments figurés du sang et le taux de l'infiltration lymphocytaire tumorale chez les patientes atteintes d'un cancer du sein triple négatif

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Keywords : *Cancer du sein triple négatif, biomarqueurs circulants, TILs, NLR, rechute métastatique*

Le Cancer du Sein Triple Négatif (CSTN) représente 10 à 20% des cancers du sein. En raison de ses caractéristiques histologiques, les stratégies thérapeutiques sont limitées et les rechutes métastatiques sont fréquentes dans les cinq premières années après les traitements. Cependant, toutes les patientes diagnostiquées avec un CSTN ne développent pas de métastases. Il a été montré que les Lymphocytes infiltrant la tumeur (TILs) sont des biomarqueurs prédictifs de la réponse aux traitements et pronostiques fiables. Cependant, il est nécessaire d'identifier de nouveaux biomarqueurs prédictifs et pronostiques, plus facile à obtenir et à mettre en pratique. De nouvelles études se sont intéressées au rôle prédictif des éléments figurés du sang dans différents types de cancer. Dans ce contexte, nous avons mis en place l'étude PERCEPTION, évaluant la corrélation entre les TILs et les éléments figurés du sang chez les patientes atteintes d'un CSTN. L'objectif principal de l'étude est d'évaluer la corrélation entre les TILs sur la biopsie et le rapport Neutrophiles/Lymphocytes (NLR) avant les traitements chez les femmes atteintes d'un CSTN. Nous nous intéressons également à la corrélation entre les TILs sur la biopsie et les autres éléments figurés du sang avant les traitements et au moment de la chirurgie. De plus, nous évaluerons tous ces paramètres sanguins en tant que biomarqueurs précoces prédictifs et pronostiques dans le CSTN. Les patientes éligibles seront incluses dans l'étude PERCEPTION un an après la fin des traitements. Dans le cadre de l'étude, deux prélèvements sanguins seront réalisés, le premier à 12 mois post-radiothérapie et le deuxième au moment de la première rechute métastatique, le cas échéant. De nouveaux biomarqueurs prédictifs et pronostiques permettraient aux cliniciens de proposer des traitements alternatifs et des essais cliniques spécifiques aux patientes atteintes de ce type de cancer, afin d'améliorer la prise en charge et la survie.

#83

Radiation-induced side-effects in breast cancers: a DNA Repair Signature as a predictor of severe toxicity

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***Keywords** : DNA repair, Biomarkers, breast cancer*

Most of the patients suffering from solid tumors receive radiotherapy (RT) which can induce health tissues toxicity with wide variation in severity. Five to 10% develop severe toxicity that can heavily impact the individual's quality of life. The identification of predictive biomarkers enabling to discriminate patients at high risk of developing radiotoxicity is needed. This clinical proof-of-concept was conceived to identify blood radiotoxicity biomarkers based on a comprehensive analysis of several DNA repair activities. To this aim 162 patients with breast cancer who underwent RT were enrolled at the Lucien Neuwirth Cancer institute. All radio-induced adverse events were recorded up to 6 months after the end of the treatment. Three blood samples per patients were collected, before and early during the treatment course. By using LXRepair multiplexed assay Glyco-SPOT, we monitored the ability of enzymes contained in PBMCs (peripheral blood mononuclear cells) to repair series of DNA lesions immobilized on the biochip. Then, we analyzed the association between the obtained repair signatures and 1) the patient's life style (smoking and alcohol consuming), 2) the patient's characteristics (age, BMI) and 3) the occurrence of adverse effects (nature, grade). Preliminary analysis showed that the patients' life style, the age and also concomitant treatments impact the activities of DNA repair enzymes contained in PBMCs. We identified certain combinations of specific repair activities that differentiate patients with Grade 3 events. In ongoing analysis, we are evaluating the association between biomarkers and the risk of developing fibrosis in certain patients. Specific biomarkers related to Base Excision Repair showed promising association with the appearance of severe side-effects in breast cancers. Our functional multiplex repair assay represents a relevant strategy for rapidly identifying patients with potential radiosensitivity.

#84

Évaluation du profil protéique plasmatique en tant que biomarqueur prédictif de la rechute métastatique du cancer du sein triple négatif

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Keywords : *Cancer du sein triple négatif, biomarqueurs prédictifs, protéines circulantes, rechute métastatique*

Le cancer du sein triple négatif (CSTN) représente environ 10 à 20% des cancers du sein et se caractérise par l'absence d'expression ou par une très faible expression des récepteurs aux œstrogènes et à la progestérone ainsi que par l'absence d'amplification du gène codant pour HER2. Le CSTN est sans thérapie spécifique et possède un mauvais pronostic, ainsi la chimiothérapie, la radiothérapie et la chirurgie restent privilégiées. Les risques de rechute métastatique du CSTN sont fortement hétérogènes en matière de dynamique et de type de rechute. En effet, certaines rechutes peuvent être précoces, d'autres tardives et peuvent être associées à un taux de survie variable. Il existe donc un réel besoin de mettre en évidence des biomarqueurs prédictifs de la rechute métastatique et du type de rechute. Les métastases peuvent naître de la réactivation de cellules « dormantes » tumorales installées à distance du site tumoral primitif. Ainsi, la recherche de biomarqueurs prédictifs de métastases parmi les molécules circulantes semble pertinente. Il a notamment été démontré qu'une inflammation chronique peut faciliter la tumorigenèse au niveau du site tumoral primitif et des sites métastatiques. Mais aucune protéine circulante n'est à ce jour considérée comme la réactivatrice spécifique de ces cellules « dormantes ». Il a cependant été montré que des concentrations élevées de protéines impliquées dans l'inflammation, comme les interleukines 6 et 8, ou impliquées dans l'angiogenèse, comme l'angiopoietin-like protein, sont associées à un risque élevé de progression métastatique des cancers du sein. Dans ce contexte, nous proposons de réaliser une étude qui mesure les concentrations d'un ensemble de protéines circulantes (interleukines, angiopoietin-like protein, HER2...) dans l'objectif de rechercher des biomarqueurs prédictifs de la rechute métastatique du cancer du sein triple négatif.

#85

Dynamique structurale du complexes de récepteurs nucléaires PPARg-RXRa

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Keywords : *Molecular Simulation, Nuclear Receptors, Allostery, Bladder cancer*

Les récepteurs nucléaires constituent une large famille de protéines impliquées dans la transcription des gènes. Leur dysfonctionnement est associé à de nombreuses maladies (cancer, inflammation, diabètes...) ce qui fait de ces protéines des cibles thérapeuthiques importantes mais avec des effets secondaires souvent indésirables. Un précédent traitement du diabète à base de thiazolidinedione ciblant le récepteur PPARg a été retiré du marché car certainement impliqué dans l'accroissement du taux de tumeurs. De même, de récentes études ont montré que certaines mutations de ce récepteur ou de son partenaire RXRa sont associées à une augmentation de la transcription des gènes en l'absence de ligands activateur des récepteurs, et présentes dans certains cas de cancers de la vessie.

L'activité des récepteurs membranaires reposent sur un mécanisme allostérique permettant la communication entre leurs différents domaine (celui lié à l'ADN, au ligand, aux protéines co-activatrices). Les méthodes de dynamique moléculaire sont idéales pour décrire ces mécanismes et mieux comprendre le fonctionnement du complexe hétérodimère PPARg-RXRa avec ou sans ligand, sauvage ou muté. Toutefois, la structure complète de ce complexe n'est pas totalement établie: il existe une structure cristallographique, incomplète, et incompatible avec les données en solution (SAXS en particuliers). Nous présentons ici nos premiers résultats de dynamique moléculaire de ce complexe, tentant de comparer les différentes possibilités structurales.

#86

Simulation of the impact of nanoparticles on physical and chemical processes in the context of innovative radiotherapy

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Keywords : *Monte Carlo simulation , gold nanoparticle, electron interaction cross section*

One of the main challenges of radiotherapy is to deliver doses high enough to the tumor, keeping the dose to normal tissues as low as possible. Nanoparticles made of heavy metals, such as gold nanoparticles (GNP), have shown particularly promising radiosensitizing properties. An increase in dose deposition and free radicals production throughout the tumour (photoelectric effect) and at sub-cellular scale (Auger cascade) might be responsible for part of the effect for low-energy X-rays.

In a previous work, we finalized and validated Monte Carlo (MC) models capable to describe, for a simple system (nanoparticle of gold + water), the physico-chemical processes radio-induced by the presence of nanoparticles. The comparison of theoretical predictions with available experimental data for gold provided good results, both in terms of secondary electron production and energy loss. This code allowed us to quantify the energy deposited in nanotargets located near the GNP, which is correlated with the probability to generate damages at the sub-cellular scale. In parallel, Chen-Hui Chan has optimized functionalized gold nanoparticles at the nanoscale, from Density Functional Theory calculations with VASP, in various conditions of surface coverage for water and PEG molecules.

In this context, the objective of this work was to improve the databases on which the MC simulations are based, some of which are still missing or imprecise. To do that, we have calculated electron interaction cross section using electrostatic potentials for Au bulk and for GNP calculated with quantum physico-chemical calculations. We then performed MC simulations in order to evaluate the impact of these calculated cross sections in electron emission yields. The obtained results for the electron cross section would allow to enhance the available data for bulk Au and for GNP in the MC codes