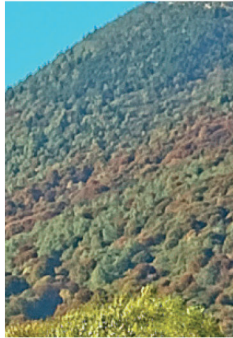
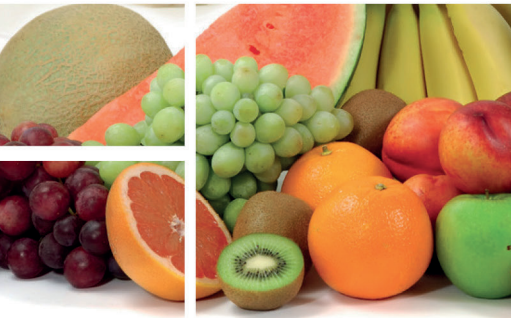


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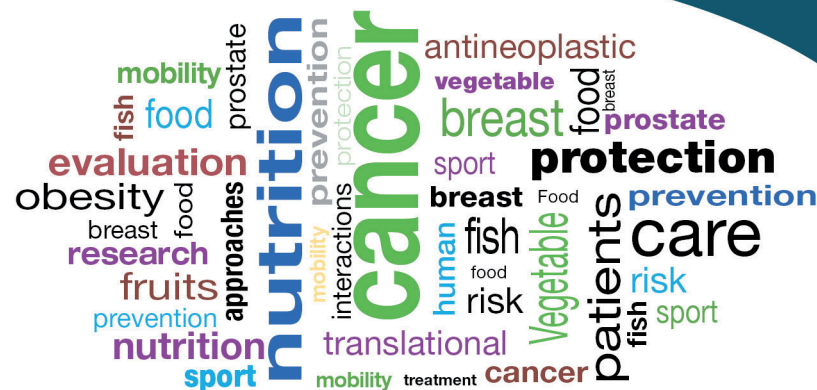
 **CRNH**
CENTRE DE RECHERCHE
EN NUTRITION HUMAINE
AUVERGNE

JUNE 22-23, 2017

FOURTH
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IN HUMAN
NUTRITION

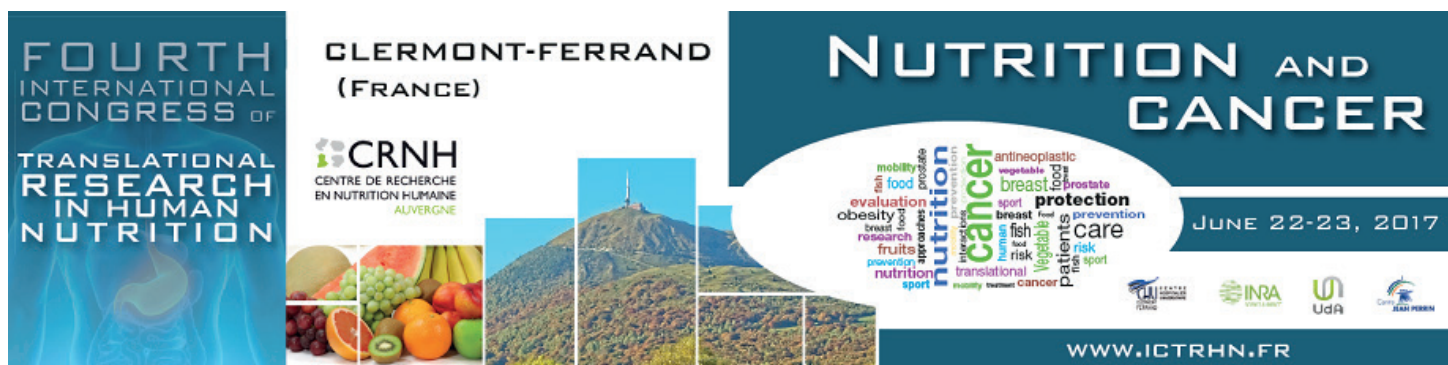


NUTRITION AND CANCER



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WELCOMING MESSAGE



Dear colleague, Dear friend,

The 4th International Congress of Translational Research in Human Nutrition focuses on Nutrition & Cancer with integrative approaches from basic science to clinical applications. Diet, in all its complexity, is considered as one of the major risk factors for cancer and is therefore a primary area of research.

Main topics during the 4th ICTRHN:

Nutritional and metabolic risk factors identified in the cancer development

Recent data highlight the underlying mechanisms of cancer prevention, the relationship between gene expression and dietary intakes, and the interplay between nutrition and the microbiome.

Nutritional care and diet support for the cancer patient during treatment

Most of cancer therapies induce side effects that affect eating and increase malnutrition risk. New individually-adapted care through nutrition, physical activity and weight management demonstrate benefits for patients in terms of quality of life and survival. In clinical settings, integrative approach is necessary to improve the understanding and management of complex nutrition-related pathological disturbances and their impact on therapy efficacy and disease recurrence.

Focus on breast and prostate cancers – Translational approaches

This meeting will take place in Clermont-Ferrand, the historic capital of Auvergne, famous for its volcanoes such as the «Puy de Dôme», its castles, Roman churches and local gastronomy.

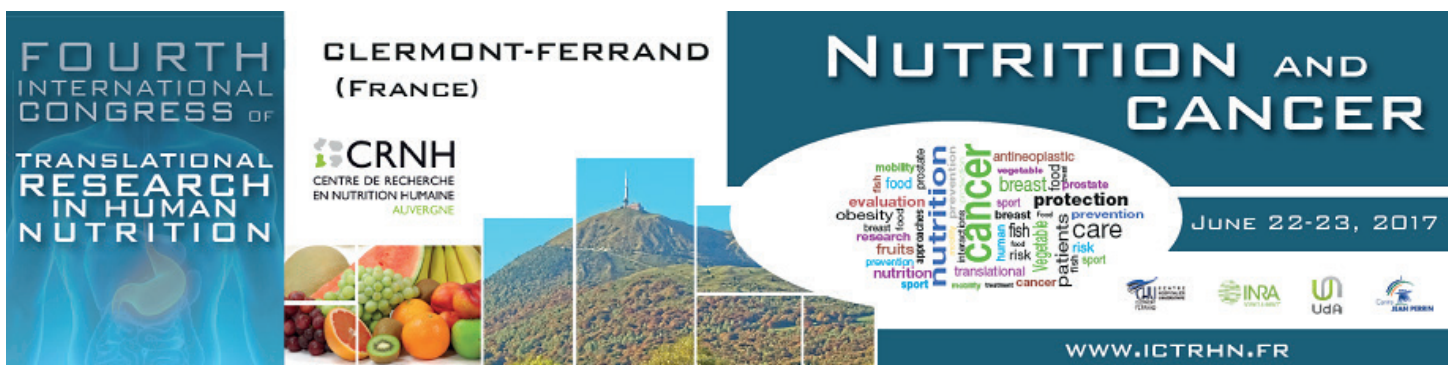
The scientific and organizing committees have set up an attractive scientific program with outstanding international speakers. We are happy to welcome you in Clermont-Ferrand and to make you discover the charms of Auvergne.

Marie-Paule Vasson
President of the congress



ACKNOWLEDGEMENT TO OUR SPONSORS





COMMITTEES

ORGANIZING



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 International Agency for
 Research Cancer
 Lyon - France



Paule Latino Martel
 NACRe Network
 Paris - France



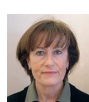
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Massimiliano Mazzone
 Vesalius Research Center
 Leuven - Belgium



Marie-Paule Vasson
 Centre Jean Perrin - INRA
 Clermont-Ferrand - France 7



GENERAL INFORMATION

CONGRESS VENUE



École Universitaire de Management
11 Boulevard Charles de Gaulle
63000 Clermont-Ferrand
Tramway stop: Lagarlaye

LUNCHES

June 22 - Lunch in the cafeteria (you will have to present your ticket distributed at the registration desk)
June 23 - Lunch in the Exhibition Hall (lunch box)

COFFEE BREAKS

Take advantage of the coffee breaks to meet our partners and read the posters.

POSTERS

The posters will be displayed in the Exhibition Hall.
6 thematic:

- Session 1 - Epidemiology - Nutritional prevention and cancer risk
- Session 2 - Nutritional care and physical activity for cancer patient
- Session 3 - Nutrition and antineoplastic interactions
- Session 4 - Breast cancer: from experimental approach to clinical
- Session 5 - Prostate cancer: from experimental approach to clinical
- Session 6 - Cancer-related malnutrition, metabolism, dysimmunity

GALA DINNER

Reservation necessary - Restaurant: «L'En-But» - Tramway stop: «Stade Marcel-Michelin»
People registered for the gala dinner will get a tram ticket with the badge.

SPEAKERS PRESENTATIONS

We will post speakers' presentations on the official website of the congress after the event (only those for which we have permission).

PROFESSIONAL CONGRESS ORGANIZER



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PROGRAM AT A GLANCE

THURSDAY JUNE 22, 2017

| | |
|----------------|---|
| 8.00-9.00 am | Welcoming participants |
| 9.00-9.15 am | Opening ceremony |
| 9.15-10.00 am | Opening lecture |
| 10.00-10.45 am | Coffee break - Exhibition Visit & Poster presentation Session 1 |
| 10.45-12.15 pm | Session 1 - Epidemiology - Nutritional prevention and cancer risk |
| 12.15-12.45 pm | Oral communication Session 1 |
| 12.45-2.00 pm | Lunch in the Cafeteria |
| 2.00-3.00 pm | Session 2 - Nutritional care and physical activity for cancer patient |
| 3.00-3.15 pm | Oral communication Session 2 |
| 3.15-4.15 pm | Coffee break - Exhibition Visit & Poster presentation Session 2 & Session 3 |
| 4.15-5.15 pm | Session 3 - Nutrition and antineoplastic interactions |
| 5.15-5.30 pm | Oral communication Session 3 |
| 5.45-7.15 pm | Visit of the Historic Center of Clermont-Ferrand |
| 7.30-11.00 pm | Gala Dinner - Restaurant «L'En-But» |

FRIDAY JUNE 23, 2017

| | |
|----------------|--|
| 8.30-9.00 am | Welcoming participants |
| 9.00-10.30 am | Session 4 - Breast cancer: from experimental approach to clinical |
| 10.30-11.00 am | Oral communication Session 4 |
| 11.00-11.30 am | Coffee break & Exhibition Visit |
| 11.30-12.30 pm | Session 5 - Prostate cancer: from experimental approach to clinical |
| 12.30-1.00 pm | Oral communication Session 5 |
| 1.00-1.45 pm | Lunch in the Exhibition Hall |
| 1.45-3.00 pm | Posters presentation Session 4, Session 5 & Session 6 |
| 3.00-4.30 pm | Session 6 - Cancer-related malnutrition, metabolism, dysimmunity |
| 4.30-5.00 pm | Awards for the best oral communication and poster Closing of the congress |

SCIENTIFIC PROGRAM

THURSDAY JUNE 22, 2017

8.00-9.00 am Welcoming participants

9.00-9.15 am **Opening ceremony**
Didier Attaix - Corinne Brugère-Malpuech - Ruddy Richard
CRNH Auvergne - Clermont-Ferrand, France

9.15-10.00 am **Opening lecture**



Vickie Baracos - Cross Cancer Institute, Alberta University - Alberta, Canada
The concurrent advancement of cancer nutritional science and oncology clinical practice

10.00-10.45 am **Coffee break - Exhibition Visit & Poster presentation Session 1**

10.45-12.15 pm **Session 1 - Epidemiology - Nutritional prevention and cancer risk**
Chair: Paule Latino-Martel & Massimiliano Mazzone



Pagona Lagiou - Athens University - Athens, Greece
Nutritional epidemiology of cancer: summary of the evidence, challenges and prospects.



Pietro Ferrari - IARC - Lyon, France
Are complex models in nutritional epidemiology always worth the trouble ?



Mathilde Touvier - Inserm/INRA/CNAM/Paris University, Paris, France
Beyond the current state of knowledge on nutrition and cancer risk: insights from the SUVIMAX and NutriNet-Santé cohorts.

12.15-12.45 pm **Oral communication Session 1**

Paule Latino-Martel - NACRe Network - Paris, France
Do alcoholic beverages, obesity and other nutritional factors modify the risk of familial colorectal cancer ? A systematic review

Sarah Lewis - University of Bristol - Bristol, United Kingdom
Does milk intake promote prostate cancer initiation or progression via effects on the insulin-like growth factor pathway ? A systematic review of a mechanism

12.45-2.00 pm **Lunch in the Cafeteria** (you've to present the ticket distributed with your badge)

2.00-3.00 pm

Session 2 - Nutritional care and physical activity for cancer patient

Chair: Yves-Jean Bignon & Pagona Lagiou



Martine Duclos - CHU Clermont-Ferrand - Clermont-Ferrand, France
Cancer : physical activity matters (prevention, treatment and survival) »



Emanuele Berardi - University of Leuven, Belgium
Global metabolic adaptations to physical activity in cancer-related cachexia

3.00-3.15 pm

Oral communication Session 2

Fabrice Kwiatkowski - Centre Jean Perrin - Clermont-Ferrand, France
Long-term adiposity control by a 2-week physical/nutritional intervention in SPA in naïve breast cancer patients treated by chemotherapy

3.15-4.15 pm

Coffee break - Exhibition Visit & Poster presentation Session 2 & Session 3

4.15-5.15 pm

Session 3 - Nutrition and antineoplastic interactions

Chair: Vickie Baracos & Xavier Durando



Bruno Raynard - IGR Villejuif - Paris, France
Fasting in cancer treatment: myth or reality ?



Romain Daillère - IGR Villejuif - Paris, France
Impact of gut microbiota in the tumoricidal activity of cyclophosphamide: *Enterococcus hirae* as an «oncomicrobiotic»

5.15-5.45 pm

Oral communication Session 3

James Thorne - University of Leeds - Leeds, United Kingdom
Towards a robust molecular understanding of how plant sterols could prevent metastatic relapse in Triple Negative Breast Cancer patients

Judith Passildas - Inserm U1240 UCA Centre Jean Perrin - Clermont-Ferrand, France
Multicenter randomized phase II study comparing docetaxel plus curcumin versus docetaxel plus placebo combination in first-line treatment of metastatic castration-resistant prostate cancer

6.00-7.30 pm

Visit of the Historic Center of Clermont-Ferrand

7.30-11.00 pm

Gala Dinner - Restaurant «L'En-But»

SCIENTIFIC PROGRAM

FRIDAY JUNE 23, 2017

8.30-9.00 am Welcoming participants

9.00-10.30 am **Session 4 - Breast cancer: from experimental approach to clinical**
Chair: Marie-Ange Mouret & Stephan Chevalier



Isabelle Romieu - IARC - Lyon, France
Life style and breast cancer



Samar Basu - University of Uppsala - Uppsala, Sweden
Eicosanoids, Inflammation and Proangiogenic factors in breast cancer: regulation by environmental enrichment.



Stephan Chevalier - INSERM - Tours, France
NaV sodium channel regulation by n-3 polyunsaturated fatty acids and PPAR β , consequences on breast cancer cell invasiveness

10.30-11.00 am **Oral communication Session 4**

Adrien Rossary - UMR 1019 INRA UCA - Clermont-Ferrand, France
Impact of physical activity on tumour immunity in C57BL/6 mouse syngeneic model of mammary cancer

Lucie Lécuyer - Inserm/INRA/CNAM/Paris University - Paris, France
NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer

11.00-11.30 am **Coffee break & Exhibition Visit**

11.30-12.30 pm **Session 5 - Prostate cancer: from experimental approach to clinical**
Chair: Silvère Baron & Amaia Zabala



Frédéric Bost - French Institute of Health and Medical Research - Nice, France
Energy restriction mimetics and prostate cancer



Amaia Zabala - CIC bioGUNE - Bizkaia, Spain
Cellular and systemic metabolic alterations impacting on prostate cancer biology

12.30-1.00 pm

Oral communication Session 5

Aurélie Charazac - C3M-U1065 - Nice, France

Quantitative image based analysis of endocrine disruptor effects on mitochondria morphology-function in prostate cancer cells

Judith Eguida - CNRS-UCA-IN2P3 - Clermont-Ferrand, France

Mitochondria: a new target for human prostate cancer cells radiosensitization ?

1.00-1.45 pm

Lunch box in the Exhibition Hall

1.45-3.00 pm

Posters presentation Session 4, Session 5 & Session 6

3.00-4.30 pm

Session 6 - Cancer-related malnutrition, metabolism, dysimmunity

Chair: Didier Attaix & Maurizio Muscaritoli



Massimiliano Mazzone - Vesalius Research Center - Leuven, Belgium

Metabolic control of tumor-associated macrophages: implications for cancer angiogenesis and immunity



Paolo Porporato - Molecular Biotechnology Center - Torino, Italy

Mitochondrial metabolism in cancer: impact on metastasis and progression



Maurizio Muscaritoli - Sapienza University of Rome - Rome, Italy

Cancer-related weight loss: from mechanism to treatment

4.30-5.00 pm

Awards for the best oral communication and poster

Arnaud Cutivet, CLARA - Guillaume Frasca, ARC Fondation

Closing of the congress

Florence Caldefie-Chézet - Adrien Rossary - Marie-Paule Vasson

ABSTRACT BOOK

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SESSION 1 - EPIDEMIOLOGY - NUTRITIONAL PREVENTION AND CANCER RISK

Paule Latino Martel - Oral communication - N°1

June, Thursday 22, 2017 - 12.15-12.30pm

Abstract title: Do alcoholic beverages, obesity and other nutritional factors modify the risk of familial colorectal cancer?

Email: paule.latino-martel@inra.fr

City: Jouy-en-Josas

Country: FRANCE

Authors: Anthony Fardet(1), Nathalie Druesne-Pecollo(2), Mathilde Touvier(2), Paule Latino-Martel(2)

Affiliations: (1) INRA, UMR 1019, UNH, CRNH Auvergne, F-63000 Clermont-Ferrand & Clermont University, University of Auvergne, Human Nutrition Unit, BP 10448, F-63000 Clermont-Ferrand, France. (2) Sorbonne Paris Cité Epidemiology and Statistics Research Centre (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 13 University, Nutritional Epidemiology Research Team (EREN), Bobigny, France; French Network on Nutrition and Cancer Research (NACRe Network), France

The abstract: Background: Familial cancers could result from inherited genes (either penetrant inherited syndromes or low-penetrance genes), environmental/lifestyle factors shared within the family especially between first degree relatives, or some combination of these. Individuals with family history of colorectal cancer are at higher risk of colorectal cancer than the general population. Until now, guidelines for familial colorectal cancer risk have only pointed at early diagnosis efforts via screening tests and surveillance, and payed scarce or no attention to lowering exposure to modifiable risk factors, notably nutritional factors.

Methods: We conducted a systematic review of epidemiological studies investigating the associations between nutritional factors, family history of colorectal cancer, and colorectal cancer risk. From the 5312 abstracts identified until December 2016, 184 full text articles were examined for eligibility. Finally, 31 studies (21 case-control, 9 cohort and 1 interventional studies) met inclusion criteria and were analyzed.

Results: Mainly, the combinations of family history of colorectal cancer and higher consumptions of alcoholic beverages, red or processed meat, or overweight/obesity increase the risk of colorectal cancer. Consistently, a strong increase is observed with the combinations of family history of colorectal cancer and unhealthy dietary patterns/lifestyles. Statistically significant interactions between these nutritional factors, family history of colorectal cancer and colorectal cancer risk are reported. This suggests that, in subjects with family history of colorectal cancer who are exposed to multiple nutritional risk factors, the probability that one (or several) risk factor(s) interact/act in synergy with one (or several) specific inherited genetic polymorphism(s) or single mutation(s) is very high.

Conclusions: For the first time, our findings highlight that addressing high consumption of alcoholic beverages, red or processed meat, and overweight/obesity, and more largely the exposure to multiple unhealthy dietary/nutritional behaviors could offer new perspectives of prevention to individuals with family history of colorectal cancer. A better information of these patients and of health professionals on these nutritional modifiable risk factors is recommended.

SESSION 1 - EPIDEMIOLOGY - NUTRITIONAL PREVENTION AND CANCER RISK

Sarah Lewis - Oral communication - N°2

June, Thursday 22, 2017 - 12.30-12.45pm

Abstract title: Does milk intake promote prostate cancer initiation or progression via effects on the insulin-like growth factor pathway? A systematic review of a mechanism

Email: s.j.lewis@bristol.ac.uk

City: Bristol

Country: UK

Authors: Sarah Lewis, Sean Harrison, Rosie Lennon, Jeff Holly, Julian PT Higgins, Mike Gardner, Claire Perks, Tom Gaunt, Vanessa Tan, Cath Borwick, Pauline Emmett, Mona Jeffreys, Kate Northstone, Sabina Rinaldi, Stephen Thomas, Suzanne Turner, Anna Pease, Vicky Vilenchick, Richard M Martin

Affiliations: 1School of Social and Community Medicine, University of Bristol, UK 2MRC Integrative Epidemiology Unit (IEU) at the University of Bristol, UK 3IGFs & Metabolic Endocrinology Group, School of Clinical Sciences at North Bristol, Southmead Hospital, BS10 5NB, Bristol, UK 4Nuffield Department of Population Health, University of Oxford, UK 5Cardiff University, Cardiff, UK 6CLAHRC West, University of Bristol, UK 7International Agency for Research on Cancer, Lyon, France 8School of Oral and Dental Sciences, University of Bristol, UK 9Department of Pathology, University of Cambridge, UK 10National Institute for Health Research Biomedical Research Unit in Nutrition, Diet and Lifestyle at University Hospitals Bristol NHS Foundation Trust and the University of Bristol, BS2 8AE, Bristol, UK

The abstract: We set out to systematically review the totality of evidence to determine whether the observed association between milk intake and prostate cancer operates via the insulin-like growth factor (IGF) pathway (including IGF-I, IGF-II, IGFBP-1, IGFBP-2 and IGFBP-3). In collaboration with WCRF UK, we developed a methodology for identifying and systematically reviewing mechanisms which may explain observed associations between diet and cancer. We used this methodology to collate data from all relevant studies examining associations of milk with IGF, and those examining associations of IGF with prostate cancer risk and progression. Data were extracted from experimental and observational studies conducted in either humans or animals, and meta-analysed where possible, with summary data presented in Albatross plots or tables otherwise. One hundred and seventy two studies met our inclusion criteria: 31 human studies examining the milk-IGF relationship; 132 human studies examining the IGF-prostate cancer relationship; and 10 animal studies examining the IGF-prostate cancer relationship. There was moderate evidence that circulating IGF-I and IGFBP-3 increase with milk (and dairy protein) intake (an estimated standardised effect size of 0.10 SD increase in IGF-I and 0.05 SD in IGFBP-3 per 1 SD increase in milk intake). There was also moderate evidence that prostate cancer risk increased with IGF-I (Random effects meta-analysis OR per SD increase in IGF-I: 1.09; 95% CI: 1.03, 1.16; N = 51 studies) and decreased with IGFBP-3 (OR: 0.90; 0.83, 0.98; N = 39 studies), but not with other growth factors. The IGFBP-3 -202A/C single nucleotide polymorphism was positively associated with prostate cancer (pooled OR for A/C vs AA = 1.22; 95% CI: 0.84, 1.79; OR for C/C vs AA = 1.51; 1.03, 2.21, N = 8 studies). No strong associations were observed for IGF-II, IGFBP-1 or IGFBP-2 with either milk intake or prostate cancer risk. The animal studies offered some support that the IGF pathway may be involved in prostate cancer, although the studies were small and very heterogeneous, so it was difficult to reach any conclusions from these. In conclusion, the IGF pathway is a potential mechanism underlying the observed associations between milk intake and prostate cancer risk, although limitations of study design mean that there is not strong support for this at present.

SESSION 1 - EPIDEMIOLOGY - NUTRITIONAL PREVENTION AND CANCER RISK

Dong Xia - Poster - N°3

June, Thursday 22, 2017 - 10.00-10.45am for the posters presentation

Abstract title: IMMUNOMODULATORY EFFECTS OF VITAMIN D: FOCUS IN THE GUT

Email: jeremie.talvas@udamail.fr

City: Clermont-Ferrand

Country: France

Authors: D Xia¹, S Rougé¹, N Goncalves-Mendes¹, MP Vasson^{1,2}, J Talvas¹

Affiliations: 1Clermont Université, UMR1019 UCA/INRA, Unité de Nutrition Humaine, CRNH-Auvergne, 2CHU Gabriel-Montpied, Centre Jean Perrin, Unité de nutrition, Clermont-Ferrand

The abstract: Introduction

Vitamin D deficiency is observed in more than 80% of the elderly in France and is correlated with the appearance of pathophysiological processes related to aging (cancers and inflammatory diseases). Owing to the expression of its receptor (VDR) in immuno-competent cells (immune cells and barrier cells), vitamin D has the capacity to modulate innate and adaptive immune responses. The richness of intestinal tissue in immuno-competent cells (GALT: Gut Associated Lymphoid Tissue) makes this organ as a preferred target of the anti-inflammatory effects of vitamin D. Several epidemiological studies have yet established a correlation between vitamin D deficiency and the risk of developing a Chronic Inflammatory Bowel Disease and colorectal cancer.

Objectives

This study aims to assess immunomodulatory effects of vitamin D in the ileum of depleted and supplemented young and old rats.

Methods

After 2 weeks acclimatization, 6 male Wistar rats aged 2 months and 8 rats aged 18 months were divided into 3 groups: Young control group (n = 6): 1 IU vitD / g diet; Elderly control group (n = 4): 1 IU vitD / g diet;- Elderly supplemented group (n = 4): 10 IU vitD / g diet.

The rats were sacrificed after 3 months of diet and ileum was removed. These tissues were disrupted and subjected to a transcriptomic analysis targeted on genes of the metabolism of vitamin D and immunity in order to characterize the immune and inflammatory profile of intestine.

Results

Our data demonstrated an overexpression of CYP24A1 with aging. This hydroxylase is known to inactivate vitamin D. Supplementation of vitamin D reduced its expression. Nevertheless, there was not significant difference of VDR expression between young and elderly rats, which remained at the same level after supplementation.

mRNA expression levels of cathelicidin, IL6 and NFkB (p65) significantly increased in the elderly group. Supplementation of vitamin D significantly decreased expression of these pro-inflammatory molecules.

Conclusion

Aging is accompanied by a major degradation of active form of vitamin D and an inflammation status at the intestinal level. This inflammation could contribute to a major risk of carcinogenesis. Supplementation of vitamin D is able to limit the pathophysiological effects associated with aging, such as the appearance of low grade inflammatory status. A better understanding of the regulatory mechanisms induced by vitamin D in gut will enable us to acquire new knowledge useful in the prospects of a re-evaluation of the vitamin D requirements of the elderly population or even the systematic administration of a complementation.

SESSION 1 - EPIDEMIOLOGY - NUTRITIONAL PREVENTION AND CANCER RISK

Philippine Fassier - Poster - N°4

June, Thursday 22, 2017 - 10.00-10.45am for the posters presentation

Abstract title: Variations of body weight, physical activity, and dietary and alcohol intake between before and after cancer diagnosis: results from the prospective population-based NutriNet-Santé cohort

Email: p.fassier@eren.smbh.univ-paris13.fr

City: Bobigny

Country: France

Authors: Philippine Fassier, Laurent Zelek, Patrick Bachmann, Marina Touillaud, Nathalie Druesne-Pecollo, Pilar Galan, Patrice Cohen, Hélène Hoarau, Paule Latino-Martel, Serge Hercberg, Mathilde Touvier

Affiliations: Sorbonne Paris Cité Epidemiology and Statistics Research Center (CRESS), Inserm U1153, Inra U1125, Cnam, Paris 5, 7 and 13 Universities, Nutritional Epidemiology Research Team (EREN), Bobigny, France

Presenting author: Mathilde Touvier

The abstract: Funding: French National Cancer Institute (INCa), French Nutrition Society (SFN) and Cancéropôle Ile-de-France.

Background: Diet, alcohol intake, physical activity, sedentary behavior and weight status are modifiable risk/protective factors that may impact prognosis, risk of recurrence and mortality in cancer survivors. Our aim was to quantify the variations of these nutritional parameters between before and after cancer diagnosis and their determinants in a prospective population-based cohort.

Methods: Subjects were incident cancer cases diagnosed in the NutriNet-Santé cohort between 2009 and 2016 (n=1051). Nutritional and anthropometric data were prospectively collected every 6 months since baseline (i.e. an average of 2y before diagnosis) with validated tools. Variations were assessed using mixed models. Factors associated with these variations were investigated by multivariable logistic regressions.

Results: In average, weight loss was observed in men (-3.54kg) and in colorectal cancer patients (-3.94kg), while breast (2.83kg) and skin (2.96kg) cancer patients tended to gain weight after diagnosis. Socio-demographic and economic factors strongly influenced the risk of weight gain. Women, those with induced menopause, younger patients, lower educated, overweight before diagnosis and who stopped smoking after diagnosis were more likely to gain weight. Overall (-32.8MET-h/week) and vigorous (-21.1MET-h/week) physical activity decreased after diagnosis, especially in prostate and skin cancers, men, those professionally inactive, and with higher physical activity before diagnosis. Overweight patients were more likely to decrease moderate physical activity and walking. Sitting time increased (+2.44h/d), especially in women, older patients, and those professionally inactive. We observed a decrease in intakes of vegetables, dairy products, soy products, sweetened soft drinks, and alcoholic drinks, and an increase of broth and fats/sauce intakes (all p<0.05). Resulting variations in nutrient intakes were assessed.

Conclusions: This large prospective study suggests that cancer diagnosis is a key period for change in nutritional behavior. It provides insights to target the sub-groups of patients requiring higher nutritional care.

Keywords: Weight, physical activity, diet, alcohol, cancer survivors

SESSION 1 - EPIDEMIOLOGY - NUTRITIONAL PREVENTION AND CANCER RISK

Claudine Manach - Poster - N°5

June, Thursday 22, 2017 - 10.00-10.45am for the posters presentation

Abstract title: Metabolomics applied to nutritional epidemiology to identify biomarkers of food intake in the framework of the Metabo-Breast cancer project, SU.VI.MAX cohort

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The abstract: The work presented is part of the Metabo-Breast cancer project (2015-2017, INCa, P.I. M. Touvier), which aims at 1) discovering predictive biomarkers of breast cancer using metabolomics 2) identifying biomarkers of the quality of the usual diet and of specific foods with putative health effects and 3) relating these biomarkers to enhance our understanding of the role of nutrition and specific dietary factors on breast cancer. Here we focus on the objective of discovering biomarkers of food intake by the exploration of the food metabolome in serum samples from the SU.VI.MAX cohort, using high-resolution mass spectrometry. Untargeted metabolomics is a holistic, data-driven approach that has proved efficient to discover dietary biomarkers through the comparison of the comprehensive profiles of plasma or urine metabolites from subjects differing according to their dietary habits or recent food consumption (Scalbert et al., AJCN 2014).

SU.VI.MAX female subjects who filled at least ten 24h dietary records during the first 2 years of follow-up were stratified in deciles according to their level of adherence to the guidelines of the Programme National Nutrition Santé, assessed by the score PNNS-GS previously described (Estaquio et al., JADA 2009) but not taking into account the physical activity component. A total of 80 women, aged 48±6.4 years old was randomly selected in the 10th decile of the PNNS-GS distribution and 80 women matched for age, baseline menopausal status, BMI, smoking and season of blood draw were selected in the 1st decile.

Plasma samples collected at baseline in the SU.VI.MAX study were analyzed using Ultra Performance Liquid Chromatography (UPLC) coupled with a quadrupole time of flight mass spectrometer (QToF, Impact II Bruker), equipped with an electrospray ionization source. Metabolic profiles were acquired in both positive and negative modes with a scan range from 50 to 1,000 mass-to-charge ratio. Data were pre-processed using Galaxy workflow4metabolomics.

A total of 1575 and 601 signals (ions) were detected in positive and negative mode, respectively. Metabolomics profiles were compared using univariate and multivariate statistical methods (ANOVA with Benjamini-Hochberg (BH) correction, PCA, HCA, PLS, correlation analyses adjusted for energy intake) to determine the ions associated with the PNNS-GS, some specific components of the score and with the level of consumption of 58 foods/food groups assessed with the FFQ.

84 ions in positive mode and 30 ions in negative mode were found correlated with specific foods/food groups ($r > 0.3$, p-value with BH < 0.1). A few of them were expected such as trigonelline, paraxanthine, actractyligenin glucuronide, known as candidate biomarkers of coffee intake and proline betaine for orange intake discovered in previous metabolomics studies. This demonstrates the relevance of our strategy. The identification of the other candidate biomarkers is ongoing. It is based on search in various in-house and online databases and literature as well as on complementary analyses with MS/MS fragmentation using an ultra-high resolution LTQ-OrbiTrap mass spectrometer and analysis of the standard when available. This work will provide a range of new candidate biomarkers of food intake that are crucially needed to improve the quality of dietary assessment in epidemiological studies.

This project was supported by the French National Cancer Institute (grant n° INCa_8085 for the project, PhD grant n° INCa_11323 for L. Lecuyer), and received the label of the French network for Nutrition And Cancer Research (NACRE, www.inra.fr/nacre).

SESSION 1 - EPIDEMIOLOGY - NUTRITIONAL PREVENTION AND CANCER RISK

Thomas Ferreira - Poster - N°6

June, Thursday 22, 2017 - 10.00-10.45am for the posters presentation

Abstract title: Analysis method of omics data for metabolic interactions modeling in predictive carcinogenesis

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The abstract: Background: Currently research focus on the identification of precece biomarkers is important in the field of Health especially in carcinogenesis. Indeed, specific biomarkers could be crucial to predict the first steps of cancer appearance and to improve cancer prevention and care. In that goal, omic approaches are massively used generating a large amount of data. Our understanding of these data flows become difficult, so it is necessary to develop adaptive tools in order to treat and apprehend them. In many omic studies on cancer-metabolism profiling, discriminant compounds are implicated in energetic pathways such as lipids, glutamin and creatin. For example, lipids are largely used for cancer cell membranes building and undergo a lesser energetic oxidation. Thus, lipids could be used to help for detection of pre cancer steps.

Objective and Methods: This study aims to discern the role of metabolic biomarkers of interest in the first step of carcinogenesis. After identification of biomolecules from MS and NMR metabolomic data, we will modelize using softwares allowing dynamic view such as Metaboflux which analyzes flux distribution in metabolic networks, Cytoscape, an open source software, or MetExplore a web server linking metabolomic experiments and genome-scale metabolic networks. We will compare the limits of each software in order to implement the most appropriate to modelize metabolic interactions in predictive carcinogenesis. In this aim, three file formats i.e. Systems Biology Markup Language, JavaScript Object Notation and MAT a format for MATLAB, will be tested.

Conclusion: Despite of the existing softwares, most of them do not allow a dynamic visualization of metabolic pathways. That's why our study plans to implement the most appropriate tool in order to optimize the dynamic modeling of metabolic interactions.

SESSION 2 - NUTRITIONAL CARE AND PHYSICAL ACTIVITY FOR CANCER PATIENT

Fabrice Kwiatkowski - Oral communication - N°7

June, Thursday 22, 2017 - 3.00-3.15pm

Abstract title: Long-term adiposity control by a 2-week physical/nutritional intervention in SPA in naïve breast cancer patients treated by chemotherapy

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The abstract: About half of breast cancer patients gain weight during chemotherapy (Demark-Wahnefried, 1993; Saquib, 2007) and only 10% recover their initial weight. A >5% weight gain during chemotherapy has been associated to 12% increase of global mortality risk (95%CI = [3-22]) (Playdon, 2015). Lower levels of physical activity (PA) contribute to this weight gain: 75% of cancer survivors exhibit insufficient PA levels (Bellizzi, 2005). Recently, a meta-analysis has evidenced that PA \geq recommended level was associated to 46% [24-62] decrease of global mortality risk and 33% [10-50] of specific mortality (Lahart, 2015). We designed an original physical/nutritional intervention to promote PA and favor weight control.

Methods:

We tested, within a prospective randomized controlled trial, a 2-week intervention in SPA centers including physiotherapy, supervised physical activity and nutritional education: it enrolled 251 breast cancer patients post-chemotherapy in complete remission. Anthropometric measures were collected by nutritionists (weight, waist girth, body composition by impedanceometry) at inclusion and 6, 12, 18, 24 and 36 months post-inclusion. At each consultation, patients were encouraged to practice PA. Patients answered questionnaires at same periods, in particular Ricci & Gagnon questionnaire (Walger, 2009) to evaluate their physical/sedentary activities.

Results:

At inclusion, 44% of patients had a PA satisfying recommendations. Between 6 months and 3 years, 78% of them followed recommendations, independently of allocation group ($p = 0.94$). Caloric inputs decreased significantly ($p = 0.00029$), but similarly in both groups ($p = 0.94$). Compared to the control group, weight decrease observed after intervention lasted 2 years: -2.7% at 1 year ($p=0.0085$), -2.5% at 2 years ($p=0.025$); for waist girth resp. -2.4% ($p=0.000014$) and - 1.3% ($p=0.0072$). In multivariate analysis, several parameters correlated weight control: higher PA level ($p < 10^{-7}$), higher initial BMI ($p = 0.0000045$), allocation to the SPA group ($p = 0.000017$) and the % reduction of caloric intakes compared to baseline ($p = 0.00002$). Age, menopausal status and hormonotherapy were not significant.

The reduction of waist girth correlated almost same parameters: allocation to SPA group ($p = 2 \cdot 10^{-7}$), higher PA level ($p = 0.000002$), younger age ($p = 0.003$), smaller initial IMC ($p = 0.025$), and lower caloric intakes ($p = 0.028$).

Conclusion:

Our 2-week intervention in Spa demonstrated a significant impact on anthropometric outcomes lasting 2 years, permitting both a reduction of caloric inputs and increased PA levels. Nutritionists' advices seemed to promote PA and food reduction as well as intervention, but impacts were mediated by the 2-week SPA stay, indicating that new strategies can catalyze motivations to adopt more efficient life habits. New researches are necessary to evidence which part of psychoeducational intervention can favor this particular aspect.

SESSION 2 - NUTRITIONAL CARE AND PHYSICAL ACTIVITY FOR CANCER PATIENT

Carmen Dupuis - Poster - N°8

June, Thursday 22, 2017 - 3.15-4.15pm for the posters presentation

Abstract title: Effect of betaine, C-phycoyanin or physical activity on tumour growth of lung cancer in rats.

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Presenting author: Marc Filaire

The abstract: Oxidative stress seems to play a crucial role as a secondary messenger in the regulation of several cellular processes such as apoptosis, survival and proliferation, and could be involved in all steps of the lung carcinogenesis (i.e. initiation, promotion and progression). Physical activity and nutrition are two factors able to modulate oxidative stress and associated mechanisms. Betaine and C-phycoyanin are two known micronutrients having antioxidant, anti-inflammatory and anti-proliferative effects. Previously, our team showed that betaine and/or C-phycoyanin treatment decreased the viability of A549 cells in vitro (pulmonary adenocarcinoma cell line).

The main objective of this work was to evaluate the effect of nutritional factors (betaine, C-phycoyanin or physical activity) on growth of implanted A549 cells in Nude rats and to determine underlying mechanisms.

Firstly, we showed that these two micronutrients, whether associated or supplied separately, slowed down the lung tumour growth through similar mechanisms (NF- κ B activation and increase of lipid peroxidation and expression of pro-inflammatory cytokines (IL-1, Cox-2 et TNF-) in tumour). Also, some mechanisms were specific for each micronutrient or their combination. C-phycoyanin induced a decrease of phosphorylated AKT / total AKT ratio, and an increase of phosphorylated p38 / total p38 ratio, both mechanisms promoting apoptosis and autophagy. On the other hand, betaine associated with C-phycoyanin increased caspase-3 / pro-caspase-3 ratio.

Secondly, we studied the effect of voluntary physical activity on growth of implanted A549 cells in Nude rats. We showed that voluntary physical activity slowed down the lung tumour growth, without significant difference if animals were supplied with betaine or/and C-phycoyanin. It seems that the increase of lipid peroxidation, NF- κ B and p38 activation, and AKT inhibition, all having a role in promotion of a cell death, are responsible for the tumour growth slowdown following the physical activity.

Diet enriched with betaine or/and C-phycoyanin slows down the growth of pulmonary adenocarcinoma cells implanted in rats, suggesting their interest in anti-cancer activity. Physical activity seems to act on similar mechanisms as these micronutrients. Our results have to be confirmed with further studies, but are already suggesting a potential application in lung cancer patients.

SESSION 2 - NUTRITIONAL CARE AND PHYSICAL ACTIVITY FOR CANCER PATIENT

Delphine Le Guennec - Poster - N°9

June, Thursday 22, 2017 - 3.15-4.15pm for the posters presentation

Abstract title: Impact of high fat diet and physical activity on tumor's inflammation and oxidative stress in a model of C57BL/6 mouse

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The abstract: Background: Accumulative evidences link breast cancer development to obesity. Several studies have demonstrated an increase of Reactive Oxygen Species (ROS) production and a decrease of antioxidant capacity resulting in an oxidative stress and a low-grade inflammation in overweight. Many epidemiologic studies have found an inverse association between physical activity and breast cancer risk, particularly for post-menopausal woman. Therefore, biological mechanisms underlying the relationship between oxidative stress, low-grade inflammation due to obesity and breast cancer are poorly understood.

Objectives: In this study, we proposed to explore the link between oxidative stress, inflammation and mammary tumor growth in a model of elderly ovariectomised mice feeding with high fat diet (HFD) and housing in enriched environment (EE).

Materials and methods: C57BL/6 mice (33 weeks) were divided in 2 groups, both fed with HFD: one housing in EE for stimulate spontaneous physical activity and the other in standard environment (SE). After eight weeks, mammary tumor cells (EO771) were implanted into the fourth right mammary gland by fat-pad technique. Tumor growth was measured twice a week with a caliper. Based on tumor-volume limit point, animals were sacrificed during a 4 weeks time-window (between 3rd and 6th week after tumor implantation). Tumors were recovered for antioxidant enzymes determination (i.e. heme oxygenase (HOx), thioredoxine reductase (TRx), glutathione reductase (GR), glutathione S-transferase (GST), glutathione assays...) and for measurement of inflammation (lipid peroxidation, isoprostanes and cyclooxygenase 2 (COX2) activity).

Results: After 2 weeks of tumor growth, mice housing in EE presented lower tumor volume (1241 ± 743 vs 634 ± 388 mm³, $p = 0,039$). At the sacrifice, despite a similar weight ($1,44 \pm 0,64$ vs $1,87 \pm 0,64$ g) between SE and EE, some differences in anti-oxidant response were observed. HOx and TRx activities were decreased in EE conditions (26 ± 12 vs 18 ± 6 mUI/g, $p = 0,038$ and 68 ± 28 vs 62 ± 21 mUI/g, $p = 0,111$), contrary to GR and GST activities which were not affected by EE. The reduced/total glutathione ratio tended to increase with EE ($0,25 \pm 0,19$ vs $0,28 \pm 0,12$, $p = 0,117$). Regarding tumor inflammation, lipid peroxidation was not impacted by EE while isoprostane content increased ($3,9 \pm 5,7$ vs $7,1 \pm 13$ ng/g, $p = 0,069$) and COX2 activity tended to reduce in this condition ($7,6 \pm 2,9$ vs $6,3 \pm 3,2$ mUI/g, $p = 0,083$).

Conclusion: An increase of reduced glutathione and a decrease of thioredoxine reductase activity correlate to a lesser requirement for protection in cells. The reducing of COX2 and HOx activities seems to demonstrate an inflammation decrease. Taken together, these results suggest that physical activity is able to reduce tumor growth, due to a modification in tumor oxidative stress and inflammation.

SESSION 2 - NUTRITIONAL CARE AND PHYSICAL ACTIVITY FOR CANCER PATIENT

Marie-Chantal Farges - Poster - N°10

June, Thursday 22, 2017 - 3.15-4.15pm for the posters presentation

Abstract title: Mammary tumor growth limits spontaneous physical activity in high-fat diet fed mice housed in an enriched environment

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The abstract: Aim: Excess weight and several pathological diseases such as cancer alter the total energy expenditure including both the resting and the activity energy expenditure. Moreover, the regular physical activity is considered as a protective factor in numerous physio-pathological situations. This study was designed to assess whether physical and social environment enrichment induces differential effects on tumor growth, and to determine their relation to metabolic consequences.

Methods: 33-week-old C57BL/6 mice were randomly assigned to a high fat diet (HFD: 4.3 kcal/g, 45% of lipids, n=10/group/2 groups) or a standard diet (SD, 3.4 kcal/g, 10% lipids, n=10/group/2 groups). Among each diet group, mice were housed in an enriched environment (EE) or in standard laboratory environment (SE). After, 4 weeks of diet, the syngeneic EO771 spontaneous mammary adenocarcinoma cell line (5x10⁵ cells) was orthotopically transplanted into the fourth right mammary gland. Tumor was allowed to growth during 1 month. Body weight, body composition (indirect calorimetry) and tumor growth were measured throughout the experiment. Mice spontaneous activity was evaluated by the PhenoMaster/LabMaster system (TSE System, Bad Homburg, Germany) connected to the calorimetric cages. Total spontaneous activity corresponded to the sum of vertical (z) and horizontal positions (xy). The distance covered by the mice were recorded during 1 week. Cages were or not equipped with a nest fixed in height or a running wheel to mimic respectively the EE and SE conditions. Data are presented as mean \pm SD, statistical analysis were made using the Mann Whitney test. Results: In SE housing, individual horizontal movements were of 22 ± 8 m/h and vertical moving were 240 ± 60 passages/h. In the EE conditions, horizontal movements decreased to 11 ± 5 m/h/mouse whereas vertical passages increased to 556 ± 83 passages/h/mouse ($p < 0,05$). This effect was related to the presence of the nest in height favoring and limiting z and yz movements. Expressed in % of the SE conditions, the total spontaneous activity was enhanced by 40% ($p < 0,05$). HFD comparatively to the SD was associated to a 39% reduction in the spontaneous locomotor activity ($p < 0,05$) and to an increase in fat mass (30 vs 11%, $p < 0,01$). After tumor implantation, HFD induced a higher tumor growth (1114 ± 793 vs 384 ± 339 mm³ at day 16, $p < 0,05$) and a less spontaneous physical activity. In this condition, EE restricted both the tumor growth (663 ± 192 mm³ vs 1114 ± 793 , $p < 0,05$) and the loss in physical activity ($p < 0,05$). However, tumor bearing reduced significantly the distance covered during the nocturnal period independently of the diets and the housing conditions. Whatever the diet and the housing condition, the tumor reduced the spontaneous locomotor activity of the diurnal period. So tumor development affects nocturnal/diurnal locomotor cycle. Conclusion: Both diet-induced-overweight and tumor reduce the mice spontaneous locomotor activity. In this context of metabolic perturbations, the enrichment of the housing allow to maintain a locomotor activity which is associated to a health benefit. This mouse model will allow to explore over time the metabolic and molecular mechanisms associated to the physical activity and its impact in the mammary carcinogenesis.

SESSION 3 - NUTRITION AND ANTINEOPLASTIC INTERACTIONS

James Thorne - Oral communication - N°11

June, Thursday 22, 2017 - 5.15-5.30pm

Abstract title: Towards a robust molecular understanding of how plant sterols could prevent metastatic relapse in Triple Negative Breast Cancer patients

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The abstract: The financial cost of cancer treatment is a significant burden on societies around the world. It is increasingly apparent that government healthcare agencies do not have the resources to treat their way out of the crisis meaning cancer prevention is the only realistic solution. Cancer prevention falls into three distinct categories and “tertiary prevention” can be defined as a successful treatment that has stopped a local or distal metastatic recurrence. By combining existing therapies with nutritional guidance that is based on a clear and robust molecular understanding, disease-free survival rates of typically hard-to-treat cancers could be improved. The key requirements of a tertiary prevention strategy as part of a permanent lifestyle change are that any side effects should be well tolerated, and should be cheap and readily available. Ideally, dietary compounds that are already be available in consumer products at concentrations sufficient for therapeutic intervention would be utilised.

Elevated cholesterol is a risk factor for both cardio-vascular disease (CVD) and breast cancer (BC). A high phytosterol (PSS) diet reduces LDL-cholesterol by 15% and is used for clinical management of CVD. PSS are cholesterol like compounds and epidemiological evidence has suggested they protect against breast cancer. If true, this protection presumably comes from lowering systemic cholesterol thus restricting a fundamental factor for tumour growth and/or skewing of signalling pathways following enzymatic modifications to cholesterol. Such modifications include cholesterol side-chain oxidation product, or hydroxycholesterols (scOHCs), at least one of which drives metastatic phenotypes in culture through the Liver X Receptor (LXR) and promotes tumour proliferation as weak ER agonists.

Here we describe the range of scOHCs in primary breast tumours and show that the scOHC complement differs between TNBC and Luminal subtype. Treating BC cell lines with scOHCs at concentrations detected in tumours led to weak but robust activation of a stable LXR reporter. PSS inhibited scOHC-induced reporter activation as well as scOHC-dependent transcription profiles, positioning them as selective modulators of the LXR in breast cancer. Individual components of the tumour micro-environment (epithelial, fibroblast) were then examined and we observed regional differences in scOHC concentration that were dependent on BC-subtype dependent.

Our data reveal a paracrine network present in multiple BC-subtypes, containing related but distinct scOHC transcriptional profiles that control tumour biology critical for therapy evasion and spread. These pathways could be interrupted by dietary intake PSS. Given the acceptability of such an intervention to BC patients, we aim next to evaluate the accumulation of dietary PSS in tumour tissue and their impact on tumour biology in situ.

SESSION 3 - NUTRITION AND ANTINEOPLASTIC INTERACTIONS

Judith Passildas - Oral communication - N°12

June, Thursday 22, 2017 - 5.30-5.45pm

Abstract title: Multicenter randomized phase II study comparing docetaxel plus curcumin versus docetaxel plus placebo combination in first-line treatment of metastatic castration-resistant prostate cancer

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The abstract: Background: Prostate cancer is the most common cancer among men. When it becomes metastatic, patients are first treated by hormone therapy in first line. Hormone refractory patients are then treated by chemotherapy with docetaxel as the standard chemotherapy regimen for prostate cancer (Tannock et al., 2004). This study tend to evaluate the efficacy of docetaxel combined with curcumin, a polyphenolic derivative extracted from *Curcuma longa* root, as a first-line treatment for metastatic castration resistant prostate cancer (CRPC) patients. Curcumin is known to have many antineoplastic properties such as antiproliferative, antiangiogenic and anti-invasive effects (Aggarwal et al., 2008). A phase I study has been conducted in advanced and metastatic breast cancer in Jean Perrin Comprehensive Cancer Center and revealed that the recommended dose of curcumin is 6,000 mg/d for seven consecutive days every 3 weeks in combination with a standard dose of docetaxel (Bayet-Robert et al., 2010). These encouraging results have permitted to conduct a phase II study which produced additional data on curcumin as a treatment for cancer, with a high response rate, good tolerability and patient acceptability (Mahammedi et al., 2016). It justifies the interest to conduct a randomized phase II trial to compare docetaxel plus curcumin versus docetaxel plus placebo combinations.

Objectives: The main objective of this study is to evaluate the efficacy of docetaxel and curcumin association in metastatic CRPC. Among the secondary objectives, we evaluate the PSA response rate, the objective tumor response rate, quality of life, pain and tolerance.

Methods: Patients receive docetaxel in standard conditions for 6 cycles in combination with per os curcumin, 6,000 mg/day (day -4 to day +2 of docetaxel). Self-questionnaires are used to evaluate the quality of life and pain. One hundred chemotherapy-naive and metastatic CRPC patients are planned to participate in this study and an interim analysis will be conducted after the enrolment of 50 patients.

SESSION 3 - NUTRITION AND ANTINEOPLASTIC INTERACTIONS

Agatha Pawlik - Poster - N°13

June, Thursday 22, 2017 - 3.15-4:15pm for the posters presentation

Abstract title: Prometastatic activity of calcitriol and its analogs in 4T1 mouse mammary gland cancer model

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Presenting author: André Mazur

Prometastatic activity of calcitriol and its analogs in 4T1 mouse mammary gland cancer model

The abstract: Emerging evidence indicates that vitamin D deficiency is correlated with an elevated incidence of breast carcinoma and is a negative prognostic factor. Furthermore, low vitamin D status increases after adjuvant cancer therapy, affecting bone metabolism and increasing the risk of osteoporosis. It is believed that vitamin D supplementation in breast cancer treatment delays the recurrence of cancer, thereby extending survival of patients. In this study, we examined the impact of calcitriol and its low-calcemic analogs, PRI-2191 and PRI-2205, on the tumor growth and metastasis in BALB/c female mice bearing 4T1 mouse mammary gland cancer. We found that experimental treatments increased the lung metastasis foci formation without influencing the primary tumor growth. The level of tumor osteopontin was elevated after these treatments. Moreover, tumor blood perfusion was improved, whereas vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF β) levels were decreased in tumors from treated mice.

In conclusion, calcitriol and its analogs enhanced the metastatic potential of 4T1 mouse mammary gland cancer by inducing the secretion of osteopontin. Additionally, tumor osteopontin overexpression prevailed over the decreasing tumor TGF β level and blood vessel normalization.

This project was funded by the Polish National Science Center granted on the basis of the decision number DEC-2013/11/B/NZ5/00162.

SESSION 3 - NUTRITION AND ANTINEOPLASTIC INTERACTIONS

Laetitia Delort - Poster - N°14

June, Thursday 22, 2017 - 3.15-4:15pm for the posters presentation

Abstract title: Impact of adipocytes and their secretome on the effectiveness of hormone therapy in breast cancer associated with overweight

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The abstract: Obesity, an established risk factor for breast cancer in postmenopausal women, is also responsible for higher rates of recurrence and mortality. In this context, our work evaluates the impact of the adipocyte secretome (AS) in the lesser response to hormone therapy.

For this, 1 / mammary cancer cells were either co-cultured with human adipose stem cells (hASC) (hMAD cell line) differentiated into mature adipocytes (MA) or cultured in the presence of hMAD conditioned media (CM), and then treated or not with an anti-estrogen treatment (anti-E, Tamoxifen Tx or Fulvestrant Fv). Cell proliferation was measured by a fluorescence test using resazurin (Fluoroskan Ascent FL[®], n=3) and followed in real time by impedancemetry (iCELLigence, n=3). 2 / The impact of overweight was assessed ex vivo using differentiated MAs from ASC of thin or obese women cultured in the presence of MCF-7 and Fv.

In our different models, AS was able to increase the proliferation of MCF-7 cells, positive for the estrogen receptor (ER+), and to totally inhibit the antiproliferative effect of Tx and Fv. The use of MDA-MB-231 (RE- cells) showed that AS increased cell proliferation and counteracted the antiproliferative effect of Tx but not Fv. These results suggest that the observed effects were not exclusively mediated through the ER pathway.

On the other hand, using AMs of thin and obese women, only the obese women AS could decrease the efficacy of the Fv. This effect was accompanied by an increase in the expression of the OB-R gene.

Thus, these preliminary results suggest that AS could reduce the effectiveness of hormone therapy, and more markedly in the case of overweight. This could contribute to the tumor escape process and to the majored risk of recidive in overweight situation. Project funded by INCA, Mammadipo Project N° 6666.

SESSION 3 - NUTRITION AND ANTINEOPLASTIC INTERACTIONS

Lamia Hamdan Ramdani- Poster - N°15

June, Thursday 22, 2017 - 3.15-4:15pm for the posters presentation

Abstract title: Effects of Spiro-bisheterocycles on Proliferation and Apoptosis in Human Breast Cancer Cell Lines

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The abstract: Breast cancer is the first cause of cancer death in women worldwide and a major concern to public health. The main axes of this work consist in studying the antiproliferative and pro-apoptotic effects of spiro-bisheterocycles on human breast cancer cell lines MCF-7 and MDA-MB-231. On the structural point of view, the compounds feature a hydantoin moiety attached to either diazole, isoxazole, diazepine, oxazepine or benzodiazepine via the privileged tetrahedral spiro-linkage. The treatment with compounds 3 and 6, corresponding to spiro [hydantoin-isoxazole] and spiro [hydantoin-oxazepine] respectively, resulted in a significant decrease of cell proliferation and the induction of the apoptosis in both breast cancer cell lines. However, the compound 4 (spiro [hydantoin-diazepine]) demonstrated an antiproliferative activity only against MDA-MB-231. The qRT-PCR revealed an up-regulation of MDM2, strictly p53-dependent, and an increase of the expression of pro-apoptotic genes such as caspase 3 and BAX in MCF-7 wild-type p53 and MDA-MB-231 mutant p53 breast cancer cells. In summary, the results suggested that our compounds promoted the apoptosis of breast cancer cell lines through p53-dependent and independent pathways.

SESSION 4 - BREAST CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Adrien Rossary - Oral communication - N°16

June, Friday 23, 2017 - 10.00-10:15am

Abstract title: Impact of physical activity on tumour immunity in C57BL/6 mouse syngeneic model of mammary cancer.

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The abstract: Background: Obesity, an increasingly prevalent health problem, is a major risk factor for recurrence and morbidity of breast cancer in postmenopausal women. Moreover, obesity increases therapy resistance and tumour escaping. To limit the obesity adverse effects, one of the health recommendations is regular physical practice. To clarify the physical activity effects on obesity and breast cancer development, it is important to consider the physical activity impact not only on metabolism but also on tumour immunity balance between pro and anti-tumour immune response.

Objectives: The purpose of this study was to examine the influence of spontaneous physical activity, promoted by an enriched environment (EE), on systemic biological markers and on tumour immune response in C57BL/6 mice (33 weeks old) ovariectomized and fed with a high fat (HFD). Systemic and tissue biological assays evaluated energetic substrates (i.e. glucose, cholesterol, triglycerides) and signalling molecules (i.e. chemokines, cytokines, adipokines). Flow cytometric analysis permitted to phenotype immunity balance in terms of pro tumour cells (myeloid derivate suppressive cells (MDSC), regulator T lymphocytes (Treg)) and anti-tumour cells (Natural Killer (NK), cytotoxic T lymphocytes (Tc)). Immune trafficking between lymphatic tissue and tumour completed this approach.

Results: Ovariectomized old mice feeding with HFD presented higher body weight and adiposity (fat mass: $+5 \pm 0.5g$, $p < 0.05$) associated with higher plasma levels for leptin, estradiol and glycaemia. This fat phenotype was associated with a decrease in spontaneous physical activity ($-22 \pm 5\%$, $p < 0.01$). At the opposite, housing in the enriched environment reduced adiposity, leptin, estradiol and glycaemic levels and increased spontaneous physical activity of the mice ($p < 0.05$). After tumour implantation, a significant decrease of spontaneous physical activity was observed in all groups, but less important in the enriched environment ($-56 \pm 10\%$ vs $-39 \pm 10\%$, $p < 0.05$). In addition, tumour growth was enhanced by HFD and linked to a worse survey. Housing in the enriched environment reduced tumour growth and increased the survey ($p < 0.05$).

HFD-tumour immune phenotyping presented an imbalance between pro- and anti-tumour cells in favour of pro-tumour cells. A significant increase of MDSC and Treg appeared (24.7 and 21.5% of the immune infiltrate) in contrast to a decline of Tc content (5.3%). Immune trafficking from spleen to inguinal lymph nodes reflected these tumour immunity modifications EE changed tumour immune phenotype, resulting in an equilibrate immune response with a higher Tc infiltration (19.9%) and a lesser MDSC and Treg content (11.1 and 1.4%).

Conclusion: These data confirmed that HFD imbalanced the anti-tumour immunity response and enhanced fat mass, leptinemia and tumour growth. Interestingly, they highlighted the beneficial effect of spontaneous physical activity to limit these carcinogenesis disorder.

SESSION 4 - BREAST CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Lucie Lécuyer - Oral communication - N°17

June, Friday 23, 2017 - 10.15-10:30am

Abstract title: NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer

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The abstract: Purpose: Combination of metabolomics and epidemiological approaches opens new perspectives for groundbreaking discoveries. The aim of the present study was to investigate for the first time whether plasma non-targeted metabolomic profiles, established from a simple blood draw from healthy women, could contribute to predict the risk of developing breast cancer within the following decade and to better understand the aetiology of this complex disease.

Methods: A prospective nested case-control study was set up in the SU.VI.MAX cohort, including 206 breast cancer cases diagnosed during a 13y follow-up, and 396 matched controls. Non-targeted NMR metabolomic profiles were established from baseline plasma samples. Multivariable conditional logistic regression models were computed for each individual NMR variable and for combinations of variables derived by principal component analysis.

Results: Several metabolomic variables from 1D NMR spectroscopy were associated with breast cancer risk. Women characterized by higher fasting plasma levels of valine, lysine, arginine, glutamine, creatine, creatinine, and glucose and lower plasma levels of lipoproteins, lipids, glycoproteins, acetone, glycerol-derived compounds and unsaturated lipids had a higher risk of developing breast cancer. P-values ranged from 0.00007 (ORT3vsT1=0.37[0.23-0.61] for glycerol-derived compounds) to 0.04 (ORT3vsT1=1.61[1.02-2.55] for glutamine).

Conclusion: This prospective study showed that baseline NMR plasma metabolomic signatures reveal predictive metabolites associated with long-term breast cancer risk. These results provide interesting insights to better understand complex mechanisms involved in breast carcinogenesis and evoke plasma metabolic disorders favourable for carcinogenesis initiation. This study may contribute to develop screening strategies for the identification of at-risk women for breast cancer well before symptoms appear.

SESSION 4 - BREAST CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Trang Huyen Luu - Poster - N°18

June, Friday 23, 2017 - 1.30-3:00pm for posters presentation

Abstract title: Lithocholic bile acid inhibits lipogenesis and induces apoptosis in adenocarcinoma breast cancer cell lines

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The abstract: Background and Purpose

Bile acids are products of cholesterol metabolism and their principal function is the solubilization of fats and liposoluble vitamins in the intestine. After their secretion into the intestine, primary bile acids are converted into secondary bile acids by intestinal bacteria. Two major secondary bile acids lithocholic acid (LCA) and deoxycholic acid (DCA) are produced from cholic acid and chenodeoxycholic acid, respectively. It has been reported that bile acids, particularly LCA have anti-carcinogenic properties in several cancer cell models such as colon cancer, neuroblastoma cells, and prostate cancer.

On the other hand, it is now recognized that the levels of the FASN enzyme (Fatty Acid Synthase) and lipogenesis are increased in the cancer cells.

The aim of our study is to evaluate the impact of lithocholic acid (LCA) on lipogenic enzymes and transcription factors related to lipogenesis in breast cancer in MCF-7 and MDA-MB-231 cell lines. The cytotoxic character of LCA on these cell lines is also examined.

Material and Methods:

In-vitro effects of LCA on MCF-7 and MDA-MB-231 cells were studied using: MTT assay, Annexin-FITC analysis and Akt phosphorylation analysis to evaluate anti-proliferative and pro-apoptotic properties; qPCR and Western Blot analysis to determine expression of G-protein coupled bile acid receptor TGR5, genes and proteins involved in lipogenesis (SREBP-1c, FASN, ACACA, SCD), as well as in apoptosis (Bax, Bcl-2 and P53). Staining lipids by Oil Red O was used to study the lipid storage.

Results:

LCA decreased the cell viability of MCF-7 and MDA-MB-231 cells in a dose (20 to 200 μ M) - dependent manner after 24h of incubation. LCA also reduced Akt phosphorylation in a dose dependent manner (50% reduction at 100 μ M, 24h) in MCF-7 cells, but not in MDA-MB-231 cells. An increase of pro-apoptotic P53 protein and a down-regulation of anti-apoptotic Bcl-2 protein were observed after LCA treatment of MCF-7 cells.

We demonstrated that LCA activates TGR5 and decreased at least by half the expression of SREBP-1c, FASN and ACACA in two cancer cell lines, compared to untreated cells. Staining lipids by Oil Red O showed that the control cells contained abundant lipid droplets in comparison to LCA-treated cells.

Conclusion

These data show that LCA has anti-proliferative and pro-apoptotic properties in MCF-7 and MDA-MB-231 cells. Our study also suggests the potential capacity of LCA to induce apoptosis cancer cells by inhibiting the storage of lipids.

SESSION 4 - BREAST CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Marie Goepp - Poster - N°19

June, Friday 23, 2017 - 1.30-3:00pm for posters presentation

Abstract title: Impact of hyperlipidic diet associated to oestrogenic modulation on tumoral lymphoid immune infiltrate in mammary carcinogenesis mouse model.

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The abstract: Obesity is a well-known risk factor for breast cancer development after menopause. The deleterious effects of obesity come from metabolic dysregulations, lesser immunity defenses and higher oxidative stress. In parallel, the modification of the estrogenic secretion by the aromatase activity of the adipose tissue contributes certainly to this major breast cancer risk. Our objective is to evaluate the impact of an hyperlipidic diet on the tumoral and systemic immune response in an orthotopic murine model of carcinogenesis submitted or not to an estrogenic modulation.

Ovariectomized female C57/bl6 mice (33 weeks old) were fed with a standard (SD : 3.4 kcal/g, lipids 10 % AET, 2 groups n = 10) or a hyperlipidic diet (HL : 4.3 kcal/g, lipids 45 % AET, 2 groups n = 10). After 4 weeks, one group on each regimen received an implantation of tumor cells (EO771) in the 4th mammary gland, in parallel or not with administration of tamoxifen

(10 mg / kg / week), one by week, during three weeks. Weight change and tumor growth were measured throughout the experiment. At the sacrifice, phenotyping of immune cells was carried out by flow cytometry from tumors and major immune tissues (thymus, spleen, lymph nodes,...). The comparisons between groups were realised using the Mann-Whitney test.

HL diet induced an increased tumor volume (1114 ± 793 vs 384 ± 339 mm³ at 16 days, $p = 0.04$). The peripheral lymphoid organs (spleen and inguinal lymph nodes) showed a hypertrophy correlated with the tumor size ($r = 0.4652$, $p = 0.0004$ for spleen - Spearman correlation test). The phenotyping of tumor infiltrated immune cells revealed an increase in immunosuppressive populations under HL diet, associated with a modification of the T cytotoxic / T regulatory cells ratio (LTc / LTreg: 1.4 ± 0.1 vs 12.8 ± 6.8 , ratio of cells/mg tissues ; $p = 0.05$). Similar alterations (LTc / LTreg ratio) were found in the peripheral lymphoid organs. Tamoxifen treatment induced a slight increase in tumor volume over time and a reduction in the immune infiltrate for the HL group (2676 ± 185 vs 1239 ± 467 cells / mg tissue, $p = 0.1$). That is particularly marked for LTc (20.1 ± 4.2 vs 10.2 ± 4.9 $p = 0.05$) and LTh2 (8.2 ± 3.6 vs 3.5 ± 1.7 , $p = 0.05$) cells. Modification of tumor immune infiltrate affected both the pro-tumoral and anti-tumor cell populations. These changes were also observed in the spleen. The HL diet elicited an accelerated tumor growth and promoted the migration of immune cells from secondary lymphoid organs to the tumor. The HL diet induced an intratumoral recruitment of immunosuppressive cells which promotes carcinogenesis, linked to a repolarization of the immune response both at the systemic and tumor levels. Tamoxifen treatment seems to act as a selective modulator of the immune infiltrate, depending on the level of estrogens provided by the adipose tissue.

SESSION 4 - BREAST CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Khaldoun Rifai - Poster - N°20

June, Friday 23, 2017 - 1.30-3:00pm for posters presentation

Abstract title: The implication of Histone deacetylase SIRT1 in Breast Cancer Carcinomas: A potentiel therapeutic target.

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The abstract: Breast cancer is the most common cancer in women; it is also the leading cause of cancer death in women worldwide. SIRT1 is a class III histone deacetylase (HDAC) involved in lipid metabolism and glucose homeostasis, as well as endocrine signaling, DNA repair and apoptosis regulation. Its role in Breast Cancer Carcinomas is controversial as both tumor-suppressive and promoting functions have been reported. Also, there are very few reports available, where expression of SIRT1 is comprehensively analyzed in breast tumors that are classified by molecular subtype. A total of 135 breast tumors and their matched normal tissues were included in this study. Firstly, we investigated SIRT1 expression levels in the 5 molecular subtypes of breast cancer. Tumor and its corresponding normal tissue samples were collected from all patients, and mRNA and protein expression levels were then examined by real-time PCR and immunoblot respectively. The results showed a dual expression profile of SIRT1, with significant overexpression in luminal and HER2-enriched subtypes and significantly reduced expression in the triple-negative subtype, in comparison with normal tissues. These findings suggest that SIRT1 plays a double role in breast tumors depending on its expression rate. We then proceeded to investigate the relation between SIRT1 and the poorly studied Histone H3 Lysine 4 acetylation (H3K4ac), a chromatin decondensation mark that promotes the transcription process. We detected a colocalization pattern between SIRT1 and H3K4ac on the promoters of 6 deregulated breast cancer genes (ESR1, ESR2, EZH2, BRCA1, AR and P300), that is similar to the pattern SIRT1-H3K9ac, H3K9ac being a well-known deacetylation target of SIRT1. We also highlighted a physical interaction SIRT1-H3K4ac in all 5 breast tumor subtypes by co-immunoprecipitation. These findings imply that SIRT1 is the element responsible for the deacetylation of H3K4ac in humans.

In conclusion, our study suggests that SIRT1 may play an important role in breast cancer pathogenesis and could be promising candidate as therapeutic target in breast cancer carcinomas.

SESSION 4 - BREAST CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Gaëlle Judes - Poster - N°21

June, Friday 23, 2017 - 1.30-3:00pm for posters presentation

Abstract title: TIP60 ACETYLTRANSFERASE IN BREAST CANCER

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The abstract: The acetyltransferase TIP60 acetylates both histone and non-histone proteins, and is acted in various molecular processes. TIP60 is reported to be downregulated in several cancers, in particular breast cancer, but the molecular mechanisms resulting from its alteration are still unclear. H3K4ac enrichment was evaluated by ChIP-QPCR on GAPDH, ADH5 and Chr4 Sata gene promoters of 22 breast tumors and their normal adjacent tissues. TIP60 expression was studied by RT-QPCR of different breast cancer subtypes. Re-ChIP technique was performed to examine the link between H3K4ac and TIP60 in breast tumors (n=54) compared to normal adjacent tissues (n=54). In vitro and in vivo assays were performed to assess the biological roles of TIP60 in breast cancer. Two cell lines of breast cancer, MDA-MB-231 (ER-) and MCF-7 (ER+) were transfected with shRNA specifically targeting TIP60, and injected to athymic Balb-c mice. We identified a new target of acetyltransferase TIP60, the lysine 4 of histone H3 (H3K4), unexpectedly present in both euchromatin (GAPDH, ADH5) and heterochromatin (Chr4 Sata). We show that an underexpression of TIP60 leads to a reduction of H3K4 acetylation. H3K4 acetylation is thus dependent on TIP60 expression in breast cancer. An increase in tumor development was noted in sh-TIP60 MDA-MB-231 xenografts, and a slowdown of tumor growth in sh-TIP60 MCF-7 xenografts. The effects of TIP60 depletion thus seem ER-dependent. This is evidence that the underexpression of TIP60 observed in breast cancer can promote the tumorigenesis of ER-negative tumors, in which the expression of TIP60 could be used as a new target and a prognostic marker in breast cancer.

SESSION 4 - BREAST CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Marwa Chehimi - Poster - N°22

June, Friday 23, 2017 - 1.30-3:00pm for posters presentation

Abstract title: Contribution of adipose stem cells from obese subjects to hepato-or breast-carcinoma tumorigenesis, through promotion of Th17 cells

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The abstract: Introduction: As opposed with lean adipose tissues (AT), obese AT are heavily infiltrated with variety of inflammatory cells. Among them, Th17 cells are found not only within AT, but also in the periphery in obese subjects. We have demonstrated that AT-derived stem cells (ASC), or their progenitors, contribute to inflammation through promotion of Th-17 cells, provided that they are issued from obese-, but not lean-AT (Diabetes, 2015; Adipocyte, 2016). Because obesity is associated with increased prevalence of various cancers, including hepatic or breast cancer, we postulated herein that ASC-mediated promotion of Th17 cells might result in tumorigenesis progression.

Materials and Methods: Human ASC were isolated from WAT of obese donors (obASC). Mononuclear cells (MNC) were collected from blood donors. PHA-activated co-cultures of obASC/MNC, which increase secretion of IL-17A, IL-1b and IL-6, were performed. Conditioned media (CM) were collected from such cultures, and added to HuH7 (hepato-carcinoma cell line) or MCF-7 / MDA-MB-231 (breast carcinoma cell line) cultures for 24h. mRNA profiles were measured by qRT-PCR. Expression of CXCR4 was measured by flow cytometry. Results: CM from 48 hr PHA-activated-ASC/MNC co-cultures enhanced IL-1b, VEGFa, IL-8 TNFa and IL-6 mRNA expression in HUH7 by almost 700, 2, 3, 3, and 6-fold, respectively. A putative effect of CM on HUH7 invasiveness was supported by 2a-fold, and 3-fold increase in MMP9, and CXCR4 expression, respectively. In addition, CM also increased IL-1b, IL-6, IL-8 and VEGF-a mRNA expression in both MCF-7 and MDA-MB-231 cell lines.

Conclusion: Our results suggest that the interaction of obASC with immune cells contribute to an inflammatory environment, able to impact hepato- or breast-carcinoma cell secretion profile, and/or invasiveness, either through propagation of inflammatory cytokines outside adipose tissues, or ASC migration inside tumors.

SESSION 5 - PROSTATE CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Aurélie Charazac - Oral communication - N°23

June, Friday 23, 2017 - 12.00-12:15pm

Abstract title: Quantitative image based analysis of endocrine disruptor effects on mitochondria morphology-function in prostate cancer cells.

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The abstract: Endocrine Disrupting Compounds (EDC) are found in many everyday products, like food packaging, food preservative or additive, pesticides residues, etc... Widely distributed throughout the environment and bioaccumulable in living organisms, persistent organic pollutants (POPs) are a specific class of EDC that accumulate in fat deposit. Some of them have been recognized as causing adverse effects on human's health such as diabetes and cancer by mimicking hormone effects on metabolism. Cancer cells display high metabolic flexibility allowing them to grow in various cellular environments and favoring their proliferative and invasive capacities. Mitochondria are key players in this complex interplay as they produce ROS, generate energy and participate in nucleotide synthesis and in glutamine metabolism of cancer cells. Regarding the importance of hormones on prostate cancer risk and outcomes, we are developing multiple parameters in vitro assays conducted in a high-throughput screening format relevant for prostate cancer metabolism and aggressiveness. This screening method includes, inter alia a microscopy based analysis of mitochondria structure and function. We analyzed the effects of five EDCs (Aldrin, BDE28, TCDD, PCB153, PFOA) identified in the plasma of patients on two prostate cancer cell lines, 22RV1 (androgen-responsive) and DU145 (androgen-unresponsive). Each compound was tested in a dose dependent manner to determine its effects on total mitochondrial mass, mitochondrial membrane potential, ROS production, mitochondrial biogenesis and mitophagy. In addition, we performed an image based computational analysis of the mitochondrial network morphology and dynamics. This strategy allows us to extract some quantitative parameters on the mitochondrial network as fragmentation index, compactness, average volume, etc. When combined, morphological and functional parameters allow us to discriminate subtle perturbations of the mitochondrial structure-function induced by POPs in prostate cancer cells. We are confident that this multiparameter analysis strategy could represent a new perspective in identification and characterization of EDC based on their effects on cell metabolism (phenoscore) in order to estimate their potential risk on human health.

SESSION 5 - PROSTATE CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Judith Eguida - Oral communication - N°24

June, Friday 23, 2017 - 12.15-12:30pm

Abstract title: Mitochondria : a new target for human prostate cancer cells radiosensitization?

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Presenting author: Judith Eguida

The abstract: Mitochondria is one of the most important metabolic crossroads of eukaryotic cells. These organelles are essential for energetic and metabolic processes and play an important role in cell signalling. All these functions are allowed by a continuous crosstalk between the nuclear compartment, vector of the majority of genetic information, and the mitochondrial compartment in which lies another DNA population: the mitochondrial DNA (mtDNA). Dysfunctions in mitochondria are encountered in many pathologies such as cancer with disturbances of the apoptosis/proliferation balance and an increase in oxidative stress. In parallel, mtDNA mutations are found in cases of tumours and emphasize these cells proliferative potential. These observations found in prostate cancer highlight the essential role of mitochondria and mtDNA upholding in tumorigenesis.

Radiotherapy is a key step in all therapeutics dedicated to prostate cancer treatment, but frequently leads to radioresistance development. This approach is mainly focused on nuclear DNA damages. However, mitochondria could be quite interesting new targets. The recent development of three Skulachev's cations-like molecules, associated with gold would constitute a new therapeutic response toward tumour escape following radiotherapy, through tumour radio-sensitization.

Our study aims to characterize the anti-proliferative potential of these compounds and their ability to potentiate X-rays radiation therapy on a model of human prostate cell line: LNCaP.

As a first step, the IC50 of all the 3 compounds were determined and range from $0.40 \pm 0.17 \mu\text{M}$ to $7.13 \pm 0.73 \mu\text{M}$ depending of the compound tested. In the meantime, gold nanoparticles with 10 nm average diameter did not display any significant toxicity. In order to analyze the anti-proliferative properties of the compounds, MTT assays were performed. For instance, for concentrations equivalent to the IC50 of one of the compounds, the proliferation was reduced by 25% after 24 hours' growth and reached 76% by 96 hours. X-rays (15 Gy) only, led to similar effects. The association of X-rays and the compound at the IC50 concentration showed an effect 24 hours post-irradiation, and this effect is increased over time since we observed a proliferation decline of 93% 96 hours post-irradiation. Interestingly, a lower concentration of the compound (0.1 μM) strongly decreased the cytotoxicity but the radio-sensitizing effect remained with X-rays. No significant radiosensitization was observed with gold nanoparticles. This preliminary study validates the anti-proliferative properties of these compounds but also the potential to radiosensitize prostate tumor cells. This effect is probably mediated through interaction with mitochondria since gold particles only do not have this property.

Our work is now orientated on biochemical and molecular characterization of the radiosensitizing effect.

SESSION 5 - PROSTATE CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Mouhamed Idrissou - Poster - N°25

June, Friday 23, 2017 - 1.30-3:00pm for posters presentation

Abstract title: EZH2 AND JMJD3 IMPLICATONS IN PROSTATE CANCER

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The abstract: Prostate cancer presented the highest incidence of death in men. It is a multifactorial disease including many risk factors such as diet, sedentarity, obesity. These factors might result from epigenetic modifications (DNA methylation, histone post-translational modifications). Histone modifications modulate gene expressions. The Histone 3 Lysine 27 Trimethylation (H3K27me3) is a repressive mark, that induces chromatin compaction and thus gene inactivation. In a previous study, on DNA chips we showed H3K27me3 enrichments on gene promoters (MGMT, RPS6KA2, TRA2A, U2FA1) in prostate tumors compared to normal tissues. These genes are involved in several metabolic pathways such as DNA repair, pre-mRNA splicing regulation, cell growth and differentiation. So, H3K27me3 might become a possible target for prostate cancer detection. EZH2 methyltransferase and JMJD3 demethylase are known as regulators of H3K27me3.

We demonstrated by chromatin immunoprecipitation (ChIP) targeting H3K27me3, EZH2 and JMJD3 followed by qPCR, their interactions with the previous cited genes. Study was realized on prostate biopsies at healthy and different stages of tumors in order to identify the impact of JMJD3 and EZH2 in the development and cancer progression.

This study will demonstrate the involvement of H3K27me3, EZH2 and JMJD3 on many gene deregulations in prostate cancer in order to identify new potential targets.

SESSION 5 - PROSTATE CANCER: FROM EXPERIMENTAL APPROACH TO CLINICAL

Marine Daurès - Poster - N°26

June, Friday 23, 2017 - 2.00-3:00pm for posters presentation

Abstract title: Identification of a gene panel exhibiting a H3K27me3-enrichment in prostate cancer and impact of JMJD3 and EZH2

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The abstract: Histone methylation is one of the epigenetic modifications, essential for gene expression regulation. The Histone 3 Lysine 27 Trimethylation (H3K27me3) is associated with gene repression and plays an important role in the prostate cancer progression. H3K27me3 levels are determined by balance between the histone methyltransferase EZH2 and the histone demethylase JMJD3. A previous microarray study permitted to identify H3K27me3 differentially-enriched regions on whole-genome in relationship with clinicopathological parameters. This study determined H3K27me3 target genes to understand their regulation in prostate cancer.

Following that, the profile expression of the 24 deduced genes from microarray promotor analysis was studied by transcriptomic analysis using TaqMan Low Density Arrays (TLDA) on prostate biopsies representing two tumor groups (Gleason score > 7 and ≤7) and a healthy one. Results exhibited discriminations between the different tumor types as well as the healthy group.

In order to evaluate the involvement of JMJD3 and EZH2 on the regulation of these gene expressions, a study was performed on prostate tumor cell lines (DU 145, PC-3 and LNCaP) with use of chemical inhibitors of JMJD3 (GSK-J4) and EZH2 (DZNep). In conclusion, this study will allow to understand the H3K27me3 impact and the role of regulators like JMJD3 and EZH2 in prostate cancer.

SESSION 6 - CANCER-RELATED MALNUTRITION, METABOLISM, DYSIMMUNITY

Aïcha Demidem - Poster - N°27

June, Friday 23, 2017 - 2.00-3:00pm for posters presentation

Abstract title: Specificities of Hepatocellular Carcinoma Developed on Non Alcoholic Fatty Liver Disease in Absence of Cirrhosis Revealed by Tissue 1H-NMR Spectroscopy

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The abstract:

Background and aims: Epidemiologic studies suggest that NAFLD increases the risk of Hepato-Cellular Carcinoma (HCC), even in non-cirrhotic NAFLD. This underlying disease is reported in up to 40% HCC.

To get insights into the biology of HCC in non-cirrhotic NAFLD and seek for putative cancer pathways, we performed metabolomics in HCC associated with cirrhosis and non-cirrhotic NAFLD.

Methods: Metabolomics was performed using 1H-NMR Spectroscopy. The analysis included 28 pairs of HCC tissue and distant Non-Involved Tissue (NIT) collected from patients undergoing hepatectomy. HCC was associated with cirrhosis (n = 9), normal liver (n=6) or NAFLD (n = 13).

Results: In HCC versus NIT, statistical analyses showed high level of lactate and phosphocholine and low level of glucose. Multivariate analysis of HCC groups showed increased level of β -hydroxybutyrate in HCC-Cirrhosis and increased level of glutamine in HCC-NAFLD. OPLS-DA models of HCC-cirrhosis vs NIT (either normal tissue or cirrhosis) and HCC-NAFLD vs NIT (either normal tissue or NAFLD) were constructed before comparing them in shared and unique structure (SUS) plots. From SUS-plots, HCC-Cirrhosis was characterized by high levels of β -hydroxybutyrate, tyrosine and phenylalanine, whereas HCC-NAFLD was characterized by high levels of glutamine/glutamate. Glutamine Synthetase (GS) immuno-staining was correlated with the NMR-spectroscopy glutamine quantification.

Conclusion: This study provides evidence of metabolic specificities of HCC associated with non-cirrhotic NAFLD versus HCC associated with cirrhosis. These alterations could suggest activation of glutamine synthetase pathway in HCC-NAFLD and mitochondrial dysfunction in HCC-cirrhosis, that may be part of specific carcinogenic processes.

SESSION 6 - CANCER-RELATED MALNUTRITION, METABOLISM, DYSIMMUNITY

Angéline Ginzac - Poster - N°28

June, Friday 23, 2017 - 2.00-3:00pm for posters presentation

Abstract title: Impact of adjuvant breast cancer treatments on weight and body composition

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The abstract: Context: Breast cancer treatments can lead to weight variations which may turn out to be pejorative if higher than 5% of initial weight. A prospective study conducted in Jean Perrin Comprehensive Cancer Center studied weight variations and body composition in 50 postmenopausal breast cancer patients treated by adjuvant Taxanes-based chemotherapy. Results showed that after 6 cycles (T1), 20% of patients lost weight, 20% gained weight. Six months post-chemotherapy (T2), these variations are maintained. Weight gain is characterized by a gain in fat mass but only 6 months after the end of chemotherapy. Long term evolution of body composition during adjuvant treatment of breast cancer remains unknown and new datas on this topic are required.

Objective: To assess the evolution of body composition of the same group of patients currently treated by anti-hormonal therapy (n=33).

Methods: Dual-Energy X-ray Absorptiometry was used to measure fat and lean body mass. Body water was assessed by impedancemetry.

Results: After receiving on average three years of anti-hormonal therapy (T3) following chemotherapy, 9% (n=3) of the patients lose more than 5% of their initial weight and 30% (n=10) gain more than 5% of their initial weight. The average lost is 5kg \pm 0.6 (8.3% \pm 1.7) and the average gain is 7.9kg \pm 5.9 (11.6% \pm 8.4). This weight gain is characterized by a fat mass gain (4kg \pm 5; p=0.034) especially in trunk (2.3kg \pm 2.8; p=0.03) and a lean body mass gain (4.6 \pm 3.5; p=0.003) mainly reflecting a water gain (2.5 \pm 2.3; p=0.018).

All patients (n=7) who have undergone a weight loss during chemotherapy (T0-T1) take thereafter more than 5% of their initial weight during anti-hormonal therapy (T2-T3). In terms of body composition, this is translated by an increase in fat mass (3.7 \pm 1.9kg) and lean body mass (2 \pm 1.7kg), both in the abdominal region. However, it is important to emphasize that these patients have the highest initial body mass index (BMI) (27.6 \pm 4.8kg/m²) compared with patients who gained weight during chemotherapy (21.5 \pm 2.8kg/m²) or to those who remained stable (26.7 \pm 5.8kg/m²). During anti-hormonal therapy (T2-T3), 100% of patients who have gained weight during chemotherapy (T0-T1) are in the group of stable weight patients.

Conclusion: In addition to being a breast cancer risk factor, abdominal fat mass excess is linked with occurrence of metabolic and/or cardiovascular complications. By the way, these results support the pejorative impact of high BMI at diagnosis. They suggest that weight loss during chemotherapy would be worse than weight gain at long-term. Promoting physical activity during treatment appears like a good way to avoid fat mass gain and maintain muscular mass. Patients should be encouraged to adopt a healthy and physically active lifestyle since diagnosis. In this sense, we are going to promote a trial in order to get patients achieve or maintain the WHO's international recommendations for physical activity during treatment.



*Thank you so much for your participation
Marie-Paule Vasson
President of the congress*

