23èmes Journées de l'Ecole Doctorale
Sciences de la vie, Santé, Agronomie et Environnement

14 - 15 OCTOBRE 2020

Clermont-Ferrand

SPORT ET PERFORMANCE

Les limites physiologiques de la performance sportive

Avec la participation du monde sportif :

Orane BROUILLET
Aurélie CHARASSE
Youna DUFOURNET
François FAURE
Benoit HEINTZ
Marie-Amélie LE FUR
Mathias MAGNAIN
Neil MCILROY
Axel PARISOT
Bertrand SEBIRE
Ramon SOPKO
Julien VELLET

Conférence et table ronde de clôture animées par le

Dr. Gaël GUILHEM

INSEP

Le 15 octobre à 14h30

Maison du Peuple
Place de la liberté
Clermont-Ferrand

Ouvert au public – Entrée libre

23èmes Journées de l'Ecole doctorale des Sciences de la Vie, Santé, Agronomie et Environnement

à la **Maison du Peuple**,
Place de la Liberté,
Clermont-Ferrand

le **14 et 15 Octobre 2020**

REMERCIEMENTS

Dans un premier temps, nous souhaitons remercier la Direction de l'Ecole Doctorale Science de la Vie, Santé, Agronomie et Environnement (SVSAE) : Monique ALRIC et Patrick VERNET, qui nous ont grandement aidé à l'organisation de ces journées ainsi que Rita BOUZABOUNE et Rosa CAMPOS pour leur aide dans la gestion financière des JED.

Nous remercions Gaël GUILHEM d'avoir accepté notre invitation et d'avoir maintenu sa participation malgré le contexte sanitaire actuel.

Nous remercions également toutes les personnes impliquées dans la recherche de sportifs pour animer notre table-ronde ainsi que les sportifs ayant répondu à nos sollicitations.

Nous tenons également à remercier grandement la ville de Clermont-Ferrand pour le prêt de la salle ainsi que du matériel de sonorisation sans quoi notre évènement n'aurait pas pu avoir lieu.

Nous remercions également nos sponsors pour le soutien financier.

Enfin, nous remercions tous les doctorants de l'Ecole Doctorale qui ont accepté de présenter leurs travaux de recherche au cours de cette édition des JED ainsi que tous les participants à ces deux journées.

PROGRAMME DES JED 2020

PROGRAMME 23EMES JOURNEES DE L'ECOLE DOCTORALE
Mercredi 14 Octobre (08h30-18h20)

8h00-8h30 : Accès salle
08h30-09h00 : Ouverture des Journées de l'Ecole Doctorale

09h00-09h20 : LAHAYE Clément – "New screening tools for body composition changes during aging"

09h20-09h40 : TOURON Julianne – "Short preoperative training program effects on mitochondrial adaptations of the intercostal muscle"

09h40-10h00 : ELSHENNAWY Mennatallah – "A study of different structures of central nervous system implicated in Parkinson's disease neuropathic pain"

10h00-10h25 : Flash Poster

DUPUIT Marine – "High intensity interval training (HIIT) and/or food plant-based supplements on body composition, gut microbiota and metabolic profile in an obesity context"

OMARA Hend – "Tramadol induced CPP and motor sensitization in the rat"

CRAVEIRO DA COSTA Daniela – "Body composition, isokinetic strength and bone health in male adolescent athletes contrasting in mechanical loading"

PERIS MORENO Dulce – "Developing new strategies to limit TRIM63/MuRF-1-mediated muscle protein loss"

SAIDI Oussama – "Do junior rugby players sleep better than their matched non sporting controls during the competitive season ? Week versus Weekend sleep discrepancy"

BIRAT Anthony – "Effect of Long-Duration Adventure Races on Cardiac Damage Biomarker Release and Muscular Fonction in Young Athletes"

10h25-10h50 : Pause Poster

10h50-11h10 : LINAS Natacha – "Impact of severe Early Childhood Caries and its treatment on masticatory parameters in 3-6 years children"

11h10-11h30 : CHOLTUS Helena – "Symphony or cacophonia of the rupture of fetal membranes: RAGE and sterile inflammation."

11h30-11h50 : KIM Jinyoung – "Postprandial responses to the dairy product intake in men : effect of the type of products and age"

11h50-12h10 : DOUADI Clara – "Quantitative proteomic analysis of macrophages from Crohn's disease patients and infected with adherent-invasive *Escherichia coli:* Impact of anti-TNFα treatment"

12h10-12h35 : Flash Poster

MACIAN Nicolas – "Impact Of Magnesium On Stress In Fibromyalgia: A Double-Blind Placebo Controlled Clinical Trial"

CHERILLAT Marie Sophie – "Representations of chronic disease in health professionnels: between negative representations and engaged reflexivity"

GUIRADO Terry – "The REMOVE study: High vs low spenders in energy expenditure during a light cycling exercise."

LAURENT Hélène – "Effect of a short home based training program in patients with COPD before lung cancer surgery"

BILLON Lise-Marie – "Mind the cuticle conductance: When resistance to cavitation is not enough for evaluating plant resistance to drought."

HALIFA Ruben – "Metabolization of flavan-3-ols by human gut bacteria"

12h35-14h05 : Pause Déjeuner

14h05-14h25 : MONROSE Mélusine – "Study of the roles of the Constitutive Androstane Receptor in testicular physiopathology"

14h25-14h45 : SAUVAITRE Thomas – "Towards a fiber-based strategy to prevent bacteria-mucus interactions in enterotoxigenic escherichia coli infections?"

14h45-15h05 : SOUIDI Anissa – "Analysis of miR-1 and its potential target Multiplexin deregulated in myotonic dystrophy type 1 (DM1)"

15h05-15h25 : PIQUERAS Justine - "Management of bacterial communities in PDO farmhouse cheeses towards optimized sensorial and sanitary qualities"

15h25-15h45 : YOTH Marianne – "Trapping a somatic endogenous retrovirus into a germline piRNA cluster immunizes the germline against further invasion"

15h45-16h10 : Flash Poster

IACHELLA Isabelle – "Evaluation of bioprotective strains and their metabolites for the control of microbiological quality of Cantal-like cheeses"

DE LA POMELIE Diane – "Impact of nitrite on the physiology of Shiga-toxin producing Escherichia coli and on the nitrosation of meat proteins in a gastrointestinal digestion model"

OURTIES Guillaume – "Involvement of Cav3.2 calcium channels in osteoarthritis"

CUSSONNEAU Laura – "Genetic reprogramming involving a shift from TGF- β to BMP signaling for muscle mass maintenance in hibernating brown bear"

POOVATHUMKADAVIL Preethi – "Bioinformatic and Functional Analyses of Muscle Cell Diversification in *Drosophila melanogaster"*

ALOUANE Tarek – "Genome-wide characterization of potential effectors of eight strains of *Fusarium graminearum* with contrasting aggressiveness"

16h10-16h40 : Pause Poster

16h40-17h00 : BOULET Manon – "Characterization of TET mode of action during Drosophila hematopoiesis"

17h00-17h20 : BACHER Louise – "Phenotyping beef cattle temperament traits using behavioural tests and accelerometers"

17h20-17h40 : DUFOUR Damien – "The role of SUMOylation in endocrine differentiation"

17h40-18h00 : ROBERT Pauline – "Phenomic selection: an original, low-cost and efficient predictive method to improve wheat-breeding schemes"

18h00-18h20 : MOM Robin – "Voltage-gating of aquaporins"

PROGRAMME 23EMES JOURNEES DE L'ECOLE DOCTORALE
Jeudi 15 Octobre (08h30-17h30)

8h00-8h30 : Accès salle

08h30-08h50 : HESKETH Amy - "DNA-methylation-independent epigenetic silencing in *Arabidopsis thaliana*"

08h50-09h10 : GUARNIDO LOPEZ Pablo - "Is protein metabolism associated to between-animal variations in feed efficiency? Evaluation of Protein turnover in growing cattle."

09h10-09h30 : EL SABBAGH Nour – "Off Resonance Correction for multi-slice and multi-shot methods in MRI"

09h30-09h50 : AUTISSIER Roxane – "The interest of combining CEST MRI and nuclear medicine imaging to detect changes in tumoral microenvironment: application to chondrosarcoma"

09h50-10h10 : Flash Poster

DEYRA Maéliane – "Investigate conceptions of the determinants of health and cancer in children aged 6 to 11"

GREZE Victoria –"Highly sensitive assessment of neuroblastoma minimal residual disease in testicular tissue using RT-qPCR – A strategy for improving the safety of fertility restoration"

SALAÜN Gaëlle – « Etude de l'interaction entre une matrice extra-cellulaire trisomique 21 et des cellules tumorales mammaires triple-négatives (MDA-MB468) : transition épithélio-mésenchymateuse, migration/invasion »

PRYBYLSKI Nastasia – "Deciphering of the adherence process of microsporidia to host cell"

JACOBS Aurélie – "Cytotoxicity and antibacterial properties of copper-doped calcium phosphate bioceramics"

10h10-10h40 : Pause Poster

10h40-11h00 : CAVAILLE Mathias – "Mendeloma analysis in new hereditary predisposition to cancer syndromes"

11h00-11h20 : DELORME Solène – "Involvement of tumoral and stromal ANXA1 in tumor development and dissemination"

11h20-11h40 : EGUIDA Judith – "Cellular and mitochondrial disturbances associated with x-rays radiations after prostate cells incubation with gold carbenes"

11h40-12h00 : LUSHO Sejdi – "Assessment of circulating and tumour-infiltrating lymphocytes as predictors of triple negative breast cancer response to neoadjuvant chemotherapy and/or metastatic recurrence after that type of treatment"

12h00-14h30 : Pause Déjeuner

14h30-15h00 : Remise des Prix

15h-17h30 : Conférence et Table ronde de Clôture

Animées par le **Dr. Gaël Guilhem (INSEP)**
Avec la participation de :

Orane Brouillet (Rugby fauteuil - ASM)

Aurélie Charasse (Responsable pôle France Para-Natation)

Youna Dufournet (Gymnastique)

François Faure (Hockey – HCCA)

Benoît Heintz (Escalade)

Marie-Amélie Le Fur (Para-athlétisme)

Mathias Magnain (Commission Nationale de Para-natation)

Neil McIlroy (Manager - ASM)

Axel Parisot (Natation Sport Adapté)

Bertrand Sebire (Entraineur national Para-Natation)

Ramón Sopko (Entraineur – HCCA)

Julien Vellet (Rugby Touch)

MERCREDI 14 OCTOBRE 2020

COMMUNICATIONS ORALES

Surname : LAHAYE

First Name : Clément

Year of PhD : 3rd year

Research Team and Laboratory : Human Nutrition Unit, UMR1019, UCA-INRAE, Clermont-Ferrand

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New screening tools for body composition changes during aging

Aging is accompanied by changes in body composition with a decrease in muscle mass and an increase in fat mass. These changes are associated with many pathologies such as sarcopenia and cardiovascular diseases. New tools are needed to screen for these changes, in order to identify at-risk populations and to adapt their management. We have carried out two studies, one at the Clermont-Ferrand University Hospital on the contribution of CT markers in the evaluation of cardiovascular risk in obesity and the other at Charles Foix hospital on early markers of sarcopenia in healthy volunteers.
For the first study, we studied epicardial fat and calcium score (markers of cardiovascular risk), and visceral hepatic fat (associated with metabolic risk) in obese patients admitted to weekly hospital. Epicardial fat was the most predictive marker of cardiovascular risk (Framingham risk $r = 0.52$; $p < 0.001$) and was associated with aging (age $r = 0.51$; $p < 0.001$).
In the second study, we measured several parameters in healthy and physically active volunteers aged 25 to 75: their muscle mass index estimated by dual X-ray absorptiometry, their grip strength measured by dynamometer, their Short Physical Performance Battery and their 6-minute walking distance were not different according to age groups. Muscle thickness of the rectus femoris measured by ultrasound decreases with age ($p < 0.001$), while at the same time the fat thickness increases ($p < 0.001$).
CT-measured epicardial fat and quadricipital muscle thickness measured by ultrasound are emerging tools to assess age-related cardiovascular risk and sarcopenia.

Surname : TOURON

First Name : Julianne

Year of PhD : 3rd year

Research Team and Laboratory : UMR1019 INRAE/UCA, UNH, équipe ASMS

PhD supervisor : Pr. Ruddy RICHARD et Pr. Frédéric COSTES

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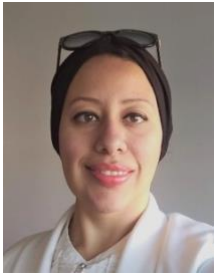
Short preoperative training program effects on mitochondrial adaptations of the intercostal muscle

Surgical treatment of bronchopulmonary cancer is accompanied by a decrease in respiratory function and exercise capacity. In order to reduce perioperative morbidity and mortality, preoperative exercise training is proposed and its benefits evaluated during pulmonary function test (PFT) and cardiorespiratory exercise test (CPET). However, the effect of short-term exercise rehabilitation on the mitochondrial oxidative adaptations of intercostal muscle has never been studied. 16 COPD patients eligible for cancer resection were included in the optional ancillary study of a randomized controlled trail. 8 patients were randomized to the control group (CG) with usual preoperative respiratory physiotherapy. The 8 patients in the trained group (TG) also underwent 15 intermittent high intensity exercise training sessions at home. PFT and CPET were performed before and after the home-based intervention in the two groups. An intercostal muscle sample was taken during surgery and mitochondrial function evaluated. FEV1 increased significantly in the TG compared to the CG (6.4±13.0 *vs* -5.9±5.7% predicted value, p=0.02), without improvement for other respiratory parameters. VO_2 did not change at the ventilator threshold or at peak exercise. At the mitochondrial intercostal level, V_{max} is more important in the TG (29.6±8.6 *vs* 21.1±3.7pmol$O_2 \cdot s^{-1} \cdot mg^{-1}$, p<0,05), and H_2O_2 release also tends to be greater (0.6±0.2 *vs* 0.4±0.2pmol$H_2O_2 \cdot s^{-1} \cdot mg^{-1}$, p=0.06). These preliminary results show that a short training period in COPD patients induces adaptations of the intercostal muscle. The increase in V_{max} and oxidative stress reflects the initiation of an adaptive muscle process in response to training. Further work is needed to better characterize the links between PFT / CPET results and tissue analyzes.



Surname : ELSHENNAWY

First Name : Mennatallah

Year of PhD : 3rd year

Research and Team and Laboratory : EA7280 (Laboratoire de Neuropsychopharmacologie des Système Dopaminergiques Sous Corticaux)

PhD supervisor : Dr HAFIDI Aziz ; Dr YOUSSEF Shahira

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A study of different structures of central nervous system implicated in Parkinson's disease neuropathic pain.

A lot of attention is now directed towards pain symptoms felt by Parkinsonian patients. Aside with new clinical methodologies developed to assess pain in clinics, basic research is directed towards discovering the fundamental causes of this painful sensation. Although there are some mechanisms that have been considered involved in allodynia in Parkinsonian patients, these mechanisms have not been totally discovered. This study aims to uncover some of the mechanisms responsible for allodynia in Parkinsonian rat models. It may lead to important applications in ameliorating treatment choices that help in relieving neuropathic pain in Parkinsonian patients. 6 – OHDA was injected bilaterally in the MFB using stereotaxic surgery technique. Cold allodynia was tested in Parkinsonian rat models using acetone stimulus. D2 agonist was tried as a treatment to ameliorate pain. Behavioral tests were used; Rotarod motor test was used to validate the Parkinsonian model, followed by flinches number, reaction time and latency for testing allodynia. Immunohistochemical studies were also done, primarily TH to validate our model, followed by pERK which is a molecular signature for pain and PKC- as excitatory molecular signature for chronic pain. Besides GAD67 & VGAT being used as inhibitory markers and GFAP was used for measuring astrocytic activity. Behavioral tests have shown an increase in flinches number, latency and reaction time in Parkinsonian rats than sham ones. In addition, in the spinal cord dorsal horn; pERK, PKC-, GAD 67 & VGAT were increased in the lesioned group, while GFAP was decreased. After treating the Parkinsonian rats with Ropinirole (5 mg/kg), their sensitivity to painful allodynic sensation was decreased, besides pERK, PKC-, GAD67, VGAT decrease and GFAP increase. These results show that cold allodynia is present in Parkinsonian rats through the decrease of inhibitory mechanisms and the increase of excitatory ones, which may be reversed using D2 agonists.

COMMUNICATIONS AFFICHEES

Surname : DUPUIT

First Name : Marine

Year of PhD : 2nd year

Research Team and Laboratory : Laboratoire AME2P

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High intensity interval training (HIIT) and/or food plant-based supplements on body composition, gut microbiota and metabolic profile in an obesity context

Obesity, and especially excess of abdominal adipose tissue, results from a combination of different factors, including hormonal status, unbalanced energy intake, sedentary lifestyle and, directly or indirectly, gut microbiota composition. In postmenopausal women, the increase of subcutaneous and particularly intra-abdominal fat mass (FM) partly explains the higher cardiovascular risk. Management of overweight and obesity with physical activity is essential. Moreover, nutritional aspects are also important to impact fat mass and gut microbiota. Food plant-based supplements had shown beneficial effects to prevent and treat metabolic diseases. In my Master's work, we demonstrated that high-intensity interval training (HIIT), associated or not with resistance training (RT) is a safe and effective strategy to reduce total and intra-abdominal FM in overweight/obese postmenopausal women. In order to understand underlying mechanisms of HIIT on fat mass loss and metabolic profile improvement, we had conducted a preclinical study in a diet-induced obesity rat model. We had also tested a plant-based compound developed by Valbiotis, a research and development start up, in combination with exercise. Nowadays we know that physical activity can modulate gut microbiota composition and function. Thus, we had conducted a new clinical study with the CREPS Auvergne Rhône Alpes in Vichy, to study the effects of HIIT combined with RT on body composition and gut microbiota composition in overweight or obese postmenopausal women.

VALBIOTIS AME2P LABORATOIRE Activité Physique Métabolisme & Santé

Surname : OMARA

First Name : Hend

Year of PhD : 2nd year

Research Team and Laboratory : EA7280

PhD supervisor : Hafidi Aziz

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Tramadol induced CPP and motor sensitization in the rat

Tramadol use disorder is a big health problem all over the world, Tramadol is a synthetic opioid used for the treatment of moderate to severe pain, there is an evidence for its abusive effect in humans but there are discrepancy on its abusive potentials in rats. Naltrexone is opioid antagonist which block the effect of Tramadol on CPP. Therefore the present study aimed to investigate the abuse potential of Tramadol in rats using the conditioned place preference (reinforcing effect of a drug). And its effect on the motor activity during the conditioning sessions. Drug which has a CPP effect and increase the motor sensitization is considered a drug of abuse. The present results show Tramadol (10mg/kg) produced CPP. In addition there was a clear motor sensitization. The Tramadol induced-CPP was significant during the 6 days after the test-day. Similarly the motor sensitization was also significant 6 days after the test-day. Naltrexone, an opioid receptor antagonist, decreased significantly the Tramadol-induced CPP. The subcutaneous administration of Naltrexone blocked completely the CPP after 4 days after the test-day. These results showed that Tramadol can be considered as a drug of abuse in the rat and that Naltrexone decrease this effect.

Hend OMARA, Omar OUACHIKH, Franck DURIF and Aziz HAFIDI, EA7280, Université Clermont Auvergne.

Surname: CRAVEIRO DA COSTA

First Name: Daniela

Research Team and Laboratory: Laboratoire AME2P

PhD supervisor : Daniel Courteix

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Body composition, isokinetic strength and bone health in male adolescent athletes contrasting in mechanical loading

Introduction: Training characterized by weight-bearing activity induces osteogenic effects on bone. It was already observed a relationship among muscular strength, Bone Mineral Density (BMD) and biochemical markers of bone remodeling in athletes. The present study aimed to analyze the differences between two groups of athletes from soccer and swimming at the baseline of two years longitudinal study on body composition, isokinetic strength, and bone composition. **Methods:** The sample included 70 adolescent athletes from two sports contrasting in mechanical loading: soccer (n=36; 12,16 ± 0,80 years) and swimming (n=34; 12,11 ± 0,90 years). Body mass, stature, and sitting height were measured. Dual-energy x-ray absorptiometry was used to examine bone parameters and isokinetic strength of knee flexors and extensors was assessed at 60 °/s in concentric and eccentric actions. Differences between groups were analyzed performing Mann-Whitney U test, according to data normality. **Results:** Chronological age, stature, body mass, lean soft tissue, fat mass and strength parameters at baseline were similar between groups. BMD and bone mineral apparent density were significantly higher in soccer than in swimming athletes. **Conclusion:** At baseline of a longitudinal study that aims to assess the effect of training and growth on body composition, isokinetic strength and bone health are expected that the groups present no differences in the study variables. The present analysis showed that adolescent soccer players however presented a higher bone density than the same age adolescent that practice swimming. This can lead to conclude that after two years of study, the differences will be higher.

Surname: PERIS MORENO

First Name: DULCE

Year of PhD: 1st year

Research Team and Laboratory: Proteostasis, UNH, INRA

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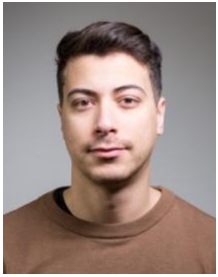
Developing new strategies to limit TRIM63/MuRF-1-mediated muscle protein loss

Skeletal muscle atrophy is defined as the *decrease in muscle mass and muscle strength owing to injury, ageing, starvation, disuse or disease*. Such muscle loss occurs upon protein homeostasis imbalance due to decreased protein synthesis and/or increased proteolysis, the latter being preponderant in most catabolic situations. Both the ubiquitin-dependent proteasome system (UPS) and the autophagy proteolytic pathways are activated during catabolic situations. In the specific case of the UPS, the muscle-specific E3-ligases, MuRF-1/TRIM63 is consistently upregulated under muscle atrophy and targets the proteins constituting the myofibrillar contractile system for subsequent degradation. In our case, due to the large overall protein content (80%) that the contractile apparatus represents for cells, it is important to study MuRF1 mechanism(s) of action and regulation. We study the modulation of MuRF1 activity by its companion ubiquitin-conjugating E2 enzymes. Indeed, MuRF1 binds to the substrates but the catalytic activity is brought by several E2 enzymes, each MuRF1-E2 couple having potentially different roles in muscle cells. *In vitro* methodologies (Surface Plasmon Resonance and MicroScale Thermophoresis) will reveal the MuRF1-E2-substrate interactions whereas *in cellulo* assays (gene overexpression and silencing) -in C2C12 muscle cells- will provide information about the impact of the MuRF-1-interacting E2s on skeletal muscle myofibers. Additionally, immunohistochemistry approaches in both C2C12 cells and mouse muscle tissue (tibialis anterior) will decipher the location of the different MuRF-1-interacting E2s. This will allow us to corroborate spatially the interactions observed *in vitro*.



Surname : SAIDI

First Name : Oussama

Year of PhD : 4th year

Research Team and Laboratory : laboratory of Adaptations to Exercise under Physiological and Pathological Conditions (AME2P)

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Do junior rugby players sleep better than their matched non sporting controls during the competitive season ? Week versus Weekend sleep discrepancy

Young athletes have to contend with constraints of sports practice on top of school commitments and physiological processes associated with adolescence. The purpose of this study was to assess week to weekend sleep in elite young rugby players during the competitive season compared to an age-matched non-athlete controls. 34 adolescents (GR: 17 elite rugby players, and GC: 17 healthy, aged matched, non-athlete) from the same boarding school filled a daily schedule of activities, sleep diary, and wear a multichannel electroencephalogram (EEG) for 14-day. Afterward they filled questionnaires regarding their daytime sleepiness: Epworth Sleepiness Scale (ESS), and stress: Perceived stress scale (PSS-10). Both groups showed insufficient sleep duration on weeknights (WN) (< 7 hours). However, GR presented an earlier bedtime ($p<0.007$), lower proportion of N2 ($p<0.05$), and higher time spent on stage N3 ($p<0.05$). During the weekend (WEN), GC increased their total sleep time ($p<0.001$), and time spent on REM stage ($p<0.001$), while sleep duration remained unchanged in GR. Otherwise GR experience a drop in sleep efficiency ($p<0.05$) marked by higher sleep onset latency (SOL) and wake after sleep onset ($p<0.01$) as well as a restriction of REM absolute time and proportion ($p<0.01$) in the WEN compared to WN. Restricted sleep duration and impaired quality during the weekend was related to increased sporting activities. Lower Δ time in bed (WEN-WN) was associated with higher sleepiness in both groups. Young rugby players exhibit poorer sleep outcomes than matched non-athlete controls during the WEN. Sleep considerations are necessary in young athletes especially when planning the Weekend sporting activities.

Surname : BIRAT

First Name : Anthony

Year of PhD : 2nd year

Research Team and Laboratory : Laboratoire AME2P

PhD supervisor : Sébastien RATEL

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Effect of Long-Duration Adventure Races on Cardiac Damage Biomarker Release and Muscular Fonction in Young Athletes

The aim of the present study was to examine the effect of 1- and 2-day adventure races on cardiac muscle damage and skeletal muscle soreness and function in young athletes. Twelve male trained adolescents (14-15 y) completed both 1-day (48.2 km) and 2-day (66.0 km) races that included trail running, mountain biking, kayaking, and in-line skating separated by 10 weeks. Myocardial damage biomarker concentrations (cTnI and CK-MB), maximal voluntary isometric contraction (MVIC) torque, perceived knee extensor (KE) muscle soreness (PMS), and drop and squat jump heights were measured before and after each race. Heart rate was also monitored throughout. Mean heart rate (% cardiac reserve) was higher during the 1-day (66.6±6.4%) than 2-day (62.6±7.8%) race. The amplitude of cardiac damage biomarker release was also higher following the 1-day than the 2-day race (peak cTnI: 0.14 vs. 0.03 ng/mL ; peak CK-MB: 20.30 vs. 11.98 ng/mL). However, cTnI and CK-MB returned to baseline at 24-48 h post-exercise. Eight and three participants exceeded the cTnI cut-off for myocardial injury in 1- and 2-day races, respectively, but none exceeded the cut-off for acute myocardial infarction. While there was a significant decrease in drop jump height (-5.9%), MVIC torque and squat jump height remained unchanged after both races. PMS was increased at 24 h after both races but returned to baseline levels by 72 h post-race. In conclusion, the shorter, more intense race produced more cardiac damage, although this probably represents a standard exercise intensity-dependent response rather than pathological response. Skeletal muscle functional and soreness responses were moderate and similar between races.

COMMUNICATIONS ORALES

Surname : LINAS

First Name : Natacha

Year of PhD : 3rd year

Research Team and Laboratory : CROC (Centre de Recherche en Odontologie Clinique), EA 4748

PhD supervisor : Dr Collado Valérie et Pr Hennequin Martine

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Impact of severe Early Childhood Caries and its treatment on masticatory parameters in 3-6 years children

Objective: The links between oral health, mastication and nutrition are poorly explored in children. This study aimed at analysing for the first time the granulometry of ready-to-swallow food boluses in children with severe Early Childhood Caries (S-ECC), and the impact of its treatment on masticatory parameters. **Method:** Thirteen children (control group) with a healthy oral state were compared to thirteen children with S-ECC (S-ECC group) before treatment under general anaesthesia (GA). An additional preliminary analysis was performed in eight children with S-ECC before and during the follow-up year after GA. Oral health criteria were collected. Number of chewing cycles (Nc), chewing time (Ti), and frequency (Fq=Nc/Ti) were recorded during mastication of raw carrot (CAR), cheese (CHS) and breakfast cereals (CER) samples until swallowing. Food boluses were collected by stopping children at their swallowing threshold (Nc), and the median particle size value (D50) was calculated. Correlations were sought between the oral health and masticatory criteria. **Results:** Before treatment, mean Fq and food bolus particle size were impaired in the S-ECC group for all three foods ($p \leq 0.001$) compared to the control group (i.e. D50CAR= 4384µm ± 929 vs. 2960µm ± 627). These alterations were related to the extent of ECC. Post-treatment analyses suggest that, overall, mean Fq values increased and mean D50 values decreased from 6 months post-GA (i.e. D50CAR: 4642µm ± 665 vs. 3320µm ± 594), without reaching the control group values. **Conclusions:** This study shows alteration of the masticatory parameters in children with S-ECC and their improvement after dental treatment. The possibility of mastication normalization, and its impact on nutrition and growth in children with ECC have to be confirmed.

Surname : CHOLTUS

First Name : Helena

Year of PhD : 2nd year

Research Team and Laboratory : Génétique, Reproduction et Développement (GReD), Team 10 «Translational approach to epithelial injury and repair»

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Symphony or cacophonia of the rupture of fetal membranes: RAGE and sterile inflammation.

Preterm premature rupture of membranes is a pregnancy complication responsible for 30% of all preterm births. This pathology seems more and more to be the consequence of an early process runaway activation usually implicated in the physiologic rupture at term called sterile inflammation. This phenomenon is dependent on some specific molecules called “alarmins” or “Damage-Associated Molecular Patterns” (DAMPs) recognized by Pattern Recognition Receptors (PRRs) leading to a microbial-free inflammatory response, called “sterile”. However, it remains unclear how exactly this activation works, and which receptor translates this inflammatory signaling in fetal membranes to manage a successful rupture not before 37 weeks. In this context, we focused our work on one actor of the sterile inflammation, the Receptor for Advanced End-Glycation products (RAGE).
Our first objective was to determine spatiotemporal expression profiles of the different actors of the RAGE signaling axis in different human fetal membranes zones. Our second goal was then to evaluate the implication of RAGE axis in the arising of fetal membranes inflammation. This work proves that fetal membranes expressed RAGE signaling actors throughout the pregnancy and at term. Moreover, RAGE was found overexpressed in the zone of rupture. All together, our results strongly suggest that alarmins led to an inflammatory response involving RAGE pathway in fetal membranes.

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Postprandial responses to the dairy product intake in men : effect of the type of products and age

Numerous studies suggest that the intake of different types of dairy products (DPs), particularly fermented DPs, are correlated with different health benefits. To fully elucidate these associations, it is necessary to improve their dietary assessment by identifying biomarkers of specific DP intake, while considering the different metabolism in diverse populations such as the elderly. Therefore, we aim to identify the metabolic signatures associated with milk (M) and yogurt (Y) intake in young (YM) and elderly men (EM). A randomised, controlled and crossover study was conducted with healthy YM (n=14, 20-35 y) and EM (n=14, 65-80 y). After a 3 weeks of run-in period, the subjects consumed 600ml of M or Y. Postprandial (PP) serum, urine, and faecal samples were collected for 24h and analysed through an integrated biochemical, metabolomic, and microbiome approach. Serum glucose levels were higher after M than Y intake for both groups at 30min (YM: 6.0±0.2 vs 5.3±0.2, EM: 5.9±0.2 vs 5.2±0.1 mmol/L, $P<0.05$). PP insulinemia was also higher at 30min after M than Y intake for both groups (YM: 9.0±1.3 vs 7.7±1.0, EM: 1.1±1.2 vs 8.7±0.8 nmol/L, $P<0.05$). Conversely, glucose dependent insulinotropic polypeptide (GIP) levels were higher after Y than M intake at 60min (YM: 347±33 vs 229±34, EM: 406±50 vs 264±28 pg/ml, $P<0.05$). PP triglyceride levels were higher in EM than YM regardless of the DP (AUC M: 72±11 vs 26±16, Y: 77±9 vs 40±15 mmol/L/min, $P<0.05$). IL-6 levels decreased in EM after Y intake (-14%, $P<0.05$), with a similar trend after M intake (-11%, $p=0.26$). These results suggest that both fermentation and age induce different metabolic responses in men consuming DPs. Ongoing metabolomic and microbiota analyses will clarify these differences and aid in the identification of candidate biomarkers of DP intake.

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Quantitative proteomic analysis of macrophages from Crohn's disease patients and infected with adherent-invasive *Escherichia coli:* Impact of anti-TNFα treatment.

Intestinal macrophages play a key role in the pathogenesis of Crohn's disease (CD). These macrophages present a defect in the control of CD-associated adherent-invasive *E. coli* (AIEC) replication. The main aim of this study was to compare the proteomic profile of macrophages from CD patients with anti-TNFα treatment, to those without anti-TNFα treatment, both at the basal state and after AIEC infection. Peripheral blood monocyte-derived macrophages (MDM) were obtained from 44 CD patients including 22 with anti-TNFα treatment and 22 without anti-TNFα treatment, infected or not with AIEC LF82 reference strain. The "bottom-up" proteomic analysis of macrophages was assessed by mass spectrometer, using the *label-free* quantification. AIEC survival was 3-fold lower in MDM from CD patients with anti-TNFα treatment compared to those without TNFα treatment. Among the 1173 proteins identified by the proteomic analysis, 46 were significantly differentially expressed at the basal state between the CD patients with anti-TNFα treatment and those without anti-TNFα treatment including 9 with a fold change superior to 1.3. The effect of AIEC infection highlighted 53 proteins which were specific in CD patients with anti-TNFα treatment and 44 in CD patients without anti-TNFα treatment. The regression analysis revealed a significant interaction between the AIEC LF82 infection and the impact of anti-TNFα treatment on the expression of CD82, ILF3, CHI3L1 and FLOT1 proteins. Our data highlighted that the anti-TNFα treatment limits bacterial replication. For the first time, the proteomic analysis revealed new proteins including CD82, ILF3, CHI3L1 and FLOT1. These proteins could play a key role in the anti-TNFα treatment/AIEC replication modulation and represent a potential therapeutic targets in CD patients.

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Impact Of Magnesium On Stress In Fibromyalgia: A Double-Blind Placebo Controlled Clinical Trial.

Background and aims: Fibromyalgia (FM) is characterized by widespread chronic pain, sleep disorders, cognitive and emotional impairment as depression, anxiety and stress. Stress has been demonstrated to be involved in FM. Moreover, studies have reported that a link exists between magnesium deficit and stress. The aim of this study is to evaluate the impact of magnesium supplementation on stress in patients suffering from fibromyalgia. Methods: A double-blind placebo controlled clinical trial in 2 parallel groups (NCT03887000) took place in the Clinical Pharmacology Center-Inserm 1405, University Hospital Clermont- Ferrand, in 76 patients suffering from fibromyalgia (2016 American College of Rheumatology Criteria (ACR)). Patients received 100 mg oral magnesium or placebo during one month between visit 1 (day 0) and visit 2 (day 28). Stress was evaluated with the Depression Anxiety Stress Scale (DASS) questionnaire before and after treatment and on visit 3 (day 84, end of study). Samplings for blood and urinary magnesium, pharmacogenetics and stool (for microbiota) were done. Pain, cognition, sleep, quality of life were evaluated. Results: At the moment 56 women suffering of fibromyalgia have been included. 20 patients are planned to be recruited and the last patient last visit is scheduled in Mars 2020. First data analysis will be realized on Mars 2020 and final results will be available in April 2020. Conclusions: This study will highlight the possible effect of magnesium on stress in a population of women suffering from fibromyalgia. Patient follow-up is still ongoing and will allow to evaluate if there is an effect of magnesium on pain, cognitive-emotional aspects, sleep, quality of life in this population.

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Representations of chronic disease in health professionnels: between negative representations and engaged reflexivity

World Health Organisation (WHO) definies therapeutic patient education (TPE) as the acquisition of skills necessary to best manage life with a chronic disease. The resulting relationship is based on partnership and takes place over time. The role of health representations of professionals of chronic disease should be taken into account in supporting care providers, as they will guide their educational practices.
Method: In TPE training, professionals choose photos that evoke the chronic disease. All the keyword per photo have been collected. The key words according to whether they were melioratives, pejorative or neutral made it possible to determine 3 categories of photos: those evoking negative, positive or neutral representations. The photos were classified by theme.
Results: 223 health professionals and other health care providers participated in the study through 15 training sessions and divided into 54 working groups. 3 photos were chosen in the majority. 9 themes were highlighted. Overall, the representations of chronic disease are negative.
Conclusion: This approach confirms the particular positioning of health professionals in terms of their view of chronic disease and reinforces us in the need to work on the representation of chronic disease and to put the improvement of the patient's life back at the centre of TPE processes.

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The REMOVE study: High vs low spenders in energy expenditure during a light cycling exercise.

The time of sedentary behaviour (SB) and level of physical activity (PA) are predictors of morbidity and mortality. Tertiary employees are spending most of their worktime at sedentary behaviours. It is crucial to investigate ways for tertiary workers to reduce their SB and increase their time of PA. The REMOVE study aims to assess the effects of a portable pedal exercise machine (PPM) set under a desk in tertiary office compared to a conventional sitting desk.
A randomized controlled trial (RCT), prospective, open-label, multicenter, two-arm parallel with office-sitting desk workers will be conducted. Office workers (N=75), having 0.8 full time equivalent hours (FTE) with 75% of this time in a sitting position, will be recruited from tertiary worksite of Clermont-Ferrand, France. Subjects will be randomly assigned to one of the two fallowing group: i) 60min of PPM per working day during 6 months, ii) 3 months with no intervention fallowed by 3 months of 60min of PPM per working day. Investigation will be conducted before (T0) at 3 months (T1) and at 6 months (T2) of protocol. At each point PA and sedentary time will be measured by accelerometer during working hours and non-working hours. Body composition, physical fitness, resting metabolic rate (RMR), will also be evaluated. Level of stress and anxiety, life span and quality will be assessed by questionnaire. Finally, an ergonomic approach will be used along the project to identify parameters that could affect adherence of the participants to this intervention.
The poster will present results of the first phase on the cardiometabolic aspect after 3 month of intervention.

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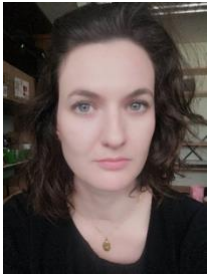
Effect of a short home based training program in patients with COPD before lung cancer surgery

Introduction : Pulmonary Rehabilitation (PR) performed at the patient's home before lung resection surgery for cancer remains to be evaluated but could be an interesting alternative. Our aim was to assess the benefit on physical capacity of a preoperative high-intensity interval training program performed at home in patients with COPD. Methods : In a multicenter randomized trial, we identically assessed before and after a 3- week high-intensity interval training program performed at home with a cycloergometer, peakwork rate (PWR) and maximum oxygen uptake (VO2peak) during a cardiopulmonary exercise test, 6-Minute Walking Distance (6MWD) and Maximum Quadriceps Strength (MQS). Results : The groups of patients [Training Group (TG, n=13) and Control Group (CG, n=15)] do not differ initially. Adherence to the training program is excellent (87%). PWR significantly increased in TG compared to CG (+12±11 vs. 0±10 W, p=0.006). VO2peak tends to increase in TG (+1.0±1.1 vs. 0.0±1.5 ml.min-1.kg-1, p=0.061). The 6MWD and the MQS do not vary significantly. Conclusion : A short duration high-intensity interval training program can be performed at home before lung resection surgery. Patient adherence is excellent. This program improves the peakwork rate. The improvement of other prognostic physical parameters such as VO2peak requires the inclusion of a larger number of patients. The effect of this training on postoperative morbidity and mortality remains to be determined.



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Mind the cuticle conductance: When resistance to cavitation is not enough for evaluating plant resistance to drought.

In the actual global warming context, drought events will tend to be more intense and more frequent, increasing the risk of dessication and death for plants induced by hydraulic failure. Under drought conditions, the higher atmospheric demand for water together with reduced water availability for plants increase the xylem tension until the xylem water columns break due to cavitation. To avoid reaching such risky xylem tensions, plants close their stomata to reduce the amount of water lost by transpiration and, therefore, keep the water potential relatively constant. However, despite stomatal closure, there are still some water losses through the plant cuticle (g_{min}) that keep the xylem tension decreasing. How efficient the plants are in reducing such water losses and how resistance are to cavitation (P50) will define the resistance of plant to drought. While the link between resistance to drought and P50 has been widely studied in the past, less is known about the link between drought resistance and variation in g_{min}. Indeed, g_{min} not only varies across species but also within species under different environmental conditions. We will evaluate here i) the link between g_{min} and cuticle composition; ii) the link between P50 and g_{min}, and iii) the role of g_{min} in plant resistance to drought.

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METABOLIZATION OF FLAVAN-3-OLS BY HUMAN GUT BACTERIA

Introduction: Flavan-3-ols are a largely consumed subclass of flavonoids and are involved in the prevention of cardiovascular diseases. The contribution of phenolic metabolites produced by the gut microbiota in the health effects of polyphenols (including flavan-3-ols) is currently an open field of investigation. The aim of our study was to identify gut bacteria degrading flavan-3-ols and the degradation products.
Materiel & Methods: Bacteria degrading flavan-3-ol were isolated from feces of healthy donors. The metabolites were then characterized using LC-MS/MS.
Results: Twenty two bacterial isolates belonging to *Eggerthella lenta* (n=20) or *Flavonifractor plautii* (n=2) species were obtained. These two species co-metabolized (+)-catechin and (-)-epicatechin into hydroxyphenylvaleric acid derivatives.
Conclusion: We obtained a collection of bacteria degrading flavan-3-ols into several phenolic metabolites whose biological activity is currently under investigation

COMMUNICATIONS ORALES

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Study of the roles of the Constitutive Androstane Receptor in testicular physiopathology

The increased incidence of fertility disorders in the last decades suggests the involvement of environmental factors. Indeed, studies have shown that exposure to pollutants in early-life periods (embryonic and neonatal), which are highly sensitive to xenobiotics, could lead to fertility disorders (Skakkebaek et al., 2016; Sèdes et al., 2018).
Interestingly, the nuclear receptor of xenobiotics CAR (Constitutive Androstane Receptor; NR1I3), which is involved in hepatic xenobiotics detoxification, is expressed and active in the adult mouse testicular germ cells (Martinot et al., 2017).
Our goal is to define the roles of the nuclear receptor CAR in testicular physiology and physiopathologies. For that purpose, we combined genetic (wild-type and CAR knock-out mice) and pharmacological approaches (agonist and inverse agonist).
The testicular impacts of neonatal modulations of CAR signaling pathways during the first 10 days of life with a CAR agonist or with a CAR inverse agonist was performed using wild-type and CAR knock-out male mice. In addition, the role of CAR in germ cells was studied using a spermatogonial cell line in which the CAR signaling pathway was modulated by pharmacological and/or Crispr/Cas9 approaches.

Combined our data indicate that the modulation of CAR signaling pathways affects the homeostasis of spermatogonial stem cells and in turn results in a decline in the spermatogenesis efficiency and by the way in altered reproductive capacities.

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Towards a fiber-based strategy to prevent bacteria-mucus interactions in enterotoxigenic escherichia coli infections?

The main pathogenic agent of travelers' diarrhea, Enterotoxigenic *Escherichia coli* (ETEC), is responsible of 45% of the 200 million cases occurring each year. The treatment of such infections remains mainly symptomatic with a frequent use of antibiotics. Given the burden of antimicrobial resistance worldwide and its negative impact on human health, it is urgent to develop new preventive strategies. Recent works in mice have suggested that a fiber-free diet promotes mucus layer erosion associated with an increase susceptibility to intestinal pathogens (Desai et al., 2016). During the infection process, ETEC also have the ability to reach the underlying intestinal epithelium through the mucus layer, suggesting that preserving mucus barrier integrity through a fiber strategy could decrease infection susceptibility. Using *in vitro* models, such as co-culture of intestinal epithelial and mucus-producing cells, we aim to (1) better understand the role of mucus layer in ETEC pathogenesis and (2) investigate a preventive strategy against ETEC pathogens using different soluble and insoluble fibers. Our *in vitro* results show that the presence of mucus promotes ETEC adhesion, virulence gene expression and LT toxin production. Among 8 candidates, lentil fibers and yeast walls have shown their ability to prevent ETEC adhesion to mucus, toxin production and intestinal epithelial inflammation. In the future, the antagonistic properties of these selected fibers against ETEC-mucus interactions will be further deciphered. In particular, the role of human gut microbiota will be investigated using *in vitro* colonic models. This work sheds light on a new possible preventive strategy against enteric infection based on the use of dietary fibers.

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Analysis of miR-1 and its potential target Multiplexin deregulated in myotonic dystrophy type 1 (DM1)

Myotonic dystrophy type 1 (DM1) is an autosomal dominant, multisystemic disease, caused by an expansion of CTG repeats in 3'-untranslated region of the dystrophia myotonica protein kinase gene, leading to conduction defects, dilated cardiomyopathy and cardiac arrhythmias. Healthy individuals have 5 to 37 CTGexp. Whereas, DM1 patients carries from >50 to ≈4,000 CTGexp. The mutated Dmpk transcripts sequesters MBNL1 (Muscleblind-like1) and stabilizes CELF1 (Elav-Like Factors1), alternative splicing factors that bind to 3'UTR of their target genes. MBNL1 regulates miR-1 maturation, muscle and heart-specific microRNA, conserved between Drosophila and human, involved in cardiogenesis, decreased in DM1. In our study, we used Drosophila to perform a functional analysis of miR-1 and it potential target multiplexin (Mp) (Collagen XV/XVIII in mammals), deregulated in DM1. First, we validated the deregulation of miR-1 in our drosophila models by single molecule fluorescence in situ hybridization. Then, we analysed miR-1 loss of function effects on cardiac structure and physiology by Semi-intact Optical Heartbeat Analysis (SOHA) approach. Second, we analysed the Mp expression in DM1 context by immunostaining and we tested Mp gain of function effects on cardiac structure and physiology. We also tested the rescue of heart dilatation observed in DM1 context by inhibiting Mp. Finally. we tested the direct regulation of Mp by miR-1 *in vivo* by generating GFP-Mp3'UTR lines. Our results show that miR-1 loss of function in heart causes an increase in it direct target, Mp, leading to dilated cardiomyopathy, similar to DM1 symptoms. Mp inhibition rescues dilated cardiomyopathy observed in DM1.

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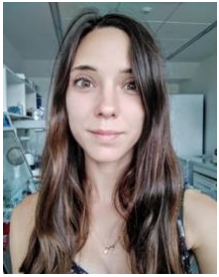
Management of bacterial communities in PDO farmhouse cheeses towards optimized sensorial and sanitary qualities

Nowadays, consumers are looking for traditional products, like raw milk cheeses, but also demand safety guarantees. For this reason, commercial lactic starters can be used to manage cheese acidification, and thus contribute to the protection against unwanted microorganisms. But an inappropriate use of starters could impact microbial diversity and sensorial qualities in raw milk cheeses. The goal of my project is to investigate the impact of the lactic starter dose, depending on the milk origin, on the microbial diversity, and sanitary and sensorial qualities in raw milk cheeses. To address this question, Saint-Nectaire-like cheeses are manufactured from raw milk added with different doses of lactic starter, between one hundred-fold lower and ten-fold higher than the recommendation (6.10^6 CFU/g). Microbial dynamics in cheese during ripening is determined by 16S and ITS gene-based metabarcoding approach. Levels of the main microbial groups and of pathogens are determined by plate count on selective media. Sensory profiles are evaluated on pathogen-free cheeses by 10 trained panelists. Gross physicochemical parameters of milk and cheeses are recorded. The results confirm that the lactic starter dose determines early acidification rate, and that the recommended one is required to ensure protection against pathogens. Regarding the microbial diversity, the results show that the lowest the dose, the highest the bacterial richness. Cheese bacterial profiles (Beta-diversity) also clustered depending on the starter dose. Dose-dependent differences tend to decrease with ripening time. Data analysis will be continued with the aim to assess the relationships between changes in microbial balances and physicochemical and sensory characteristics of cheeses.



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Trapping a somatic endogenous retrovirus into a germline piRNA cluster immunizes the germline against further invasion

The genetic and epigenetic information of the germline is particularly sensitive since it needs to be transmitted to the progeny. Due to their mobilization capacity, transposable elements (TEs), one of the main components of eukaryotic genomes, constitute a significant threat to genome stability. Hence, metazoans germline has developed dedicated mechanisms to limit their mobilization via a specific class of small RNAs, called piRNAs (PIWI-interacting RNAs). This project aims to better characterise this pathway using female gonadal tissue of *Drosophila melanogaster* as a model. Most piRNAs required for TE silencing are produced by particular loci called piRNA clusters. Here, we studied a mutant line in which a major ovarian piRNA cluster, the flamenco locus, is partially deleted, leading to the abolishment of piRNA production from the deleted region in somatic follicular cells. This resulted in germline genome invasion by some TEs including *ZAM*, a prototypic somatic transposon. The aim of the study was to understand whether, after the invasion, new protective mechanisms appear against *ZAM* mobilization in germinal cells.
We identified sense and antisense ZAM-derived piRNAs produced in the germ cells of mutant ovaries. These piRNAs efficiently silenced ZAM expression in the mutant germline and were produced from a germline dual-strand piRNA cluster localized on the X chromosome.
Our results show how the germline protects itself and controls genome invasion by TEs. Transposon trapping in piRNA clusters is a general mechanism, which allows to keep information of past TE invasions and ensure transposon silencing.

COMMUNICATIONS AFFICHEES

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Evaluation of bioprotective strains and their metabolites for the control of microbiological quality of Cantal-like cheeses.

The population of micro-organisms in raw milk, contributes to the development of a richer flavour and taste in raw milk cheeses than in pasteurized milk cheeses. However, raw milk can be contaminated by different unwanted microorganisms such as Clostridia and Listeria. The presence of *Clostridium tyrobutyricum* causes the cheese to inflate leading to the late blowing defect which makes cheeses unsuitable for consumption. *Listeria monocytogenes* can also occur in raw milk cheese and causes listeriosis. Because of thermic resistance of clostridium's spores and the will to maintain the biodiversity of micro-organisms in cheeses, thermic treatment may not be the most suitable way to control unwanted microorganisms. Biosourced peptides with anti-microbial activity against pathogens and bioprotective strains could be an alternative. Among them, nisin and a nisin-producing Lactococcus *lactis* strain (UL32) have shown activity against *L.monocytogenes* and *C.tyrobutyricum*. The broad spectrum of action nisin might make it interesting to use in dairy productions but its impact on the microbiota of cheese and on the cheese matrix isn't yet fully understood. To address this question, two cheese-making tests have been designed to evaluate the effect of nisin and of UL32 on cantal-like cheeses made from raw milk supplemented either with *C. tyrobutyricum* or with *L. monocytogenes.* Gross physicochemical parameters of milk and cheeses during ripening were recorded. Levels of the main microbial groups and of pathogens will be determined by plate count on selective media. Microbial diversity profiles will be determined by a metagenetic approach. The first results show that different doses of nisin and different levels of inoculation of UL32 (10^3UFC/ml and 10^5UFC/mL) have an impact on the acidification of the milk which, at 5.4mg/mL of nisin, is out of the specifications of the cantal cheese technology. These results suggest that nisin and UL32 might have a pernicious effect on the lactic acid bacteria starter. To understand this effect, biocompatibility and acidification tests in co-cultures of starter strains and nisin or UL32 strain will be performed.

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Impact of nitrite on the physiology of Shiga-toxin producing *Escherichia coli* and on the nitrosation of meat proteins in a gastrointestinal digestion model

Human infection with enterohemorrhagic *Escherichia coli* (EHEC) occurs through the ingestion of contaminated food. This zoonotic infection can lead to aqueous or bloody diarrhea and in 5 to 10% of the patients to more severe hemolytic uremic syndrome (HUS). Children under the age of 5 are particularly at risk. EHEC infections are associated with the consumption of contaminated foodstuff, especially meat and cheese, the consumption of ground beef is by far one of the main source of infection. In our study, we characterized the physiology of EHEC in raw ground beef meat during digestion using a controlled digestion system. In order to mimic a meal, digestions were performed in a meat matrix with and without nitrite and ascorbic acid (provided by vegetables). The digestion lasted 4 hours. The first 2 hours were in gastric condition in the presence of pepsin and a gradual drop in pH from 5 to 2. The intestinal stage lasted an additional 2 hours, with trypsin, chymotrypsin, intestinal lipase and bile salts and a raising the pH to 7. Biochemical, microbial and molecular analyzes were carried out throughout the kinetics of digestion. The presence of nitrite during digestion influenced the oxidation of the meat compounds, nitrite having an antioxidant effect. Regarding the survival of EHEC, we observed a decrease of 2 log CFU / mL at the end of gastric digestion (with and without nitrite). In absence of nitrite, the population remained stable during the intestinal digestion, whereas in presence of nitrite, a further decrease of 1 additional log CFU / mL was recorded. A transcriptomic approach will allow us to characterize the response of EHEC to digestive and nitric stresses during the first steps of digestion.

Surname : OURTIES

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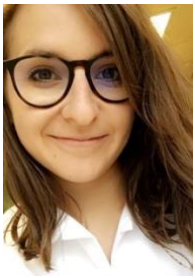
Involvement of Cav3.2 calcium channels in osteoarthritis

Osteoarthritis (OA) is the most common musculoskeletal disease affecting millions of people worldwide. Pain is the dominant symptom of OA. Current treatments are unable to recover from OA and they are not very effective on pain. Therefore, development of new therapeutic approaches are needed. The role of $Ca_V3.2$ channels, which are involved in other chronic pain conditions, was investigated in a murine model of osteoarthritis.
Male C57BL/6 mice (10-week-old) underwent destabilization of the medial meniscus (DMM) surgery to induce OA. Mechanical hypersensitivity was assessed during OA progression. The involvement of Ca_v 3.2 channels was assessed with different pharmacological (TTA-A2, ethosuximide) and genetic (knock-out) strategies. Human articular chondrocytes (hAC) were used for cellular and molecular approach.
After DMM surgery, an alteration of the joint cartilage and a decrease in mechanical threshold were observed in mice. This latter was increased in $Ca_v3.2$ KO mice or in animals treated with $Ca_v3.2$ inhibitors, TTA-A2 or ethosuximide. Contrary to a spinal Cav3.2 inhibition (TTA-A2 intrathecally injected) which reduced OA hypersensitivity, inhibition of Cav3.2 located on the primary afferent neurons (using conditional KO mice) did not have an effect. Interestingly, the alteration of cartilage was reduced in $Ca_v3.2$ KO mice. Furthermore, Cav3.2 channels are expressed in human articular chondrocytes. Thus, in DMM model, spinal Cav3.2 contributed to OA-induced hypersensitivity. In addition, Cav3.2 channels seems also involved in the joint cartilage alteration. Even if more studies are needed, this latter effect could be mediated by Cav3.2 channels located in chondrocytes. These results suggest that Cav3.2 inhibition could be a promising new therapeutic solution for the management of osteoarthritis pain.



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Genetic reprogramming involving a shift from TGF- β to BMP signaling for muscle mass maintenance in hibernating brown bear

Muscle atrophy arises from a multiplicity of situations (disuse, cancer, myopathies, aging etc), caused by an imbalance between protein synthesis and breakdown. The E3/E2s enzymes play a predominant role in muscle proteolytic machinery by targeting contractile proteins for degradation ; hence some of are refered as atrogenes (atrophy-related genes). Even though knowledge about the underlying mechanisms keep expand from induced-atrophy models, there is still no therapeutic or preventive treatment to date. In this context, we propose a non-common approach using a model of muscle atrophy resistance, the hibernating brown bear. Remarkably, this mammalian does not display muscle wasting during hibernation, being evolutionarily adapted to the two major atrophic inducers, immobilization and fasting. Consequently, to discern the adaptive mechanisms involved in muscle atrophy resistance, we explore brown bear muscle transcriptomic in summer active versus winter hibernating period. Expression of the usual atrogenes did not vary between the two seasons. Interestingly, we noted changes in expression of some E3s identified as participating in TGF-β super family inhibition, a cellular pathway divided in two canonical signaling: TGF-β signaling known to be overregulated in muscle atrophy and BMP signaling involved in muscle mass maintenance. First, TGF-β signaling appears to be curbed with i) a downregulation of the ligands *TGF-β1/3* expression, and ii) an overexpression of the E3s *NEDD4L*, *TRIM33* restraining the signal transduction. On the other hand, BMP signaling seems to be reinforced with i) an upregulation of SMAD1, BMP14, HOXC8 and ii) a down-regulation of the BMP signaling negative regulator, STUB1. Collectively, our data suggest a shift from TGF-β to BMP signaling for muscle mass maintenance in hibernating brown bear and highlight the BMP pathway as a potential therapeutic target to prevent muscle atrophy.

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Bioinformatic and Functional Analyses of Muscle Cell Diversification in *Drosophila melanogaster*

The somatic or body wall muscles of the fruitfly, *Drosophila melanogaster* embryo are analogous to vertebrate skeletal muscles. *Drosophila* somatic muscles present a simpler model to study muscle development since they consist of a single muscle fiber unlike vertebrates having multiple muscle fibers.

This project aims to unveil the genes and processes involved in conferring identity to specific embryonic somatic muscle subsets in *Drosophila* given that certain human muscular disorders are known to affect only certain muscle subsets. In the *Drosophila* embryo, each muscle's specific morphology, attachment site and innervation defines its identity which is specified by identity transcription factors or iTFs and their downstream unknown realisator genes. We generated high throughput TRAP data to capture mRNA under translation followed by microarray hybridization for 2 specific muscle subsets expressing specific iTFs.

A bioinformatic analysis for differential expression between the muscle subsets has unveiled a potential role for the Chip/LDB/Ssdp complex which is a known interactor for the known iTF Ap in the Lateral Transverse (LT) muscles.

Functional validation of this and other differentially expressed candidates and an snRNASeq for the somatic muscle population is in progress to reveal iTF specificities and the realisators responsible for the identity of muscle subsets.

Surname : ALOUANE

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Genome-wide characterization of potential effectors of eight strains of *Fusarium graminearum* with contrasting aggressiveness

During plant-pathogen interactions, microorganisms use a large number of pathogenesis-related molecules, including mainly secreted enzymes and effectors that can respectively degrade various defense compounds and further target plant susceptibility factors. In the fungal species *Fusarium graminearum* (*Fg*), the main causal agent of the Fusarium head blight (FHB) in cereal crops around the world, the diversity of such proteins is far to be characterized and their role remains widely unknown.

A genome-wide comparative study was carried out on eight European strains (four Frenches, three Italians and a German one) dispalying large differences in their aggresiveness in wheat cultivars. A pan-genome analysis was conducted to study the genomic diversity and evolutionary relationships with twelve other *Fg* genomes of different geographical origins. This revealed 20,807 non-redundant orthologous protein clusters while the core genome gathered 9,247 clusters (~52%) systematically found in all the genomes. About 5% of the whole predicted proteins in each strains displayed specific features of secretion, of which at least 29% corresponded to CAZyme ~16% to peptidases and ~20% to effectors (predicted by EffectorP).

In comparison with the reference PH1 strain, this work identified 1,283 genes containing mutations that could lead to a loss of function (LOF), ranging from 396 to 582 LOF genes. Of these, 79 LOF genes were shared in the eight genomes, while more than 30 genes were specifically lost in each genome. This work illustrates the association of comparative genomics with the contrasting aggressiveness of *Fg* and provides candidate genes for future functional studies.

COMMUNICATIONS ORALES

Surname : BOULET

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Characterization of TET mode of action during Drosophila hematopoiesis

Epigenetic modifications play a key role in the regulation of gene expression and alterations of the activity of epigenetic enzymes controlling these modifications are associated with numerous pathologies. Enzymes of the TET (Ten Eleven Translocation) family are critical regulators of gene expression in particular thanks to their capacity to oxidise methylCystosines (5mC) on DNA, and TET genes are frequently mutated in cancer, especially in leukemia. Drosophila, whose genome is lacking 5mC but codes for a TET enzyme, provides a unique model to assess TET function beyond 5mC DNA oxidation. In Drosophila, recent researches suggest that TET can demethylate 6-methylAdenine (6mA) on DNA, an epigenetic mark also recently found in mammals. Besides, many aspects of hematopoiesis are conserved between Human and Drosophila. This insect thus stands as a valuable model to study blood cell development and TET function during this process.

Accordingly, the main objectives of my thesis are to characterise TET function in Drosophila blood cells and to shed new lights on the mechanisms by which TET control gene expression. My results show that TET play an important role in regulating Drosophila blood cell homeostasis and control the expression of specific set of genes in the hematopoietic and nervous systems. We are currently studying the impact of TET on the 6mA epigenetic mark at genomic scale in these two tissues. In parallel, I aim at identifying the physical partners of TET to gain a better understanding of its mode of action. Ultimately, my results should help understand the functions of TET enzymes that are independent of 5mC DNA oxidation.

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Phenotyping beef cattle temperament traits using behavioural tests and accelerometers

Human-farm animals relationships are based on genetic predispositions. These individual predispositions, also called temperament traits, can be revealed through the observation of behavioural responses consistent over time and across situations. The study of temperament traits uses often short behavioural tests during handling procedures. However studies highlighted the possible interest of characterising them in their home pen using monitoring tools such as accelerometers and recording in particular their daily activity. The aim of this PhD project is to phenotype the temperament traits of beef cattle by using these two methods, connecting their results and calculate their heritabilities.

This study is carried out in partnership with France Limousin Sélection, the genetic association for limousine breeding. For revealing potential traits of temperament, six hundred young limousine bulls were scored during handling, or in their home pen for their reaction to human and novelty. These bulls wear tri-axial accelerometers equipment. These accelerometers provide the bulls' activity every five minutes (ingestion, rumination, rest, etc.) The proportion, frequency, bouts duration of each activity will be calculated and compared with behavioural scores. Preliminary results will be presented.

If temperament traits would be demonstrated using monitoring tools, this could facilitate their integration in the genetic selection program. This may lead to improvement of human- farm animals relationship.

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The role of SUMOylation in endocrine differentiation

Located between the capsule and medulla of the adrenal gland is the adrenal cortex, which is responsible for producing steroids, needed for mineral and metabolic homeostasis of the organism. It is composed of two distinct regions, the outer zona glomerulosa (zG) and inner zona fasciculata (zF). The cells composing these zones are renewed throughout life from progenitors located in capsular periphery. The balance between WNT/β-catenin and ACTH/PKA signalling controls cortical zonation renewal and maintenance, allowing for progenitor recruitment and appropriate differentiation into zG and zF cells. SUMOylation is a post-translational modification whose excess or lack is incompatible with early development, but whose importance in cortical cell differentiation is yet to be explored. In order to study the impact of hyperSUMOylation in endocrine differentiation, we used Cre-LoxP recombinase technology to develop a mouse model lacking Senp2 (coding a deSUMOylase) throughout adrenal cortex. Senp2 loss did not affect zG but was associated with an excess of progenitors and glucocorticoid insufficiency starting as soon as 1 month of age and caused by zF hypoplasia. HyperSUMOylation seems to affect zF renewal and ACTH/PKA sensitivity without having an impact on WNT/β-catenin signalling. The necessity of SENP2 and proper SUMOylation in adrenal maintenance has been confirmed by the arising of cells which escaped Cre-lox recombination, partly compensating the adverse effects of the mutation. Altogether these results show that SUMOylation has to be well regulated for adrenocortical cells to differentiate properly.

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Phenomic selection: an original, low-cost and efficient predictive method to improve wheat-breeding schemes

Since the 1990s, the yields of cereal crops have stagnated despite a constant genetic progress in crop breeding. Plant breeding consists in choosing the best offspring from a cross or population for a target trait based on phenotypic records. However, the effects of climate change and crop management evolution counterbalance genetic gain. One of the strategies identified to improve genetic progress is to use efficient predictive methods to increase the number of candidates in selection. The reference method called Genomic Selection (GS) puts together high-density molecular markers and phenotypes to calibrate a predictive model and then predict the yield of varieties not observed in the fields. Nonetheless, implementation of GS in selection remains limited due to the high cost of genotyping. Instead of molecular markers, a new method called Phenomic Selection (PS) uses the near infrared spectroscopy (NIRS). For each wavelength, a variety will absorb more or less light depending on its chemical and genetic compositions. It is then possible to characterize the variety by an absorbance spectrum. This technique has the advantage to be more affordable for breeders. The objective of this thesis is to improve wheat-breeding schemes in order to get a substantial genetic gain thanks to Phenomic Selection. Because of its recent development, PS has not been used yet in plant breeding so first, we will identify the program key steps in which PS can be applied. Then, we will compare PS and GS efficiency in different prediction scenarios using spectra from various origins: different environments, generations, tissues. Currently, in the few scenarios tested, better prediction accuracies were obtained with PS compared to GS for yield and heading date. Finally, the thesis work applied here on bread wheat is transposable to other species in particular to other cereals like maize or orphan species where access to high-density molecular markers is limited.

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Voltage-gating of aquaporins

Aquaporins are transmembrane water channels found in almost every living organism and therefore appear as of major significance in the well-function of cells. Although some simple organisms such as bacteria contain only a few isoforms encoded in their genomes, other more complex lifeforms like plants have maintained dozens of them. A lot of studies have brought a good understanding of water transport through the aquaporin's pores and the regulations that can take place at the molecular level but still a part of this diversity remains unclear. Recently a new voltage-related gating-mechanism has been presented for human aquaporins through molecular dynamics studies. Here we show that this voltage-gating could be conserved among the aquaporin family and that it could be of biological relevance in contexts of high ionic concentrations such as drought for plants, ensuring a closed/non-functional conformational state of aquaporins during such stresses. Moreover, we highlight a diversity in the ionic concentration tolerance threshold among the isoforms studied which might help explaining the genetic diversity of this channel family. Finally we identified some residues that could explain this functional diversity.

JEUDI 15 OCTOBRE 2020

COMMUNICATIONS ORALES

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DNA-methylation-independent epigenetic silencing in *Arabidopsis thaliana*

Transcriptional gene silencing is an essential mechanism for controlling the expression of genes and transposable elements (TEs) and is commonly associated with a high methylation level of DNA cytosines. Thus, release of silencing is frequently observed in mutants for genes involved in DNA methylation maintenance. However, studies in Arabidopsis thaliana have revealed that transcriptional repression of some DNA-methylated genes and TEs also relies on repressors that operate through pathways largely independent from DNA methylation. One such pathway seems to be linked to the DNA metabolism processes, DNA replication and DNA repair. Indeed, factors involved in these processes such as the polymerases *alpha, delta* and *epsilon* have been shown to cause global release of silencing upon depletion. To get a better view and understanding of these DNA-methylation-independent silencing pathways, we screened a mutant population specifically for mutants releasing transcription of a DNA-methylated silent transgene without decreasing its DNA methylation level. The analysis of this mutant population allowed us to isolate a new mutant allele of the helicase REGULATOR OF TELOMERE ELONGATION 1 (RTEL1) which we are currently characterising. RTEL1 is highly conserved among eukaryotes and plays an important role in the resolution of DNA secondary structures during DNA replication. This protein, along with other silencing factors linked to DNA metabolism, carries an Iron-Sulfur cluster binding motif. In addition, two mutant candidates isolated from the screen could be factors implicated in the formation and loading of Fe-S clusters suggesting a role for these clusters in transcriptional gene silencing.

Surname : GUARNIDO LOPEZ

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Is protein metabolism associated to between-animal variations in feed efficiency? Evaluation of Protein turnover in growing cattle.

The human population is expected to growth up to 9.2 million by 2050 and consequently the global demand of animal proteins. Thus, sustainable livestock systems need to improve the efficiency by which animals transform the feed resources into human food (i.e. feed efficiency) and face concerns related to profitability, environmental footprint and competition between animal and human feeding. In ruminants, feed efficiency is low compared to other livestock animals but the animal to animal variability is huge. Given this individual variability, the animal feed efficiency could be improved by genetic selection. However, genetic selection on a given animal trait might involve undesirable effects over others leading to trade-offs between animal traits. For this, research is needed to understand the biological mechanisms underlying feed efficiency and their potential impacts on other animal phenotypes. Protein turnover is essential for ensuring the maintenance of living organisms, it is an energy-consuming process accounting for 23% of total energy expenditure in ruminants. Higher turnover rates will impact in energy requirements and indeed, in feed efficiency. The hypothesis of my PhD thesis is that efficient animals have lower protein turnover rates compared to inefficient cattle. The objective of my thesis is to evaluate whether divergent growing cattle in terms of feed efficiency differ in protein metabolism and turnover.

Surname : EL SABBAGH

First Name : Nour

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Off Resonance Correction for multi-slice and multi-shot methods in MRI

Hyperpolarisation is a very popular technique used nowadays for increasing the Nuclear Magnetic Resonance (NMR) sensibility of half-spin nuclei other than ^{1}H. Metabolic imaging, i.e., obtaining one image per metabolite, can then be performed. However, a rapid acquisition strategy is required as the hyperpolarized signal is rapidly lost. In the first year of my thesis, I set up a fast imaging method for spectral/spatial encoding called « IDEAL SPIRAL » on a 11.7 T horizontal 9 cm bore magnet. Recording such information is performed thanks to a few MRI images obtained with slightly different timing. As an *a priori* knowledge, the frequency of each metabolite must be set in the algorithm to reconstruct the metabolic images.

Based on phantom (i.e., metabolites in different tubes) experiments, the IDEAL SPIRAL method led to excellent ^{13}C metabolic image reconstruction. However, this was only the case for images recorded at the centre of the magnet. As soon as the slice position was shifted, the metabolic images could not be reconstructed anymore, which is highly problematic for future *in vivo* experiments. This limitation was not described or discussed in the literature.

By shifting the slice from the magnetic centre, a slice-position related frequency was added to the metabolite ones. I demonstrated that, because images were recorded with different timing, the effect of this new frequency was different for each one. The NMR signal (more precisely, its phase) could not then be exploited. I proposed an easy-to-implement method to discard the undesirable effect of this added frequency.

I also demonstrated that this correction method must be applied in more general cases of multi-slice and multi-shot imaging. A manuscript describing these results is in preparation.

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The interest of combining CEST MRI and nuclear medicine imaging to detect changes in tumoral microenvironment: application to chondrosarcoma

Chondrosarcoma, the malignant tumor of the cartilage is the second most common bone cancer after osteosarcoma. This tumor is considered to be highly chemo- and radio-resistant due to a hypoxic tissue and a chondrogenic extracellular matrix (ECM). To oncologists, chondrosarcoma still presents a challenge in specific diagnostic imaging and therapy.
Recently, Chemical Exchange Saturation Transfer (CEST) MRI has emerged for its ability to monitor and quantify simultaneously *in vivo* phenotypical features of tumoral microenvironment such as hypoxia and components of ECM. In this context, we propose to evaluate the relevance of CEST MRI *in vivo* in a Swarm rat chondrosarcoma model (n=6) to monitor longitudinally, from day 4 to day 39 post implantation, both hypoxia and glycosaminoglycans (GAGs) of ECM. CEST MRI was compared to nuclear imaging: GAG concentration was determined by SPECT imaging, using the ^{99m}Tc-NTP 15-5 (n=12), a radiotracer developed in our group and hypoxia was monitored by PET imaging using, ^{18}F-FMISO (n=4), the referent clinical radiotracer. GAGs and hypoxia distribution within tumor microenvironment were controlled by *ex vivo* analysis in histology and immunofluorescence.
The combination of CEST MRI with nuclear imaging and *ex vivo* analysis were consistent to evidence GAGs remodeling during chondrosarcoma growth. Indeed, an average increase of 23% was observed with ^{99m}Tc-NTP 15-5 and 208% with *ex vivo* GAG assay. Work is still in progress to compare CEST MRI and PET for their performances to map tumoral hypoxic core.
To conclude, using multimodality imaging of phenotypes highly responsible of resistances to treatments open new perspectives in personalized oncology.
Grant: Ligue contre le cancer Auvergne-Rhône-Alpes

COMMUNICATIONS AFFICHEES

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Investigate conceptions of the determinants of health and cancer in children aged 6 to 11

Goals: Our goal is to map, using a multi-phase qualitative protocol, the conceptions and systems of conceptions of the determinants of health and of cancers perceived by children from 6 to 11 years old and to analyze our capacity to collect these conceptions.
Methodology: Four different tools were used in four schools: photo expression, QC (Questions / Certitudes), photo narration and focal group. This open and exploratory method, combining the use of photographs and focus groups, provides a better understanding of how children view the determinants of cancer and health. These methods of image mediation play an essential ethical role in ensuring the distance between the theme addressed and the child.
Results: 2554 productions were collected from 320 children aged 6 to 11 with a wealth of available data thanks to the complementarity of methodologies. This qualitative mass collection made it possible to validate a mixed analysis protocol (qualitative and quantitative) necessary for the production of the results. The concepts collected make it possible to identify the determinants of health and cancer perceived by children with an approach of risk factors and protective factors: relation to the environment, factors of fulfillment and personal development, health themes (activity physical, food ...), hygiene, care, protection, recommendation and support in health in the social sphere, affective dimension in social relationships, health capital. The different productions of each pupil nevertheless make it possible to obtain complementarity in the speech as and when the collection phases. This guarantees a "traceability" of each child which allows to deepen his conceptions and to know how he thinks the coherences between the determinants of health and cancer.
Conclusion: This study provides elements of methodological understanding that can contribute to the development of prevention tools for young audiences.

Surname : GRÈZE

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Highly sensitive assessment of neuroblastoma minimal residual disease in testicular tissue using RT-qPCR – A strategy for improving the safety of fertility restoration

Cryopreservation of testicular tissue (TT) is the only option to preserve fertility in prepubertal boys with neuroblastoma (NB). NB is the most common extracranial solid tumor in children and affects typically infants and has a high dissemination potential. TT may contain malignant cells which could lead to recurrence of the primary disease if the tissue is used after to restore fertility. High levels of TH (Tyrosine Hydroxylase), PHOX2B (Paired-Like Homeobox 2b) and DCX (Doublecortin) transcripts in bone marrow and blood at diagnosis and at the end of induction treatment were recently shown to be poor prognostic factors in NB patients.
Detection of residual disease was performed on fresh and frozen TT from 20 men with azoospermia by RT-PCR after contamination by increasing amount of two human neuroblastoma cell lines (IMR-32 and SK-N-SH) before detection of TH, PHOX2B and DCX transcripts by RTqPCR.
TH and DCX transcripts were detected in uncontaminated TT. PHOX2B was not detected in any uncontaminated testicular fragment. We observed a positive correlation between the expression level of PHOX2B transcripts and the amount of contaminating cells. PHOX2B enables sensitive and specific detection of NB cells contaminating TT and can be used for molecular diagnosis of residual disease in testis of prepubertal boys with NB.
These results offer hope in the near future to use testicular tissue without oncological risk in men who survive NB, whose fertility has been jeopardized, and who have benefited from TT cryopreservation.

Surname : SALAÜN

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Study of the interaction between an extracellular matrix with Down's syndrome and triple-negative breast tumor cells (MDA-MB468): epithelial-mesenchymal transition, migration.

Introduction / objective: The incidence of breast cancer is lower in patients with Down's syndrome (T21) and a protective role of the T21 extra-cellular matrix (ECM-T21) has been advanced. Triple-negative breast tumors are characterized by a strong invasive potential for which the epithelial to mesenchymal transition (EMT) and the migratory capacity of cells play an important role. Our objective is to determine whether an interaction between a triple-negative mammary adenocarcinoma cell line and an *in vitro*-secreted ECM-T21 could modify cell EMT and migration. **Materials and Methods**: MDA-MB 468 cells were cultured on ECM-T21, euploid (ECM-Eup) or on a plastic support. i / Expression of genes encoding E-Cadherin, occludin, claudin-1 (epithelial markers), vimentin and fibronectin (mesenchymal markers) was evaluated after 1, 2, 3 and 4 days of contact on ECM (J1 to J4). ii / Cellular migration testing was carried out after 6 days of contact on the ECM with scratch measurement at 0, 2, 4 and 6 hours (ImageJ®). **Results / Discussion**: i / The expression level of the genes coding for occludin and claudin-1 was higher at J3 in cells cultured on ECM-T21 than on ECM-Eup ($p < 0.001$). The genes coding for vimentin and fibronectin were less expressed in cells cultured on ECM-T21 than on ECM-Eup at J4 ($p < 0.001$). These results suggest that the interactions of cells with ECM-T21 could modify the regulation of genes involved in EMT and that the MDA-MB 468 transdifferentiation could be altered on ECM-T21. ii / There was no significant difference in cell migration on ECM-Eup and ECM-T21. However, cells on plastic support migrated faster than those on ECM. These results do not suggest a role for ECM-T21 on the migratory capacity of MDA-MB 468 but show that the presence of ECM in two-dimensional culture modifies the migration properties of cells.

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Deciphering of the adherence process of microsporidia to host cell.

Microsporidia are spore-forming, fungi-related intracellular parasites that infect both invertebrates and vertebrates. These parasites are important in human health, especially in immunocompromised patients, and in animal health as they cause losses in beekeeping, sericulture, aquaculture and fish farming. Microsporidia infect cells via a unique process involving extrusion of a polar tube, which injects the sporal content into the host cell. This process needs a prior adherence of spores that is mediated in part by host cell surface glycosaminoglycans. Exogenous sulfated glycans can reduce the spore adherence. Several glycosaminoglycan mimetics have been successfully tested as antimicrosporidian agents, in particular through their capacity of interfering with the adherence process. A sulphated heteroxylan purified from the microalgae *Porphyridium marinum* (PM) has shown to reduce in vitro growth of *Encephalitozoon cuniculi*, a microsporidia infecting mammals and to induce a reduction of mortality and parasite load in *Nosema ceranae* infected honeybees in laboratory and semi-field experiments. This project aims to characterize parasite spore surface proteins that could be involved in spore adherence and infection of host cells of the microsporidian models *E. cuniculi* and *Anncaliia algerae*. To identify proteins that are located at the spore surface, surfomics approaches will be done as well as an *in sillico* approach as 7 proteins have been selected by bioinformatics prediction. These proteins will then be produced in heterologous systems (the bacteria *Escherichia coli* and the yeast *Pichia pastoris* for post-translational modifications). Adherence and infection assays will then be undertaken to evaluate the inhibitory ability of the recombinant spore surface proteins or antibodies against these proteins on the spore adherence and infection. The interaction between parasite recombinant proteins and host glycosaminoglycans will be evaluated by Isothermal Titration Calorimetry (ITC) analysis. This project will help to better understand the adherence processes of microsporidia to host cells and paves the way for new solutions against microsporidiosis.

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Cytotoxicity and antibacterial properties of copper-doped calcium phosphate bioceramics

In front of bone substances loss, the use of synthetic materials increases. Among these, biphasic calcium phosphates (BCP) ceramics composed of hydroxyapatite (HAp, Ca10(PO4)6(OH)2) and β-TCP (Ca3(PO4)2) are promising bone substitutes because of their strong similarity with bio-mineral part of bones. Moreover, their chemical synthesis can be modulated by doping, in order to respond to the biological needs. Metal copper ions Cu^{2+} appears to be promising dopant considering its high antibacterial properties and its low cytotoxicity.

We present here the cytotoxicity of different Cu-doped BCP (Ca10Cux(PO4)6(OH)2-2xO2x), with x = proportion of copper) on human Bone Marrow cells (BMC). We also investigate the antibacterial property of these BCP on four bacterial strains.

The sol-gel route has been used to prepare the BCP ceramics. Human BMC were obtained from metaphysal cancellous bone collected during hip arthroplasty. We evaluate the antibacterial property on strains of *S. aureus*, *E. Coli*, *P. aeruginosa* and MRSA.

Regarding doped BCP, results indicate that there is no difference in metabolic activity compare to undoped BCP after 7 days of culture. We also demonstrate that several of our Cu-doped BCP samples induced an antibacterial effect after 24 hours on 3 of the 4 strains evaluated.

This work illustrates the biological interests of using copper ions in biomaterials. These synthetic bone substitutes seem to be a promising alternative in the tissue engineering field

COMMUNICATIONS ORALES

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Mendeloma analysis in new hereditary predisposition to cancer syndromes

Hereditary predisposition to cancer affects 5 to 10% of cancers. The genes involved in the predisposition to the most common cancers, such as breast cancer and colon cancer, have been identified. However, familial forms of less frequent, multiple or atypical forms of cancers remain unexplored. **Objective:** Identification of new genes of predisposition to cancer using Mendoma analysis, combining gene, transcriptomic, protein and functional data. **Material and Methodes:** Twenty-six families suspected of hereditary predisposition to cancer with no mutation identified using panel sequencing were included. An exome sequencing was performed for each family, and variants of interest were conserved, according to the type of mutation, biological functions, protein / gene expression in the target tissues and the literature data. Gene and protein expression analyzes, case - controls studies were performed to validate the candidates genes (CG) identified. **Results:** Twenty-one candidate gene of predispostion have been identified, including four CG to familial non-medullary thyroid carcinoma, 5 CG to ovarian cancer (including one oncogene), 5 to kidney cancer, and 6 modifiers genes in RB1 and PTEN constitutional mutation carriers. Genetic and protein expression analysis of the CG in familial thyroid carcinoma patient, wich are tumor suppressor and pro-apoptotic genes, confirme the loss of function of the mutant allele, and loss-of-heterozygotie in tumor samples **Perspectives:** The CG in predisposition to thyroid and ovarian cancer is currently explored in vitro in culture cells, using siRNA and apoptosis measures for the first ones, and plasmide transfection _ proliferation measures for the the second, which is oncogene. Cases – control studies are currently performed for these CG, using Sanger and Fluidigm sequencing in cases from our Departement, and Gnomad population for control.

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Involvement of tumoral and stromal ANXA1 in tumor development and dissemination

Annexin A1 (ANXA1) belongs to annexin superfamily composed of calcium-dependent membrane-binding proteins that can link phospholipid membranes. ANXA1 plays its major roles in inflammation through its membrane and secreted location. Indeed, extracellular forms of ANXA1 (full-length or N-terminus (Nter) domain) are also active in autocrine and paracrine manner by the activation of formyl peptide receptors (FPRs) that triggers phosphorylation of downstream proteins (*e.g* MAPK, PI3K). Due to its involvement in proliferation, apoptosis, survival, differentiation, migration and invasion, it is not surprising that deregulation of ANXA1 expression has been observed in several cancers such as melanoma and breast cancer. However, previous studies have not clearly documented the role of tumoral and stromal ANXA1 in the development of these tumors.
We first characterized ANXA1 expression in human and murine breast cancer and melanoma cell lines using RT-qPCR, Western Blot and flow cytometry. These experiments allowed us to show presence at variable levels of intracellular and extracellular ANXA1 in tested cell lines. We confirmed that a peptide Ac2-26 mimicking Nter domain of the protein increased *in vitro* migration of melanomas while decreasing ANXA1 content by siRNA decreased cell growth. In parallel, we took advantage of mice knock-out for *AnxA1* gene to assess the role of stromal ANXA1 *in vivo* in a melanoma syngeneic model. We showed that host ANXA1 favors subcutaneous B16Bl6 engraft and dissemination to lung. Preliminary results sustained that tumor vascular system might be impaired in KO mice.

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Cellular and mitochondrial disturbances associated with X-Rays radiations after prostate cells incubation with gold carbenes

Prostate cancer is the most frequent cancer and the third cause of death due to a cancer in men. Cancers are characterized by the perturbation of many cellular parameters such as proliferation, metabolism, in which mitochondria are involved. In this latter is found a specific DNA population: the mitochondrial DNA (mtDNA). Some mtDNA mutations are correlated to tumorigenesis and cancer progression. These facts strengthen the important role of mitochondria in tumorigenesis. Radiotherapy which induces cell damages mainly through nuclear DNA modifications is one important therapeutic strategy against prostate cancer despite the development of radioresistance. The recent synthesis of organometallic compounds such as gold carbenes, with the ability to target mitochondria could be a new therapeutic strategy toward tumor escape following radiotherapy through tumor radio-sensitization. Our study aims to characterize the anti-proliferative potential of these compounds and their ability to potentiate X-rays radiation therapy on two models of human prostate cell lines: LNCaP and PC3. Inductively Coupled Plasma Mass Spectrometry (ICPMS) experiments have revealed gold carbenes accumulation in the mitochondria. One another note, the tested compounds are intrinsically cytotoxic and also cytostatic as demonstrated respectively by the values of IC_{50} and IG_{50} on the two prostate cell lines. Coupled with that, a drop in cell proliferation was observed when the cells were incubated in the presence of carbenes and then irradiated, suggesting a potentiating effect of the carbenes. Moreover, the irradiation of cells previously treated with gold carbenes increased the apoptotic processes and induced disturbances in the cell cycle. At the mitochondrial level, the membrane potential was also significantly altered. Overall, the disturbances occurred as a function of time, the concentration of carbenes, and the radiation dose. These results show the potential of gold organic compounds to radiosensitize cells through mitochondrial targeting.

Surname: LUSHO

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Assessment of circulating and tumour-infiltrating lymphocytes as predictors of triple negative breast cancer response to neoadjuvant chemotherapy and/or metastatic recurrence after that type of treatment

Triple negative breast cancer (TNBC) affects 10 to 20% of all women diagnosed with breast cancer. Due to its characteristics, treatment strategies are limited and metastatic recurrences are common in the first five years after treatment. However, not all patients affected by this disease develop metastases. Tumor-Infiltrating Lymphocytes (TILs) have shown to be reliable predictive biomarkers of treatment response and metastatic recurrences. However, we need to develop simpler and faster ways to predict response to cytotoxic treatment and the possibility of eventual cancer relapse by identifying new biomarkers. Recently, new studies are emerging, suggesting a predictive role of blood cells in different types of cancer. Departments of Clinical Research and Pathology of the Jean PERRIN Cancer Centre have created, by joint forces, a database of patients diagnosed with TNBC since 2008 in the establishment. As of this day, over 640 cases are reported in this database. A part of my doctoral work has been to review all the cases included in this database, as well as to add new cases and blood cell counts for all the patients. Our goal is to assess the capacity of various blood cell counts, before or after neoadjuvant chemotherapy, to predict TNBC response to that treatment as well as metastatic recurrence. Besides retrospective data, we will analyse the data gathered by a prospective clinical trial that we have set up, aiming to evaluate the correlation between TILs and various blood counts, in TNBC patients included into the database. If demonstrated to have recurrence-predicting capacity, the blood counts can be used as simple, fast and cheap biomarkers, to help clinicians in deciding the best treatment for TNBC patients.

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De gauche à droite **:**

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