ULB UNIVERSITÉ LIBRE DE BRUXELLES, UNIVERSITÉ D'EUROPE

FACULTÉ DE MÉDECINE
Campus Erasme
Bâtiment F – Auditoire Bordet (RDC) & Salle d'Exposition (1er étage)
Route de Lennik, 808
B-1070 Bruxelles

Jeudi 25 avril 2019

18ème Journée des Doctorants

Sciences Biomédicales, Sciences Dentaires, Sciences Médicales & Sciences Pharmaceutiques

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O =ORAL LONG ; P=POSTER ; O = ORAL COURT

8.30-9.00 **Accueil des participants, Salle Exposition (1er étage bâtiment F)**
9.00-9.10 **Introduction, Auditoire Bordet**

SESSION 1 : COMMUNICATIONS ORALES
Modérateurs : Eléonore Dupuis & Serge Schiffmann

9.10 - 9.30 **Ferrero Giuliano**, Mahony C B, Dupuis E, Yvernogeau L , Di Ruggiero E, Miserocchi M, Caron M, Robin C, Traver D, Bertrand J Y, Wittamer V. *Embryonic microglia derive from primitive macrophages and are replaced by cmyb-dependent definitive microglia in zebrafish*

9.30 - 9.50 **Piumatti Matteo**, Hasche A, Limame R, Zaratin M, Tanaka DH, Herpoel A, Bilheu A**,** Van Benthem A, Pirson I, Matthijs G, Keymolen K, Désir J, Passemard S, Abramowicz M, Ledent C and Vanderhaeghen P.
Searching for the molecular mechanisms of action of ASPM, a major gene affected in human microcephaly

9.50 - 10.10 **Vandenberghe Pierre**, Delvaux M, Hague P, Erneux C, Vanderwinden J-M.
PDE3A, a major player in development of interstitial cells of Cajal and a new therapeutic target in gastrointestinal stromal tumors

10.10 - 10.30 **Marloye Michael**, Ingels A, Mathieu V, Debaille V, Lawler S E, Gelbcke M, Meyer F, Dufrasne F and Berger G.
Self-assembling neurosphere-potent Ru^{II} and Os^{II} complexes with enhanced cellular uptake

10h30 – 11h00 : PAUSE CAFE ET DEMOS

SESSION 2 : COMMUNICATIONS ORALES
Modérateurs : Audrey Penning & Stéphane Louryan

11.00 - 11.20 **Daumas Mathilde**, Polet C, Beauthier J-P and Louryan S.
Activity reconstruction from osteoarthritis and entheseal changes: evidence of physical activity and social differentiation in a Belgium monastic medieval population

11.20 - 11.40 **Lytrivi Maria**, De Franco E, Patel K, Igoillo-Esteve M, Consentino C, Wakeling M, Haliloglu B, Unal E, Godbole T, Yildiz M, Ellard S, Bilheu A, Vanderhaeghen P, Hattersley A T, Cnop M.
Mutations in YIPF5 are a novel cause of neonatal diabetes and microcephaly, highlighting the critical role of endoplasmic reticulum-to-Golgi trafficking in human β-cells and neurons

11.40 - 12.00 **Chrysanthi Alexandri**, Stamatopoulos B, Rothé F, Devos M, Grosbois J, Daniel A, Retout M, Demeestere I.
Identification and efficiency of potential miRNAs targets for developing new pharmacological drugs against chemotherapy- induced ovarian damage using mice model

12.00 - 12.20 **Allende Gustavo**, Surriabre P, Ovando N, Calle P, Villaroel J, Bossens M, Fontaine V and Rodriguez P.
Evaluation of the self-sampling HPV test as an alternative for cervical cancer screening in Cochabamba, Bolivia

12h20 à 13h40

Salle Exposition

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SESSION 3 : COMMUNICATIONS ORALES
Modérateurs : Pia Di Campli & Marc Parmentier

13.40 - 14.00 **Al Delbany Diana**, Gavioli V, Dubois-Vedrenne I, de Henau O, Parmentier M.
Characterization of CCRL2, an atypical chemokine receptor, in skin cancer

14.00 - 14.20 **Istaces Nicolas**, Splittgerber M, Lima Silva V, Nguyen M, Thomas S, Lé A, Achouri Y, Calonne E, Defrance M, Fuks F, Goriely S and Azouz A.
Transcriptional control of innate memory CD8 T cells

14.20 - 14.40 **Spilleboudt Chloé**, De Wilde V, Maury S, Le Moine A.
Donor-derived myeloid heme oxygenase-1 controls the development of graft-versus-host disease

14.40 - 15.00 **Benhadou Farida**, Glitzner E, Brisebarre A, Dubois C, Rozzi M, Paulissen C, del Marmol V, Sibila M, Blanpain C.
Epidermal autonomous Flt1/Nrp1 functions mediate psoriasis-like disease

15h00 – 15h30 : PAUSE CAFE ET DEMOS

SESSION 4 : « MON PROJET DE THESE EN 3 MINUTES POUR LES NULS »

Cyrine Ben Dhaou
Régulation de l'angiogenèse par la Chémerine et ses trois récepteurs : ChemR23, CCRL2 et GPR1
Promoteur de thèse : Parmentier M.
IRIBHM, Faculté de Médecine, Université Libre de Bruxelles

Meriem BEN HAMADI
Craquer le code neuronal de la flexibilité cognitive et l'attention
Promoteur de thèse : De Kerchove d'Exaerde A.
Laboratoire de Neurophysiologie, Faculté de Médecine, Université Libre de Bruxelles

Pierre CASIMIR
Mécanismes génétiques de la connectivité et du développement neuronaux humains
Promoteur de thèse (doctorat conjoint ULB-KUL): Gall D. & Vanderhaeghen P.
Stem cell and Developmental neurobiology lab, VIB-KU Leuven Center for Brain &Disease, Department of Neurosciences, Leuven Brain Institute, at KULeuven; IRIBHM, Faculté de Médecine, ULB Brussels, at ULB.

Geoffrey DENEUBOURG
Etude des interactions hôte-pathogène pendant l'infection aux Streptocoques du groupe A : caractérisation d'une souche clinique à haut potentiel nécrotique
Promoteur de thèse : Botteaux A.
Laboratoire de Bactériologie Moléculaire, Faculté de Médecine

Camille GROSSE
Caractérisation de la mupirochéline, un nouveau sidérophore à activité antimicrobienne
Promoteur de thèse : Wintjens R.
Laboratoire de microbiologie, chimie bioorganique et macromoléculaire, Faculté de Pharmacie, ULB

Alia HADEFI
Communications foie-intestin dans la stéato-hépatite non alcoolique
Promoteur de thèse : Trépo E
Laboratoire de gastroentérologie expérimentale, Faculté de Médecine, ULB
IRIBHM, faculté de Médecine, ULB.

Géraldine HUBESCH
Les effets de l'obésité sur l'homéostasie de la circulation pulmonaire et sur le développement de l'hypertension pulmonaire chez le rat
Promoteur de thèse : Mc Entee K.
Laboratoire de Physiologie et Pharmacologie, Faculté de Médecine, ULB

Marie LE MOINE
Le fabuleux destin d'un globule blanc
Identification de voies transcriptionnelles et épigénétiques participant à la différentiation du lymphocyte T CD8.
Promoteur de thèse : Goriely S.
Institut d'Immunologie Médicale, Faculté de Médecine, Université Libre de Bruxelles

Faustine RAVON
Etude de faisabilité d'une nouvelle combinaison médicamenteuse brevetée en tant que médicament antituberculeux potentiel
Promoteur de thèse : Fontaine V.
Unité de Recherche Microbiologie, Chimie bioorganique et macromoléculaire, Faculté de Pharmacie, Université Libre de Bruxelles

Martin TATON
Influence de la grossesse et de l'infection au VIH sur la réponse au vaccin contre la coqueluche
Promoteur de thèse: Willems F.
Institut d'Immunologie Médicale (IMI), Faculté de Médecine, Université libre de Bruxelles (ULB)

Tania VANHEE
Le dentiste : même pas peur !
Promoteurs de thèse (doctorat conjoint ULB-VUB) : Vanden Abbeele A. & Bottenberg P.
Laboratoire des travaux pratiques de Dentisterie, Faculté de Médecine, Université Libre de Bruxelles
Tandheelkundige Kliniek, Geneeskunde en Farmacie Faculteit, Vrij Universiteit Brussel

~17h00: DELIBERATIONS DES JURYS et PROCLAMATION

en présence de

J. Rasschaert, Doyenne de la Faculté de Médecine
F. Meyer, représentant de la Commission doctorale de la Faculté de Pharmacie

Remise du prix de la meilleure présentation orale par

Remise du prix du meilleur poster par

Remise du prix de la meilleure présentation orale « MON PROJET DE THESE EN 3 MINUTES POUR LES NULS » par

J. Rasschaert, Doyenne de la Faculté de Médecine

DRINK DE CLÔTURE

POSTERS

1. ABDALKARIM Tanina, WINTJENS R.
A comprehensive analysis of the protein-ligand interactions in crystal structures of Mycobacterium tuberculosis EthR.

2. BEVILACQUA Elisa, ORDÓÑEZ E, HURTADO I, RUEDA L, MAZZONE E, CIRIGLIANO V, JANI J.
Screening for sex chromosome aneuploidy by cfDNA testing: patient choice and performance.

3. BOUYSRAN Houssef, REGGIANI C, SMITS G.
Improve clinical dignosis of rare genetic disorders with GEne-specific Missense VAriant redictor (GEMVAP) framework.

4. CAPPELLE Sylvie, PAESMANS M, MOREAU M, BERGMANN P, KARMALI R, BODY J-J.
Ten years follow-up of postmenopausal women with similar FRAX score: why only some patients do fracture? - An evaluation of the role of several clinical risk factors and f bone quality assessed by HR-pQCT.

5. COLIN Margaux, DECHÊN L, CALVO EPOSITO R, CEUSTERS J, LAGNEAUX L, VAN ANTWERPEN P, GOORMAGHTIGH E, RENARD P, SERTEYN D AND MATHIEU V.
Preliminary evaluation of the effects of drug loading in muscles' derived mesenchymal stem cells for delivery purposes: the example of curcumin.

6. COQUELET Nicolas, WENS V, BOURGUIGNON M, MARY A, NIESEN M, DESTOKY F, ROSHCHUPKINA L, PEIGNEUX P, GOLDMAN S AND DE TIÈGE X.
Resting-state related brain functional connectivity across lifespan : a connectomic approach.

7. COREMANS Catherine, NUYENS V, ROUSSEAU A, VAN DE BORNE P, ZOUAOUI BOUDJELTIA K, DELPORTE C AND VAN ANTWERPEN P.
Monitoring of apolipoproteins oxidation to improve the estimation of lipoprotein quality in cardiovascular diseases.

8. DE FISENNE Marie-Ange, ANDO K, YILMAZ Z, MANSOUR S, BUÉE L, BRION J-P, LEROY K.
Intraocular injection of fibrillary PHF-tau isolated from Alzheimer's disease brain : effect on tau pathology development in wild-type and tau transgenic mice.

9. DEGROOT Gaêtan-Nagim, SPRINGAEL J-Y.
Role of chemerin in the splenic organization and function of CMKLR1^{+} leukocytes.

10. FROST Hannah, BOTQUIN G, LAKHLOUFI D, SANDERSON-SMITH M, LY D, CLEARY A, DAVIES M, WALKER M, STEER A, BOTTEAUX A AND SMEESTERS A.
The Group A streptococcal Enn proteins bind numerous human plasma proteins.

11. GHANDEHARIAN Omid, DI RUGGIERO E, PARMENTIER M AND WITTAMERV.
Characterization of chemerin axis in zebrafish.

12. HELALI Yosra, FIUME CD, VAN ANTWERPEN V, AND DELPORTE C.
Rapid sample preparation for the profiling of N-glycans by liquid chromatography mass spectrometry.

13. HOYOIS Alice, GU-TRANTIEN C, LE MOINE C, PAPADOPOULOU M, BOUZIN C, KOMUTA M, DELFORGE ML, DE MAGNÉE C, LE MOINE A, REDING R AND MARCHANT A.
Human CMV infection as a co-factor of disease progression in biliary atresia.

14. IBRAHIM Mostafa, EL-MIKKAWY A., ABDEL HAMID M., ABDALLA H, LEMMERS A, MOSTAFA I, DEVIÈRE J.
Development and assessment of new technology for variceal bleeding.

15. JACQUEMIN Valérie, DUERINCKX S, PERAZZOLO C, PIRSON I, AND ABRAMOWICZ M.
Genetic architecture of congenital primary hydrocephalus: novel genes in consanguineous families and digenic inheritance in an outbred cohort.

16. KEHAGIAS Pashalina, AMEYE L, EL HOUSNI H, DELEPORTE A, GEBOES K, DELAUNOIT T, DEMOLIN G, PEETERS M, D'HONDT L, JANSSENS J, CARRASCO J, GOMEZ GALDON M, HEIMANN P, PAESMANS M, FLAMEN P, HENDLISZ A, VANDEPUTTE C.
Is a single driver gene mutation sufficient for monitoring early response in advanced colorectal cancer?

17. LARABI Illyes, AOUR B., EVRARD L.
Finite element analysis of biomechanical behaviour of zygomatic implants techniques in case of edentulous and severely atrophic maxilla: a systematic review.

18. LE Aurore, ASSABBAN A, ISTACES N, THOMAS S, NGUYEN M, WUNDERLICHT T, BRUNING J AND GORIELY S.
Understanding the role of JNK1 in the context of skin inflammation.

19. MARIN Gwennaëlle, VANDERLINDEN B, KARFIS I, GUIOT T, WIMANA Z, REYNAERT N, VANDENBERGHE S, FLAMEN P.
Towards a quality assurance for dosimetry in peptide receptor radionuclide therapy with 177Lu-DOTATATE.

20. RIMOUCHE Asma, CARAVITAS, DEWACHTER L, DEWACHTER C, MÉLOT C, BONDUE A, VACHIÉRY J-L.
Predisposition to pulmonary arterial hypertension in hig risk populations: contribution of echocardiography.

21. SOARES DA COSTA Christelle, DE BONY DE LAVERGNE E, MA HL, CALONNE E, HASSABI B, PUTMANS P, BIZET M, DUBE G, LI A, ZHANG B, DANIELS D, YANG YG, FUKS F.
An innovative approach to study the role of RNA epigenetics in cancer.

22. VANROSSOMME Axel, CHODZYNSKI K J, CORREDOR RA, EKER O F AND ZOUAOUI BOUDJELTIA K.
Aneurysm wall motion: optimization of dynamic CTA.

ABSTRACTS

I. Présentations orales

1. Embryonic microglia derive from primitive macrophages and are replaced by *cmyb*-dependent definitive microglia in zebrafish

Giuliano Ferrero[1,2], Chris B Mahony[3], Eléonore Dupuis[1], Laurent Yvernogeau[4] Elodie Di Ruggiero[1,2], Magali Miserocchi[1,2], Marianne Caron[1], Catherine Robin[4], David Traver[5], Julien Y. Bertrand[3] , Valerie Wittamer[1,2]
[1]Institut de Recherche Interdisciplinaire en Biologie Humaine et Moléculaire (IRIBHM)
[2]ULB Institute of Neuroscience (UNI)
[3]Department of Pathology and Immunology, University of Geneva, School of Medicine, Geneva, Switzerland
[4]Hubrecht Institute-KNAW and University Medical Center, Utrecht, the Netherlands
[5]Department of Cellular and Molecular Medicine, University of California, San Diego, La Jolla, CA, USA

With no current cure and an increasing prevalence in our ageing society, neurodegenerative disorders such as Alzheimer's and Parkinson's diseases represent a burden to industrialized countries. Because these diseases are often associated with neuroinflammation, microglia, the resident macrophages in the central nervous system, represent a potential target for the development of novel therapeutic approaches. Our current understanding of microglia ontogeny suggests that maintenance and expansion of steady-state microglia are strictly dependent on self-renewing local progenitors that seed the brain early during embryogenesis. Although several candidates have been suggested, the identity of these local progenitors is currently a controversial topic and remained to be determined. Utilizing the unique attributes of the zebrafish embryo, we have investigated the cellular and molecular mechanisms underlying microglia ontogeny in vertebrates. Here, we show that microglia arise in two independent waves during zebrafish development. First, primitive macrophages generate a transient wave of embryonic microglia. This primitive wave is replaced by definitive microglia that persist throughout adulthood. Using fluorescent reporter lines that specifically track embryonic and adult microglia, we show that the second wave takes place later during development, at the larval stage. Through fate mapping analyses, we also show that adult microglia derive from a vascular endothelium with hemogenic properties, a concept that is reminiscent of the endothelial origin of Hematopoietic Stem Cells (HSCs) during embryogenesis. Although a recent study ruled out HSCs as the precursors of adult microglia, our preliminary observations using a number of hematopoietic mutants suggest that HSCs may in fact contribute to the emergence of adult microglia *in vivo*. We are currently investigating this hypothesis. Insights into the cellular and molecular events that instruct microglia development may ultimately contribute to the generation of microglia-like cells *in vivo* and *in vitro*, a goal that has been largely unmet so far.

2. Searching for the molecular mechanisms of action of ASPM, a major gene affected in human microcephaly

Matteo Piumatti[1,9], Anja Hasche[1,9], Ridha Limame[1,9], Maurine Zaratin[1], Daisuke H. Tanaka[1], Adèle Herpoel[1], Angéline Bilheu[1], Harmen van Benthem[1], Isabelle Pirson[2], Gert Matthijs[3], Kathelijn Keymolen[4], Julie Désir[5], Sandrine Passemard[6], Marc Abramowicz[2,7], Catherine Ledent[1], and Pierre Vanderhaeghen[1,8,9]
(1) Université Libre de Bruxelles (ULB), WELBIO, Institute for Interdisciplinary Research (IRIBHM), and ULB Institute of Neuroscience (UNI), Brussels, Belgium; (2) Institut de Pathologie et de Génétique (IPG), Gosselies, Belgium; (3) IRIBHM, ULB and Hôpital Erasme, Brussels, Belgium; (4) Centre for Human Genetics, KULeuven, Belgium; (5) Center for Medical Genetics, Vrije Universiteit Brussels (VUB), Brussels Belgium; (6) Département de Génétique et Inserm, U1141, Hôpital Robert Debré, Paris, France; (7) Department of Medical Genetics, Hopital Erasme, Brussels, Belgium; (8) WELBIO, Université Libre de Bruxelles, Brussels, Belgium ; (9) VIB-KULeuven Center for Brain & Disease Research, 3000 Leuven, Belgium; Department of Neurosciences, Leuven Brain Institute, KUL, 3000 Leuven, Belgium.

Human primary microcephaly (MCPH) is an autosomal-recessive neurodevelopmental disorder characterized by major reduction in brain size.
More then 18 genes have been associated with MCPH. Mutations in *ASPM* (Abnormal Spindle-like, Microcephaly-associated) gene are the most common cause for MCPH, and so far the function of the protein, which is mostly located at mitotic spindle, remains elusive.

In order to investigate, at the molecular level, how ASPM deficiency leads to microcephaly, we aim at the identification of ASPM interactors. Taking advantage of Crispr-Cas9 technology, we generated human embryonic stem cells (hES) and HEK293T knock-in lines, where the first exon on *ASPM* was tagged with VENUS. We performed immunoprecipitation experiments using the GFP-Trap technology on HEK293T and hES-derived cortical progenitor knock-in lines followed by mass spectrometry. We identified 55 ASPM interactors, including 14 localized at the mitotic spindle and we are now characterizing the localisation and the function of those candidates in ASPM knockout hES-derived cortical progenitors.
In parallel, ASPM knockout hES cells are being used to explore the effect of *ASPM* mutation in the contest of neurogenesis taking advantage of different 3D differentiation models.

3. PDE3A, a major player in development of interstitial cells of Cajal and a new therapeutic target in gastrointestinal stromal tumors

Vandenberghe P, Delvaux M, Hague P, Erneux C, Vanderwinden J-M

Gastrointestinal stromal tumors (GIST) are the most common sarcomas of the gastrointestinal tract and despite the introduction of tyrosine kinase inhibitors, GIST resistance remains a major clinical challenge. We have previously shown the expression of phosphodiesterase 3A (PDE3A) in interstitial cells of Cajal (ICC) and their derived tumor GIST. However, its role in ICC development/maintenance and in GIST physiopathology remained unknown. Using *in vivo* and *in vitro* approach, we found that PDE3A was expressed early during ICC development and PDE3A-deficient mice harbor 50% reduction of the ICC network. We also showed the expression of PDE3A in human ICC and in 92% of human GIST tissue samples. In imatinib sensitive (GIST882) and resistant (GIST48) human GIST cell lines, cilostazol, a selective PDE3 inhibitor, potentiate imatinib effect on cell viability reduction. Mechanistically, PDE3A inhibition by cilostazol induced a nuclear exclusion, hence inactivation, of the transcriptional coactivator YAP and study of its expression in human GIST tissue samples revealed that 90% of GIST were YAP positive. Finally, we showed that YAP inhibition by verteporfin induced a drastic viability reduction of both GIST882 and GIST48 cells lines. Our results highlight the potential use of compounds targeting PDE3A and/or YAP in combined multitherapy to tackle GIST resistance.

4. Self-assembling neurosphere-potent Ru^{II} and Os^{II} complexes with enhanced cellular uptake

Marloye M,[1] Ingels A,[2] Mathieu V,[2] Debaille V,[3] Lawler S E,[4] Gelbcke M,[1] Meyer F,[1] Dufrasne F[1] and Berger G.[1]
[1] Microbiology, Bioorganic & Macromolecular Chemistry Research Unit, Faculté de Pharmacie, Université libre de Bruxelles, Boulevard du Triomphe, 1050 Brussels, Belgium.
[2] Department of Pharmacotherapy and Pharmaceutics, Faculté de Pharmacie, Université libre de Bruxelles, Boulevard du Triomphe, 1050 Brussels, Belgium.
[3] Laboratoire G-Time, Faculté des Sciences, Université Libre de Bruxelles, avenue F.D. Roosevelt 50, 1050 Brussels, Belgium.
[4] Harvey Cushing Neuro-Oncology Laboratories, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

Piano-stool arene ruthenium(II) and osmium(II) complexes have attracted growing interest as promising anticancer agents.[1] Novel Ru^{II} and Os^{II} half-sandwich complexes were synthesized from $[(M(p\text{-cymene})Cl_2]_2$ (where M = Ru^{II} or Os^{II}), using 1,10-phenanthroline (phen) derivatives as *N*,*N*-bidentate ligands. These ligands were further modified with fatty alkyl chains (C_{16}) to facilitate diffusion across cell membranes and thus enhance cellular accumulation.[2] *In vitro* antiproliferative effects were first assessed by means of MTT on a panel of five cancer cell lines (A459, MCF7, Hs683, M109, B16F10). C_{16}-modified Ru^{II} and Os^{II} phenanthroline complexes showed potent antiproliferative effects with IC_{50} values typically below the micromolar range. This is an order of magnitude lower than cisplatin, whereas the parent phenanthroline complexes $[M(p\text{-cymene})(phen)Cl]PF_6$ have very limited antiproliferative activity. The lipophilic modification therefore resulted in a 100 to 1000 fold increase in the antiproliferative potency.[3,4] Cellular uptake experiments revealed higher intracellular metal contents and binding affinity for human serum albumin for C16-modified complexes. The obtained amphiphilic structures lead to vesicular nanoparticules arrangement in aqueous media, as evidenced by transmission electronic microscopy. Videomicroscopy tracking revealed altered morphologies but no cell death occuring upon treatment with the complexes, which is confirmed by annexin V staining. Measurements of reactive oxygen species and propidium iodide staining revealed low oxidative stress and no major impact on the cell cycle. Our complexes were then tested on patient-derived glioblastoma stem cells grown as neurospheres, showing very

promising activity. Mechanistic studies were realized by ^{1}H NMR to determine eventual activation mode of our complexes with bionucleophiles such as water and glutathione. Physico-chemical properties were further examined through experimental work such as solution-state conformation by ROESY and theoretical models such as molecular orbital diagrams, excited states from TD-DFT and transition structures for aquation.

*[1] Meier-menches, S. M.; Keppler, B. K.. **Chem. Soc. Rev.**, **2018,47**, 909-928*
*[2] Palmucci, J.; Dyson, P.J. Inorg. Chem., **2016**, 55 (22), 11770.*
*[3]Habtemariam, A.; Sadler, P. J., J. Med. Chem. **2006**, 49, 6858-6868.*
*[4] Peacock, A. F. A.; Sadler, P. J., Inorg.Chem. **2007**, 46, 4049−4059.*

5. Activity reconstruction from osteoarthritis and entheseal changes: evidence of physical activity and social differentiation in a Belgium monastic medieval population

Daumas M, Polet C, Beauthier J-P and Louryan S
Laboratoire d'Anatomie, Biomécanique et Organogénèse, Faculté de Médecine, Université Libre de Bruxelles.

The aim of this PhD project is to reconstruct levels and types of physical activity and associated social differences of a medieval population. We used human skeletal remains from the cemetery of the Dunes' Abbey in Koksijde (XII – XV century).
Based on burial characteristics, we were able to differentiate monks, benefactors (higher ranking members of the society such as noblemen/women buried in the Cloister and Maes chapels) and lay brothers (low born religious non-monks employed by the abbey). Life of lay brothers was centred around daily farming, with an expected higher class of wealthier individuals performing less manual labour.
The two markers of activity commonly used as indicators are osteoarthritis (OA) and entheseal changes (EC, also call musculoskeletal stress markers). OA is a disease occurring in synovial joints. EC are the attachment sites of muscle onto bone, whose morphology is correlate with muscle use and so physical activity. Focused on upper limb, we also evaluate 20 asymptomatic osseous variations (AOV) on the postcranial skeleton.
As OA and EC are not exclusively influenced by physical activity, but also age, sex and environmental background, we established the biological profile (age and gender) of our individuals (n=200). We also created preservation records and assessed minimum number of individuals for each grave.
The aim of this talk is not to present the entire version of the thesis, but to describe the context, how the study proceeded, and its main results.
The frequencies of each AOV from each subsample were calculated. Results displayed different frequencies compare to "normal" population, which may suggest a selection (lineage effect or activity related?). We cannot distinct a gendered division of labour because of the unbalanced sex ratio of our sample (male congregation). As expected, our study indicated that OA and EC reflect the age of individuals. The correlation between OA and EC illustrate their complex aetiologies. Even if correlation remains ambiguous, we were able to highlight farming evidences in our lay brothers' sample. Results and bone overall robusticity supported the hypothesis that most of the population was engaged in high levels of physical activity.

6. Mutations in *YIPF5* are a novel cause of neonatal diabetes and microcephaly, highlighting the critical role of endoplasmic reticulum-to-Golgi trafficking in human β-cells and neurons

Maria Lytrivi[1,8*], Elisa De Franco[2*], Kashyap Patel[2], Mariana Igoillo-Esteve[1], Cristina Consentino[1], Matthew Wakeling[2], Belma Haliloglu[3], Edip Unal[4], Tushar Godbole[5], Melek Yildiz[6], Sian Ellard[2], Angeline Bilheu[7], Pierre Vanderhaeghen[7], Andrew T Hattersley[2*], Miriam Cnop[1,8*]
[1]ULB Center for Diabetes Research, Université Libre de Bruxelles, [2]University of Exeter Medical School, Exeter, UK,[3]Yeditepe University Hospital, Istanbul, Turkey, [4]Dicle University, Diyarbakır, Turkey, [5]Harmony Health Hub, Nashik, India,[6]Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey,[7]Institute of Interdisciplinary Research (IRIBHM), ULB Neuroscience Institute, Université Libre de Bruxelles, [8]Division of Endocrinology, Erasmus Hospital, Université Libre de Bruxelles *Contributed equally

Neonatal diabetes is caused by single gene mutations affecting fundamental β-cell function and mass pathways. 20% of cases of neonatal diabetes remain genetically unexplained. Our aim was to explore the genetic basis of a syndrome characterized by neonatal diabetes, microcephaly and epilepsy, present in 2 unrelated patients. The patients were of Turkish and Indian origin, born to consanguineous parents. After excluding mutations in known monogenic diabetes genes, we performed whole genome sequencing and focused on homozygous rare coding variants shared by the two patients. These analyses revealed that the patients harbored homozygous likely

deleterious variants in *YIPF5* (missense, p.(Ala181Val) and in-frame deletion p.(Lys106del) respectively). We then performed replication studies in 112 patients with neonatal/early-onset diabetes by targeted next generation sequencing. These identified 2 homozygous missense *YIPF5* mutations (p.(Trp218Arg) and p.(Ile98Ser)) in 3 patients (2 siblings). All 5 patients had diabetes diagnosed between 1-20 months of age and treated with insulin, severe microcephaly (median -6 SD), epilepsy diagnosed in the neonatal period and low birth weight. In functional studies, *YIPF5* was expressed in human islets and fetal brain cortex, as evaluated by qPCR and in situ hybridization. Studies in other cell types have shown that YIPF5 is involved in endoplasmic reticulum (ER)-to-Golgi trafficking. Based on its presumed function, we examined the impact of YIPF5 loss-of-function on β-cell survival during ER stress. YIPF5 was silenced in the human β-cell line EndoC-βH1 and in human islets by RNA interference. YIPF5 silencing sensitized β-cells to apoptosis induced by the ER stressors thapsigargin and brefeldin A. Upon exposure to the ER stressors, YIPF5-depleted cells showed enhanced CHOP, BiP and spliced XBP1 expression compared to control cells, indicating increased ER stress signaling. Expression of the proapoptotic proteins PUMA and DP5 was also enhanced by YIPF5 silencing. CHOP and DP5 knockdown partially protected YIPF5-deficient cells from apoptosis, suggesting that they mediate apoptosis. In conclusion, we describe a novel autosomal recessive syndrome of early-onset diabetes, microcephaly and epilepsy due to *YIPF5* mutations. This syndrome unveils a critical role of *YIPF5* and ER-to-Golgi trafficking in the function and survival of human β-cells and neurons.

7. Identification and efficiency of potential miRNAs targets for developing new pharmacological drugs against chemotherapy- induced ovarian damage using mice model

Chrysanthi Alexandri[1], Basile Stamatopoulos[2], Françoise Rothé[3], Melody Devos[1], Johanne Grosbois[1], Amélie Daniel[1], Maurice. Retout[4], Isabelle Demeestere[1]
1Research Laboratory on Human Reproduction, 2 Laboratory of Clinical Cell Therapy, 3 Breast Cancer Translational Research Laboratory, 4 Engineering of Molecular NanoSystems, École polytechnique de Bruxelles, Université libre de Bruxelles (Belgium)

It is well-known that gonadotoxicity of chemotherapy agents may lead to follicle depletion, premature ovarian failure and infertility. This study aims to develop a new ovarian-protective drug by modulating genes' transcription using miRNAs involved in apoptosis, DNA damage and in primordial follicle activation during chemotherapy. Therefore, postnatal-day-3 mouse ovaries were cultured under control and treated conditions exposed to the metabolites of a well-known alkylating abent- 4-hydroxycyclophosphamide (4-HC/ 20µM/ 1-24h). TaqMan Low Density Arrays were used for miRNA expression profiling in ovaries, which revealed that amongst the 245 expressed miRNAs, 74 stayed stable, 81 were upregulated and 40 downregulated after 4-HC exposure during 1h. Custom-Cards and QPCR-assays validated the differently expressed miRNAs; amongst them let-7a and miR-10a had a stable and profound downregulated profile while the functional annotation clustering revealed that they target genes involved in crucial cellular pathways. In order to test their potential ovarian protective effect, mimic-let-7a or -miR-10a were delivered in ovaries in vitro by a liposome-based system. After the evaluation of transfection's safety and efficiency, four conditions were created: control, miRNA-mimic, 4-HC, 4-HC+miRNA-mimic. The evaluation of apoptosis revealed that the restoration of let-7a had a protective effect on the ovaries in response to chemotherapy and was able to prevent the upregulation of the selected miRNA-targets, as well as genes involved in apoptosis and cell growth. Contrariwise, miR-10a could not prevent chemotherapy-induced apoptosis. In vivo experiments of ovarian transplantation were performed aiming to evaluate the long-term effects of chemotherapy and let-7a-mimic transfection on the ovarian reserve. Spontaneous follicle activation was detected in all transplanted ovaries whatever the condition. However, the evaluation of apoptosis indicates that let-7a has a protective effect on the follicles after grafting. Consequently, the replacement of the let-7a is efficient to reduce chemotherapy-induced ovarian damage but this must be further evaluated using an appropriate delivery system. For this reason, we proceed with the design of gold nano-carriers able to specifically transfer the mimic-miRNA into the ovaries and we believe that this approach will bring us one step closer to innovative means of pharmacological protection in fertility preservation field.

8. Evaluation of the self-sampling HPV test as an alternative for cervical cancer screening in Cochabamba, Bolivia.

Allende G [1,2], Surriabre P[1,2], Ovando N[2], Calle P[2], Villaroel J[2], Bossens M[3], Fontaine V[2] and Rodriguez P[2]. [1]Faculty of Pharmacy, Université libre de Bruxelles, Belgium; [2]Faculty of Medicine, Universidad Mayor San Simon, Bolivia; [3]Faculty of Medicine, Université libre de Bruxelles, Belgium

Incidence and mortality rates of cervical cancer in Bolivia are the highest in Latin America. The coverage of the standard screening methods - (PAP) smear and visual inspection - is no more that 18% for the Bolivian women. Therefore, we evaluated the high risk human papillomavirus (HR-HPV) DNA detection test on self-collected samples as a screening alternative. In a first follow-up survey, we aimed to determine the degree of acceptability and confidence towards vaginal self-sampling amongst Bolivian women from urban, peri-urban and rural areas of Cochabamba. We also assessed the impact of self-sampling on cervical cancer screening coverage in a peri-urban area. Finally, we determined the efficiency of the HR-HPV DNA detection test using self-collected samples, to detect high grade intraepithelial lesions and cervical cancer in a primary screening or triage test. Our work has significant implications, as it proposes a reliable, low-cost cervical cancer screening strategy which may greatly reduce disease-associated mortality rates in Bolivia.

9. Characterization of CCRL2, an atypical chemokine receptor, in skin cancer

Diana Al Delbany, Virginie Gavioli, Ingrid Dubois-Vedrenne, Oliviert de Henau, Marc Parmentier.
IRIBHM, Faculty of Medicine, Université Libre de Bruxelles (ULB).

Chemoattractant factors for leukocytes, including chemokines, can play multiple roles in cancer progression, affecting anti-tumor responses, inflammation, proliferation, angiogenesis, cell migration and the metastastic process. Chemerin is a chemotactic protein for dendritic cell subsets, macrophages, and NK cells. It is a multifunctional protein acting through three receptors ChemR23/CMKLR1, GPR1 and CCRL2. Chemerin expression is frequently downregulated in human tumors. We have demonstrated that the expression of a bioactive chemerin form by B16 melanoma, Lewis lung carcinoma (LLC) cells delays the growth of tumors in vivo and a similar tumor growth delay is observed when bioactive chemerin is expressed in the basal keratinocytes of the host mice. In these tumors, the neoangiogenesis process is impaired, resulting in hypoxia, necrosis and growth delay. A similar phenotype is observed for LLC and B16 tumors grown in CCRL2 KO mice. In contrast, in a chemical carcinogenesis model (DMBA/TPA), the development of papillomas is delayed in CCRL2 KO mice and this affect is abrogated by invalidation of CMKLR1. CCRL2 is therefore considered to act solely by regulating local concentrations of chemerin, presenting the ligand to cells expressing functional chemerin receptors (ChemR23/CMKLR1 and possibly GPR1). CCRL2 expression is strongly upregulated by inflammatory signals but its function in physiological and pathological processes remains poorly characterized. We presently investigate further the role of CCRL2 on the chemerin-CMKLR1 axis in tumor progression by testing tumoral cell lines overexpressing or invalidated for CCRL2.

10. Transcriptional control of innate memory CD8 T cells

Istaces N[1], Splittgerber M[1], Lima Silva V[1], Nguyen M[1], Thomas S[1], Lé A[1], Achouri Y[2], Calonne E[3], Defrance M[4], Fuks F[3], Goriely S[1]* and Azouz A[1]*.
[1]Université Libre de Bruxelles, Institute for Medical Immunology, Gosselies, Belgium, [2]Université Catholique de Louvain, Institut de Duve, Brussels, Belgium,
[3]Université Libre de Bruxelles, Laboratory of Cancer Epigenetics, Brussels, Belgium,
[4]Université Libre de Bruxelles, Interuniversity Institute of Bioinformatics in Brussels, Belgium.
* These authors share senior authorship.

Memory CD8 T cells have the ability to provide lifelong immunity against pathogens. Although memory features generally arise after challenge with a foreign antigen, naïve CD8 single positive (SP) thymocytes may already acquire phenotypic and functional characteristics of memory cells in
response to cytokines such as interleukin-4. This process is associated with the induction of the T-box transcription factor Eomesodermin (EOMES). However, the underlying molecular mechanisms remain ill-defined. Using epigenomic profiling, we show that these “innate memory” CD8SP cells acquire only a portion of the active enhancer repertoire of conventional memory cells. This reprograming was secondary to EOMES recruitment, mostly to RUNX3-bound enhancers. Furthermore, we identified direct interactions between EOMES and BRG1 and showed that the *in vivo* acquisition of EOMES-dependent program by CD8SP thymocytes

was dependent on this chromatin remodeling factor. In conclusion, our results support a strong epigenetic basis for EOMES-driven establishment of CD8 T cell unconventional memory program.

11. Donor-derived myeloid heme oxygenase-1 controls the development of graft-versus-host disease
Spilleboudt C, De Wilde V, Maury S, Le Moine A.

Graft-versus-host disease (GVHD) remains a major clinical drawback of allogeneic hematopoietic stem cell transplantation (HSCT). Here we investigated how the stress responsive heme catabolizing enzyme heme oxygenase-1 (HO-1, encoded by *HMOX1*) regulates GVHD in response to allogeneic hematopoietic stem cell transplantation in mice and humans. We found that deletion of the *Hmox1* allele, specifically in the myeloid compartment of mouse donor bone marrow, promotes the development of GVHD after allogeneic transplantation. In contrast, deletion of the *Hmox1* allele in the transplanted host plays no apparent role in GVHD. The mechanism driving GVHD in mice transplanted with allogeneic bone marrows lacking HO-1 expression in the myeloid compartment involves enhanced alloreactive T helper cell and to a lesser extent cytotoxic T cells responses. The clinical relevance of these observations were validated in two independent cohorts of HSCT patients. Individuals transplanted with bone marrow cells from donors carrying a long homozygous $(GT)_n$ repeat polymorphism (L/L) in the *HMOX1* promoter associated with low HO-1 expression, were at higher risk of developing severe acute GVHD, as compared to donors carrying a short $(GT)_n$ repeat (S/L or S/S) polymorphism associated with higher HO-1 expression. In conclusion, GVHD associated with allogeneic HSCT is controlled by HO-1 expression in donor myeloid cells, suggesting that pharmacologic targeting this enzyme might be used therapeutically to overcome this major shortcoming of HSCT.

12. Epidermal autonomous Flt1/Nrp1 functions mediate psoriasis-like disease
Farida Benhadou[1,2], Elisabeth Glitzner[3], Audrey Brisebarre[1], Christine Dubois[1], Milena Rozzi[1], Catherine Paulissen[1], Veronique del Marmol[2], Maria Sibila[3], Cédric Blanpain[1,4*]
1. Laboratory of Stem Cells and Cancer, Université Libre de Bruxelles, Brussels, Belgium.
2. Dermatology Department, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium.
3. Institute of Cancer Research, Department of Medicine I, Medical University of Vienna and Comprehensive Cancer Center, Austria.
4.WELBIO, Université Libre de Bruxelles, Brussels B-1070, Belgium
* Corresponding author

Psoriasis is a common chronic skin disorder characterized by keratinocyte hyperproliferation with altered differentiation accompanied by inflammation and increased angiogenesis. It remains unclear whether the first events that initiate psoriasis development occur in keratinocytes or inflammatory cells. Here, using different psoriasis mouse models, we showed that conditional deletion of Flt1 or Nrp1 in epidermal cells inhibited psoriasis mediated by Vegfa-overexpression or cJun/JunB deletion. Administration of anti-Nrp1 antibody reverted the psoriasis phenotype. Using transcriptional and chromatin profiling of epidermal cells following Vegfa-overexpression together with Flt1 or Nrp1 deletion, we identified the gene regulatory network regulated by Vegfa/Nrp1/Flt1 during psoriasis development and uncovered a key role of Fosl1 in regulating the chromatin remodeling mediated by Vegfa overexpression in keratinocytes. In conclusion, our study identifies an epidermal autonomous function of Vegfa/Nrp1/Flt1 that mediates psoriatic-like disease and demonstrates the clinical relevance of blocking Vegfa/Nrp1/Flt1 axis in psoriasis.

II. Posters

1. A comprehensive analysis of the protein-ligand interactions in crystal structures of Mycobacterium tuberculosis EthR

Abdalkarim T, Wintjens R.
Unité de recherche en Microbiologie, Chimie bioorganique et macromoléculaire (MCBM), Faculté de Pharmacie, Université Libre de Bruxelles.

The Mycobacterium tuberculosis EthR is a member of the TetR family of repressors, controlling the expression of EthA, a mono-oxygenase responsible for the bioactivation of the prodrug ethionamide. This protein was established as a promising therapeutic target against tuberculosis, allowing, when inhibited by a drug-like molecule, to boost the action of ethionamide. Dozens of EthR crystal structures have been solved in complex with ligands. Herein, we disclose EthR structures in complex with 18 different small molecules and then performed in-depth analysis on the complete set of EthR structures that provides insights on EthR-ligand interactions. The 81 molecules solved in complex with EthR show a large diversity of chemical structures that were split up into several chemical clusters. Two of the most striking common points of EthR-ligand interactions are the quasi-omnipresence of a hydrogen bond bridging compounds with Asn179 and the high occurrence of π-π interactions involving Phe110. A systematic analysis of the protein-ligand contacts identified eight hot spot residues that defined the basic structural features governing the binding mode of small molecules to EthR. Implications for the design of new potent inhibitors are discussed.

2. Screening for sex chromosome aneuploidy by cfDNA testing: patient choice and performance.

Bevilacqua E[1], Ordóñez E[2], Hurtado I[1], Rueda L[2], Mazzone E[1], Cirigliano V[2], Jani J[1].
[1]Department of Obstetrics and Gynecology, University Hospital Brugmann, Université Libre de Bruxelles, Brussels , Belgium.
[2]Department of Molecular Genetics, Labco Diagnostic---Synlab Group, Esplugues de Llobregat, Barcelona, Spain.

Objective: To study patient choice regarding testing for sex chromosome aneuploidy (SCA) and the performance of cellfree DNA (cfDNA) screening for SCA. **Methods:** Patient choice regarding screening for SCA and factors influencing this choice were evaluated in a single center. In a subsequent two-center study, cases that screened positive for SCA were analyzed to determine the positive predictive value (PPV) for each SCA. Results: In all, 1,957 (61.9%) of the 3,162 patients undergoing cfDNA testing opted for SCA screening. Regression analysis demonstrated that independent predictors of a patient's decision for SCA were earlier gestational age, spontaneous conception, and cfDNA chosen as a primary method of screening. A total of 161 cases screened positive for SCA and follow-up data were available for 118 (73.3%). Forty-six of the 61 cases of 45, X were false-positive results and 15 were concordant with the fetal karyotype (PPV = 24.6%). Seventeen of the 22 cases of 47, XXX were false positive and 5 concordant (PPV = 22.7%). Eleven of the 30 cases of 47, XXY were false positive and 19 concordant (PPV = 63.3%). All 5 cases of 47, XYY were correctly identified, thus yielding a PPV of 100%. **Conclusion:** More than half of the patients undergoing cfDNA aneuploidy screening also opted for SCA testing, but they were less likely to do so in the presence of an increased risk of trisomy. SCAs involving the X chromosome had a lower PPV than those involving the Y chromosome.

3. Improve clinical diagnosis of rare genetic disorders with GEne-specific Missense VAriant Predictor (GEMVAP) framework

Youssef Bouysran MEng, Claudio Reggiani MEng PhD , Guillaume Smits MD PhD
ULB Center of Human Genetics, Université Libre de Bruxelles
(IB)² Interuniversity Institute of Bioinformatics in Brussels, Université Libre de Bruxelles

The identification of pathogenic missense mutations in rare genetic disorders is one of the most challenging task a bioanalyst can face. Bioinformatics predictors widely used in clinical diagnosis leverage functional or evolutive knowledge to assess the deleteriousness of variants. While they provide a gene-agnostic approach, they may

underperform for specific genes because of disease factors responsible for intrafamilial variability, modificator variants or incomplete penetrance.
With the availability of large databases of disease-specific variants and genetic variations in the healthy population, we are developping a framework to design gene-specific missense variant predictors to improve clinical diagnosis of rare genetic disorders, to better our understanding of variant pathogenicity and to personalize recall for healthy individuals with high prediction score.
We are assessing the GEMVAP framework with the design of an FBN1 gene-specific predictor, which is a gene associated with the Marfan Syndrome.

4. Ten years follow-up of postmenopausal women with similar FRAX score: why only some patients do fracture? - An evaluation of the role of several clinical risk factors and of bone quality assessed by HR-pQCT

Sylvie CAPPELLE[1], Marianne PAESMANS[2], Michel MOREAU[2], Pierre BERGMANN[3], Rafik KARMALI[1], Jean-Jacques BODY[1]
[1]Department of Medecine, CHU-Brugmann, ULB, [2]Data center, Institut J.Bordet, ULB, [3]Department of Nuclear Medecine and Laboratoty Experimental Medecine, CHU-Brugmann, ULB, Brussels, Belgium CHU-Brugmann, ULB, Brussels, Belgium

Prevention of fragility fractures remains the main challenge in the management of osteoporosis. Bone densitometry (DXA) is useful for the diagnosis of osteoporosis, but is not sufficient to accurately predict the fracture risk (for an individual). As osseous resistance depends on bone density but also on bone microarchitecture and/or mechanical properties, determining the individual risk of fracture should consider all these parameters. Various clinical risk factors (CRFs) have an impact on the bone structure and quality. Hence, the FRAX® algorithm utilizes a combination of some CRFs and bone density to improve the prediction of low-trauma fractures. This tool was a major achievement, but it presents several limitations: for example, some conditions known to increase the fracture risk (eg. Falls and sedentary lifestyle) are not taken into account.
Furthermore, recent technological advances have made possible a non-invasive assessment of bone quality. High-resolution peripheral quantitative computed tomography (HR-pQCT) can bring information on the cortical and trabecular structures, on bone geometry and microarchitecture. It also allows, in combination with micro-finite element (μFE) models, a non-invasive quantification of bone strength and mechanical features.

Here, our objective is to evaluate the association between fragility fracture occurrence and the bone microarchitecture assessed by HR-pQCT and a series of clinical risk factors – included, or not, in the FRAX® model – in the framework of a vast prospective epidemiological study (FRISBEE).
The Fracture RISk Brussels Epidemiological Enquiry (FRISBEE) study is a population-based cohort study on risk factors for osteoporotic fractures in 3650 post-menopausal Belgian women. Is final aim consists of validating and integrating several independent CRFs in a new fracture risk model.
Women included in the three first years of the FRISBEE study and who fractured after their inclusion (n=189 / 1740 women) were compared with control women - who did not present a fracture during the same follow-up period, but had a similar probability of fracture at baseline according to the FRAX® score (n=398).
We present here the results of the analysis of the predictive value of clinical risk factors. Differences between HRpQCT parameters (retro and prospective analyses) will be discussed in another paper.

5. Preliminary evaluation of the effects of drug loading in muscles' derived mesenchymal stem cells for delivery purposes: the example of curcumin

Margaux Colin[1,2], Lola Dechêne[3,4], Rafaele Calvo Eposito[1], Justine Ceusters[4,5], Laurence Lagneaux[6], Pierre Van Antwerpen[2], Erik Goormaghtigh[7], Patricia Renard[3], Didier Serteyn[4] and Véronique Mathieu[1].
[1] Department of Pharmacotherapy and Pharmaceuticals, Faculty of Pharmacy, Université Libre de Bruxelles (ULB), 1050 Brussels, Belgium
[2] RD3- Pharmacognosy, Bioanalysis and Drug Discovery Unit and Analytical Platform, Faculty of Pharmacy, Université Libre de Bruxelles (ULB), 1050 Brussels, Belgium
[3] Laboratory of Biochemistry and Cell Biology (URBC)-Namur Research Institute for Life Sciences (NARILIS), University of Namur, 61, rue de Bruxelles, 5000 Namur, Belgium
[4] Centre of Oxygen, Research and Development CIRM, Institute of Chemistry B6a, University of Liege, Sart Tilman, Liège, Belgium
[5] RevaTis SA, rue de la Science, 8 6900 Aye, Belgium

[6] Laboratory of Clinical Cell Therapy, Jules Bordet Institute, Université Libre de Bruxelles (ULB), Campus Erasme, Bâtiment de Transfusion (Level +1), Brussels 1070, Belgium
[7] Center for Structural Biology and Bioinformatics, Laboratory for the Structure and Function of Biological Membranes; Université Libre de Bruxelles, Campus Plaine, Bld du Triomphe 2, CP206/2, B1050 Brussels, Belgium

A new therapeutic perspective of stem cells (MSCs) concerns their potential use for drug delivery purposes [1-2]. However, when considering MSCs as delivery agents, it is important to consider that incorporation of the therapeutic agent may possibly affect their biology and particularly their mesenchymal stem cell properties. A minimally-invasive process to obtain MSCs from muscles of different species has been previously developed [3]. These muscles' derived MSCs are easy to sample but their knowledge remains more limited than bone-marrow derived MSCs. In our study, we aim to evaluate i) variability of MSCs sampled from different horses and overtime in culture and ii) whether drug loading affects their mesenchymal stem cell properties. For this purpose, we started first with a well-tolerated and widely used medicinal polyphenol, i.e. curcumin whose pharmacokinetic properties are not favourable for use as a drug. The preliminary analyses of the biochemical signature of MSCs in culture by means of Fourier transformed infrared spectroscopic microscopy (FTIR) suggest high degree of similarity among MSCs from 5 different donors, a feature that seems to remain till passage 8. Those cells efficiently uptake a hydrosoluble curcumin salt complexed with cyclodextrin (NDS27). Importantly, we have found that this drug loading does not alter their viability, cellular proliferation and immunomodulation potential of the MSCs on T lymphocytes. Also FTIR analyses did not evidenced significant changes following NDS27 loading. Finally, although curcumin has been shown to exert pro-oxidant effects in cancer cells [4], preliminar flow cytometry results suggests that MSCs loading with NDS27 has only limited effects on the levels of mitochondrial reactive oxygen species. Those preliminary results encourage further investigations of muscles' derived MSCs as therapeutic delivery agents for various purposes including inflammatory diseases.

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6. Resting-state related brain functional connectivity across lifespan : a connectomic approach

Coquelet N, Wens V, Bourguignon M, Mary A, Niesen M, Destoky F, Roshchupkina L, Peigneux P, Goldman S and De Tiège X.
Laboratoire de Cartographie fonctionnelle du Cerveau, UNI-ULB Neuroscience Institute, Université libre de Bruxelles (ULB), Brussels, Belgium.

This research project aims at providing a better understanding of resting-state functional connectivity (rsFC), a measure of correlation between spatially remote brain regions at rest, across lifespan. To this end, we investigated the following research questions: (1) Is rsFC changed in healthy aging? and (2) how is modulated the dynamic of rsFC from childhood to advanced age? In order to answer those questions, we made use of magnetoencephalography (MEG) and high-density electroencephalography (hdEEG), two electrophysiology neuroimaging techniques that records brain activity directly. Both techniques, although sensitive to different neuronal orientation, possesses an excellent temporal resolution making them appropriate to tackle the dynamic of brain activity at rest. Compared to functional magnetic resonance imaging (fMRI), the neuro-imaging technique the most used to investigate brain activity, both techniques offer the advantage of being free of neurovascular coupling bias, which are of utmost interest to address our research questions. In this PhD thesis, resting-state related brain activity has been investigated on the basis of resting-state networks (RSNs), a small

number of well-structured spatio-temporal brain patterns emerging at rest that rely upon the concept of rsFC. One of the original features of this project has been to evaluation rsFC using a connectomic approach, a method that enable to assess of within- and cross-networks interactions, thereby offering a global view of rsFC. As results, we firstly showed that healthy aging is characterized by a maintenance of rsFC when compared to young adults. Secondly, the investigation of dynamic related RSNs between children, young adults and elders are still in progress, and should provide new insights about how RSNs are modulated depending on age. Finally, along with the main goals, the use of two neuroimaging techniques raised the need to compare them in terms of rsFC evaluation, and we highlighted that the two facilities return similar rsFC patterns provided that only static investigation are at stake. Taking together, those results might pave the way to the investigation of pathophysiology in childhood and in aging using MEG and hdEEG, the latter receiving growing attention for its attractive features such as portability and accessibility.

7. Monitoring of apolipoproteins oxidation to improve the estimation of lipoprotein quality in cardiovascular diseases

Catherine Coremans[1], Vincent Nuyens[2], Alexandre Rousseau[2], Philippe Van de Borne[3], Karim Zouaoui Boudjeltia[2], Cédric Delporte[1] and Pierre Van Antwerpen[1]

[1]Pharmacognosy, Bioanalysis and Drug Discovery and Analytical Platform of the Faculty of Pharmacy (RD3 department), Université libre de Bruxelles, Brussels, Belgium

[2]Laboratory of experimental Medicine (CHU Charleroi), Faculty of Medicine, Université libre de Bruxelles, Montigny-le-Tilleul, Belgium

[3]Cardiology department, Erasme's Hospital, Université libre de Bruxelles, Brussels, Belgium

The oxidation of low- and high-density lipoproteins (LDL and HDL) is important in the development of atherosclerosis. Myeloperoxidase (MPO) oxidation is one of the most relevant oxidation processes. By oxidizing apoA-1, MPO leads to dysfunctional HDL and cholesterol efflux deficiency. Modifications on apoB-100 promote atherosclerosis by foam cell formation and pro-inflammatory properties of oxidized-LDL. Several modifications of apoA-1 and apoB-100 have already been described in the literature and seem relevant in patients with CVD. However, it is not clear yet whether new lipoprotein biomarkers can provide better predictability of CVD risk. It is then necessary to update knowledge about new biomarkers, such as apolipoproteins A-1 and B and their quality.

The aim is to develop a method to quantify the native and the oxidized forms of apoA-1 and apoB-100 in plasma. The analytical method is based on liquid chromatography coupled to mass spectrometry (LC-MS/MS). *In vitro* oxidations of purified HDLs and LDLs were performed to previously optimize LC-MS parameters, to detect relevant oxidized peptides from apolipoproteins. Sample preparation was optimized with isolation of lipoproteins from plasma samples by lipid removal agent (LRA).

Plasma from healthy volunteers and patients were analysed. When regarding the ratio of oxidized peptides, we observe a difference between volunteers and patients for peptides from apoA-1 with respectively 2.36 and 5.14 % for Trp72. In contrast, no oxidized peptide from apoB-100 were detected even if relevant oxidized peptides from apoB-100 were identified in purified LDL from patients. *In vitro* oxidized plasma was tested to assess our method. The formation of oxidized peptides was relevant with the proportion of oxidized plasma for both apoA-1 and B-100. Then, we performed supplementation of characterized plasma with *in vitro* oxidized-LDL. Difference between plasma without and with supplementation of 2.5, 5, 10, 15 and 20% of oxidized-LDL was not significant even if ratio of oxidized peptides tended to increase with supplementation.

The isolation of lipoproteins with LRA allowed us to detect apoA-1 oxidized peptides directly in plasma of patients with cardiovascular diseases. However, oxidized peptides from apoB-100 were not detected. Future investigations will be needed to increase the sensitivity of the method.

8. Intraocular injection of fibrillary PHF-tau isolated from Alzheimer's disease brain : effect on tau pathology development in wild-type and tau transgenic mice

Marie-Ange De Fisenne[1], Kunie Ando[1], Zehra Yilmaz[1] , Salwa Mansour[1], Luc Buée[2], Jean-Pierre Brion[1], Karelle Leroy[1]
[1] Laboratory of Histology, Neuroanatomy and Neuropathology, ULB Neuroscience Institute, Université Libre de Bruxelles, Faculty of Medicine, Brussels, Belgium.
[2]Université de Lille, INSERM, CHU-Lille, UMR-S 1172, LabEx DISTALZ, Lille, France.

The development of tau pathology in brain of Alzheimer's disease (AD) patients is ranked into 6 stages according to the neuroanatomical localisation of neurofibrillary tangles (NFT). Interestingly, NFT do not form randomly in the brain but follows neuroanatomical pathway suggesting that synaptically connected neurons could transmit tau pathology by the recruitment of normal tau by abnormal tau proteins.
We have studied the possible transsynaptic transmission of tau pathology in vivo by using the visual pathways in which the connections between neuronal areas are well known. Neuronal ganglion cells from the retina project their axons to the geniculate nucleus and superior colliculus and further away to the visual cortex. Fibrillary PHF-tau proteins isolated from AD brains (or control brain) were injected in the vitreous body of the eye of WT, htau (expressing human WT tau) and Tg22 (expressing human mutant tau) mice. The development of tau pathology was studied along the visual pathway (retina, geniculate nucleus, superior colliculus and secondary visual cortex).
Whereas fibrillary PHF-tau proteins induced the recruitment of murine tau and its phosphorylation in WT mice after stereotaxic injection in the hippocampus and the cortex, no development of tau pathology along the visual pathways was observed in WT and htau mice after injection of fibrillary PHF-tau proteins in the vitreous body of the eye (6 months of incubation), using immunocytochemistry with PHF1, AT8, and MC1 antibodies and Gallyas staining. After eye injection In Tg22 mice (expressing a human mutated tau and developing neurofibrillary tangles), the number of AT8 and MC1 positive cells showed a tendency to increase, after 6 months of incubation, in the superior colliculus of mice injected with fibrillary PHF-tau proteins compared to mice injected with control material. This effect was not observed in the geniculate nucleus and in the visual cortex. Our observation suggests that abnormal human PHF-tau proteins in the form of high molecular weight fibrillary assembly do not efficiently recruit endogenous murine wild-type tau or mutated human tau after injection in the eye and along visual pathways.

9. Role of chemerin in the splenic organization and function of CMKLR1$^+$ leukocytes

PhD student: Degroot G-N Promoter: Springael J-Y
IRIBHM, Faculty of Medicine, Université Libre de Bruxelles (ULB).

The spleen is the largest blood filter and the largest secondary lymphoid organ of the body. It is divided in two functional and morphological compartments, the red pulp and the white pulp. The red pulp is a specialized filtering structure removing old and damaged erythrocytes from blood and recycling iron. The white pulp is the lymphoid compartment of the spleen, responsible of the blood pathogen filtration and of the innate and the adaptive immune response. The white pulp is composed of three sub-compartments: the periarteriolar lymphoid sheath (PALS) composed of T-cells and DCs, the B-cell follicles and the marginal zone composed of subsets of lymphocytes, macrophages and DCs. The distribution and the migration of those leukocyte populations through the red and the white pulp depend of a complex distribution of chemokines and other chemoattractant molecules. The chemerin is a small chemoattractant protein binding two receptors, CMKLR1 and GPR1. The binding of chemerin to CMKLR1 induces the chemotaxis of leukocytes populations that express the receptor, including dendritic cells, macrophages and natural killer cells. In contrast, the binding of the chemerin to GPR1 does not activate G proteins and GPR1 is thereby considered as an atypical receptor. The actual hypothesis is that GPR1 could regulate locally the extracellular concentration of chemerin. In this work, we show by immunofluorescence that chemerin has a unique distribution pattern in the spleen with a strong immunodetected signal in the marginal zone. We also show that both types of marginal zone macrophages express CMKLR1. We used CMKLR1$^{-/-}$ and GPR1$^{-/-}$ mice to determine the implication of the two receptors in the distribution of the chemerin and of the marginal zone macrophages. We will pursue our immunofluorescence and flow cytometry analysis to identify the cells producing the chemerin and to determine the implication of the marginal zone macrophages redistribution in the filtration of the blood pathogen.

10. The Group A streptococcal Enn proteins bind numerous human plasma proteins

Frost H (1), Botquin G (1), Lakhloufi D (1), Sanderson-Smith M (2), Ly D (2), Cleary A (2), Davies M (3), Walker M (4), Steer A (5), Botteaux A* (1) and Smeesters A* (1)
*Contributed equally
1. Laboratoire de Bactériologie moléculaire, ULB
2. Illawarra Health and Medical Research Institute, University of Wollongong, Australia
3. Department of Microbiology and Immunology, University of Melbourne, Australia
4. Australian Infectious Diseases Research Centre, University of Queensland, Australia
5. Group A Streptococcus Research Group, MCRI, Melbourne, Australia

The Group A Streptococcus (GAS) has developed a myriad of immune evasion techniques to allow effective colonisation and infection of humans and the establishment of diverse diseases. In particular, GAS are known to target the the innate immune system, in particular the complement system, by binding host serum proteins to the bacterial surface. Many of these functions are attributed to the GAS M protein, the archetypal GAS virulence factor and leading GAS vaccine candidate, however 85% of GAS strains also encode M-like proteins, whose functions have been relatively poorly characterised to date.
We determined that one family of M-like proteins, Enn proteins, are able to bind many human serum proteins in a similar manner to M proteins, which may aid in immune evasion. We produced 9 recombinant Enn proteins, from a variety of GAS strains, and measured their ability to bind human plasma proteins using pull-down assays. We determined that individual Enn proteins have a diverse array of binding capacities for human plasma proteins, much like what is observed for M proteins. Enn proteins are able to bind to negative regulators of complement C4 binding protein (C4BP), fibrinogen and factor H (and derivatives), immunoglobulins IgG and IgA by the Fc region and albumin, the latter of which may play a role in immune masking. Through peptide deletions and targeted mutagenesis the domains of interaction and fine-mapping for some binding has been determined.
The ability of Enn proteins to bind numerous host plasma proteins indicates these proteins are likely more important to GAS virulence than previously predicted. The redundancy in function between M and Enn proteins also suggests these processes are key to survival and dissemination of the bacteria. These findings may be useful in the development of a GAS vaccine that specifically targets the structure of the interactions, to inhibit the function of both M and Enn proteins.

11. Characterization of chemerin axis in zebrafish

O. Ghandeharian, E. Di Ruggiero, M. Parmentier and V. Wittamer
Institut de Recherche Interdisciplinaire en Biologie Humaine et Moléculaire (IRIBHM) Université Libre de Bruxelles (ULB), Campus Erasme, 808 Route de Lennik, B-1070 Brussels, Belgium.

Zebrafish became over the recent years a major animal model in many research fields, including inflammation, regeneration and cancer. Here, we propose to utilize the unique strengths of this model system to obtain new insights into key functional aspects of chemerin, an extracellular mediator that was identified in our lab as the natural ligand of CMKLR1, and was initially showed to display potent chemotactic activity for macrophages, dendritic and natural killer cells. Work performed by us and by others suggests that chemerin displays complex activities, that are either pro- or anti-inflammatory, depending on the disease model used. These investigations have also highlighted the possible tumor-suppressive properties of this chemoattractant in cancer biology, as well as a possible function in metabolism. However, these studies rely mostly on experiments performed *in vitro* or on cell lines, and their results are often conflicting. The multifunctional nature of chemerin *in vivo* remains therefore an open question.
Sequence and phylogenetic analyses indicate the chemerin system is relatively well conserved between zebrafish and mammalian species. Due to a whole-genome duplication event in the evolution of teleosts, it appears however that zebrafish possess more chemerin and receptor genes than their mammalian counterparts. These observations strongly suggest that subfunctionalization contributed to the evolution of the chemerin family in zebrafish, which may provide an advantage for the *in vivo* functional dissection of chemerin activities in physiology and disease.
As a first step towards using the zebrafish to gain insights into chemerin biology, we have performed a thorough analysis of the chemerin system in this animal model. Here, we show that the different chemerin paralogs exhibit distinct pharmacological and expression properties. Using an approach that relies on protein fractionation by

affinity chromatography, receptor functional testing and mass spectrometry analyses, we were able to pair each chemerin paralog to its functional receptor. This allowed us to show that the ligands and receptors are not redundant in term of pharmacology. In addition, we also demonstrated that, as in human and mouse, accurate and specific C-terminal processing of chemerin is required for bioactivity in zebrafish. Finally, determination of the expression profiles of the different chemerin paralogs also revealed specificity. The validation of a functional conservation of the chemerin system in teleosts has now opened new avenues in utilizing zebrafish to complement studies performed on mouse models, and should ultimately lead to uncovering important new functions of this evolutionary conserved immune factor.

12. Rapid sample preparation for the profiling of N-glycans by liquid chromatography mass spectrometry.

Y Helali, CD Fiume, P Van Antwerpen, and C Delporte.
1RD3-Pharmacognosy, Bioanalysis and Drug Discovery Unit and Analytical Platform of the Faculty of Pharmacy, Faculty of Pharmacy, Université Libre de Bruxelles, Brussels, Belgium.

Biopharmaceuticals are becoming one of the most promising drugs on the market mainly due to their successful treatment of a vast array of serious diseases. More than 60 % of the approved therapeutic proteins are glycosylated. Glycosylation requires a detailed monitoring and controlling. This modification may alter the functioning of the therapeutic glycoproteins, such as their half-life, immunogenicity, toxicity, stability, and solubility. The main goal of our study was to develop a rapid sample preparation using procainamide labelling to better monitor the *N*-glycans and to compare the procedure with other commercial kits like the GlycoWorks RapiFluor-MS *N*-Glycan Kit (RFMS kit). This analytical approach will be used to monitor batch-to-batch sample of glycosylated biotherapeutics but also to describe and to understand the impact of *N*-glycosylation at the time of transmitting a primary infection with cytomegalovirus in the case of the pregnant women.
Briefly, *N*-glycans were (i) enzymatically released using PNGase F, (ii) labelled with procainamide, (iii) cleaned with µHILIC SPE and (iv) analysed by HILIC coupled to a high-resolution mass spectrometer.
In first place, we used different times for digestion andlabelling to find the best combination (respectively 5 min-5 min or 5min-60min or 120 min-5 min or 120 min-60 min). The best result was 5min-60min.Then we compared this approach to RFMS kit protocol and the latter presented a higher sensitivity than the procainamide labelling protocol [1]. However, we found also interesting results with the procainamide labelling that might be optimized to increase its sensitivity [1].
The present approach shows very encouraging results that we will improve by using online SPE purification. Our final goal will be to get a reliable method to describe and understand the *N*-glycosylation in several biopharmaceutics and to investigate of *N*-glycan profiles in diseases.

13. Human CMV infection as a co-factor of disease progression in biliary atresia

Hoyois A[1], Gu-Trantien C[1], Le Moine C[1], Papadopoulou M[1], Bouzin C[2], Komuta M[3], Delforge ML[4], De Magnée C[5], Le Moine A[1,6], Reding R[5] and Marchant A[1]
[1] Institute for Medical Immunology, Université libre de Bruxelles, Charleroi, Belgium; [2] Institute of Experimental and Clinical Research, Université Catholique de Louvain, Brussels, Belgium; [3] Department of Pathology, Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium; [4] Department of Microbiology, National Reference Center for Congenital Infections, CUB-Hôpital Erasme, Université libre de Bruxelles, Brussels, Belgium; [5] Department of Surgery and Transplantation, Cliniques Universitaires Saint Luc, Brussels, Belgium; [6] Department of Nephrology, CUB-Hôpital Erasme, Université libre de Bruxelles, Brussels, Belgium.

Biliary Atresia (BA) is a rare inflammatory disease affecting the extrahepatic biliary ducts of the newborn. Despite early surgical treatment, the disease often progresses to cirrhosis, and liver transplantation is then the only therapeutic option. The pathogenesis of BA remains unclear and probably involves genetic and environmental factors, including viral infections. Epidemiological studies have shown an association between CMV infection and the severity of BA. This study was undertaken to characterize liver-infiltrating T lymphocytes (LIL) in CMV-seropositive and seronegative BA patients. Liver tissue and peripheral blood were analyzed in 31 BA patients at the time of liver transplantation. Immunohistochemistry analyses indicated that LIL co-localized and correlated with liver fibrosis. CMV-positive patients showed more intense fibrosis and LIL density than CMV-negative patients. Flow cytometry analyses revealed that LIL of CMV-positive patients included higher proportions of effector memory CD4 and CD8 T cells expressing a Th1/Tc1 phenotype and cytotoxic functions as compared to

CMV-negative patients. These cells expressed the fractalkin receptor CX3CR1 and were enriched in CMV-specific cells. T cell receptor repertoire analysis by RNA sequencing identified clonotypes present at high frequencies in the liver and shared with the peripheral blood lymphocyte compartment, suggesting local recruitment. These results support the notion that CMV infection could be a co-factor of BA disease progression by recruiting cytotoxic T cells promoting liver tissue damage and fibrosis.

14. Development and assessment of new technology for variceal bleeding.

Mostafa Ibrahim MD [1,2], Ahmed El-Mikkawy MD [2], Mohamed Abdel Hamid [2], Haitham Abdalla [2], Arnaud Lemmers MD PhD [1], Ibrahim Mostafa MD PhD [2], Jacques Devière MD PhD [1]

1. Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
2. Department of Gastroenterology and Hepatology, Theodor Bilharz Research Institute Cairo, Egypt

Acute variceal bleeding (AVB) is the most dramatic complication of portal hypertension. it occurs in one third of patients with varices and causes 70% of all upper gastrointestinal (GI) bleeding in cirrhotic patients. Improvements in general management and available hemostasis treatments have led to a marked reduction in AVB-related mortality.

Endoscopic management combined with pharmacotherapy is the ideal strategy to control variceal bleeding and it can be challenging.

Early management of acute bleeding episodes is considered to be mandatory within 24 hours of admission. Better outcomes are reported in those patients who receive endoscopic therapy within 12 hours. However, the situation in daily practice is different and delays in performing endoscopy occur, often because of the lack of available expert endoscopists able to manage upper GI bleeding. Therefore, urgency of development of a simple and effective technique of early endoscopic hemostasis that would have impact on the treatment of active gastrointestinal bleeding in its early stages has become mandatory. An ideal endoscopic hemostasis device would be one that does not require a direct contact with the bleeding point and one that does not cause further tissue damage that may result in more severe bleeding.

The Hemospray powder (Hemospray, TC-325; Cook Medical Inc., Winston-Salem, NC, USA) is an FDA approved organic powder made of proprietary mineral blend. It works in two different ways: as a mechanical barrier and by absorption. When in contact with the bleeding site, the powder forms a barrier over the vessel wall, quickly stopping the bleeding, and secondly, the absorbent powder increases the local concentration of clotting factors and enhances clot formation. The present work included pilot study followed by two confirmatory prospective clinical trials (The first was single arm and the second was randomized clinical trial) investigating the safety and efficacy of haemostatic powder added to the standard of pharmacological treatment for acute variceal bleeding (AVB) in patients with portal hypertension due to liver cirrhosis.

15. Genetic architecture of congenital primary hydrocephalus: novel genes in consanguineous families and digenic inheritance in an outbred cohort

Jacquemin V, Duerinckx S, Perazzolo C, Pirson I, and Abramowicz M
Human Genetics Research Lab, IRIBHM, Universite Libre de Bruxelles
Jacquemin V, Duerinckx S, Perazzolo C, Antoine M, Gillotay P, Rooman M, Lenaerts T, Costagliola S, Pirson I, Abramowicz M

Hydrocephalus is a devastating, potentially lethal neurological condition. A subgroup with prenatal onset and no apparent cause is called congenital primary hydrocephalus, affecting 1/10,000 newborns. Some of these cases result from monogenic (X-linked or autosomal recessive) causes, with three genes identified as of today, and a larger genetic heterogeneity still unresolved. This leads us to believe that the majority of cases are likely to have an oligo- or multigenic origin, with several biological processes involved. Identifying new genes, and unraveling oligogenic inheritance, is needed to better understand the pathophysiology of hydrocephalus, and hence for better prognosis and new therapeutic approaches.

Our project consists of: identifying novel gene with a Mendelian effect in our consanguineous families; validating novel genes in a zebrafish model; testing for digenic inheritance using a gene mutation burden test is a predefined subset of ciliary genes and a machine learning approach for ranking genetic variant in a digenic model, developed for our study of primary microcephaly.

To this day, we have gathered a vast cohort of patients (47) with primary congenital hydrocephalus for which 33 patients have been exomed. We perform exome analysis using a bio-informatics program (Highlander) to uncover potential candidate genes associated with the presented pathology, and thus far a genetic diagnostic was found for 7 patients as well as the identification of potential candidate genes. Implication of potential candidate genes are tested in the zebrafish animal model using CRISP-Cas9 technology to obtain knockout lines. In one of our families a recently implicated gene in congenital hydrocephalus, KIDINS220, was identified. Functional testing for the implication of the particular variant is ongoing.
Based on the literature, most of the gene products responsible for hydrocephalus in animal models are molecules involved in cell signaling pathways during early brain development, or in ciliary function. The potential implication of this last group of genes in an oligogenic inheritance model, is being investigated through statistic models.

16. Is a single driver gene mutation sufficient for monitoring early response in advanced colorectal cancer?

Pashalina Kehagias[1], Lieveke Ameye[2], Hakim El Housni[3], Amélie Deleporte[1], Karen Geboes[4], Thierry Delaunoit[5], Gauthier Demolin[6], Marc Peeters[7], Lionel D'Hondt[8], Jos Janssens[9], Javier Carrasco[10], Maria Gomez Galdon[11], Pierre Heimann[3], Marianne Paesmans[2], Patrick Flamen[12], Alain Hendlisz[1], Caroline Vandeputte[1]
[1] Gastro Intestinal Oncology Unit, Medical Oncology, Institut Jules Bordet, Brussels, Belgium
[2] Data Centre, Institut Jules Bordet, Brussels, Belgium
[3] Department of medical Genetics, Hôpital Erasme-ULB, Brussels, Belgium
[4] Service of digestive oncology, Universitair Ziekenhuis Gent, Gent, Belgium
[5] Oncology department, Hôpital de Jolimont, La Louvière, Belgium
[6] Gastroenterology Department, Centre Hospitalier Chrétien St-Joseph, Liège, Belgium
[7] Oncology department, Universitair Ziekenhuis Antwerpen, Antwerpen, Belgium
[8] Oncology department, Centre Hospitalier Universitaire, UCL Namur (site de Godinne), Belgium
[9] Department of Gastroenterology, AZ Turnhout, Turnhout, Belgium
[10] Oncology department, Grand Hôpital de Charleroi, Charleroi, Belgium
[11] Department of Pathology, Jules Bordet Institute, Free University of Brussels, Brussels, Belgium
[12] Nuclear medicine Imaging and Therapy Department, Institut Jules Bordet, Brussels, Belgium

Purpose: Circulating tumor DNA (ctDNA) monitoring during therapy is under intense investigation in modern oncology. We previously reported that the increase of ≥50% of ≥1 somatic mutation among multiple monitored mutations/patient is associated with a significantly worse outcome. This study investigates whether the ctDNA monitoring of one driver gene mutation, provides enough information as compared to multiple mutations to assess response to regorafenib in advanced chemorefractory colorectal cancer (aCRC) at an early timepoint.
Experimental procedures: Archival tumor tissue and plasma samples (PL) at baseline (BL) and 14 days (D14) after treatment initiation in aCRC patients (n=141) were prospectively collected in the RegARd-C multicenter clinical trial (NCT01929616). Somatic mutations were identified based on a CRC-oriented targeted gene sequencing of tumor tissue. All available (median 2 (1-4)) driver gene mutations were monitored/patient in PL at BL and D14 via droplet digital PCR (Bio-Rad QX200 ddPCR system) to assess ctDNA dynamics. ***Results:*** In 96 evaluable patients, most frequently monitored mutated genes were *APC* (73%), *TP53* (72%), *KRAS* (66%), and *PI3KCA* (23%). Among patients with ≥2 monitored mutations (73/96), one was selected at random and compared to previous methodology taking in account dynamics of all followed mutations. Optimal cutoff (CO) evaluation separated patients (n=96) according to a ctDNA increase of ≥50% *versus* an increase of <50% or a decrease. CtDNA dynamics concordance based on one randomly selected mutation and multiple monitored mutations was 91%. Our data demonstrated that a ctDNA increase based on one single mutation taken at random is significantly associated with a worse progression-free survival (HR 2.42, 95% CI (1.56-3.74), P<0.001) and overall-survival (HR 2.17, 95% CI (1.41-3.34), P<0.001). In addition, when combining patients' ctDNA dynamics to BL ctDNA levels (≥ or < 5 ng/mL) or BL cell-free DNA (cfDNA) levels (≥ or < 50 ng/m), we could distinguish 4 patients' subgroups with different prognosis. ***Conclusion:*** The monitoring of ctDNA dynamics based on only one randomly selected driver gene mutation versus multiple is equally informative to describe adequately aCRC patients' outcome under regorafenib after 14 days of treatment onset. Especially, combined with pre-treatment ctDNA levels, this simplifies a personalized patient monitoring.

17. Finite element analysis of biomechanical behaviour of zygomatic implants techniques in case of edentulous and severely atrophic maxilla: a systematic review

Larabi I.[1], Aour B.[2], Evrard L.[1]
[1]Implantology Clinic - Stomatology and Maxillofacial Surgery Department –Hôpital Erasme
Université libre de Bruxelles, Belgium
[2]Laboratory of Applied Biomechanics and Biomaterials, National Polytechnic School of Oran, Algeria

Objectives : Implant-fixed prosthetic rehabilitation in case of edentulous and severely atrophic maxilla is a challenging situation. Surgical techniques for zygomatic implant placement have evolved since they were first introduced by PI Bränemark in 1990's and a growing number of recent finite element (FE) studies have aimed at analysing their biomechanical behaviour.
The aim of this work is to review the literature focused on surgical techniques of zygomatic implants analysed by the FE method and to define new 3D FE analysis study guidelines.
Materials and methods : A PRISMA type systematic literature review based on 5 data sources (Pubmed, Scopus, Elsevier Direct Science, Springer Link and Cochrane Library), identified 10 articles according to the following inclusion criteria: (1) FE studies, (2) in case of edentulous and severely atrophic maxilla treated by implant-supported fixed prosthesis, (3) without bone defect resulting from tumor resection or congenital abnormality and not requiring obturator prosthesis, (4) using zygomatic implants, (5) in men and / or women, (6) written in English or French. Studies were analysed and compared qualitatively.
Results: The initial search done through the 5 search engines identified 329 titles. After excluding off-topic, non-scientific articles, duplicates and adding research from other sources, 68 full articles were analysed. We excluded 58 off-inclusions criteria studies. This systematic review allowed the qualitative analysis of 10 scientific studies concerning the biomechanical behaviour of zygomatic implants by the FE method. The first FE simulation was the Bränemark's technique and is the most modeled. The second was the extra-maxillary approach proposed by Maló *et al.* and the last is the the externalised technique described by Chow and Aparicio *et al.* Maximum stress values found remained within acceptable limits for zygomatic implants (<900 MPa).
Conclusion : FE analysis indicates the choice of prosthetic rehabilitations using zygomatic implants as biomechanically acceptable. The externalised approach has the most favourable distribution of stresses and deformations. These FE studies, although dealing with the same subjects, are not all completely comparable to each other because of differences in modeling, pre-treatments and calculations. Following this, it appears interesting to conduct studies on complete fatigue FE analysis on 3D models.

18. Understanding the role of JNK1 in the context of skin inflammation

Le A**[1]**, Assabban A[1], Istaces N[1], Thomas S[1], Nguyen M[1] Wunderlicht T[2], Bruning J[2] and Goriely S[1]
[1]Laboratory of Institute of Medical Immunology (IMI), Université Libre de Bruxelles (ULB), Gosselies, Belgium
[2] Institute for Genetics, University of Cologne, Cologne, Germany

JNK1 is an ubiquitously expressed kinase involved in multiple biological processes including embryological development, insulin signaling, cancer and immunity. It is activated downstream of pathogen recognition and cytokine receptors. However, its implication in inflammatory diseases is still poorly defined. In order to better understand these mechanisms, we studied the role of JNK1 in the context of imiquimod-induced skin inflammation. This classical experimental model presents many features of human psoriasis, including the central involvement of the IL-23/IL-17A axis.
We observed that ablation of *Jnk1* in all tissues (PGK-Cre $Jnk^{fl/fl}$ mice) strongly reduced the epidermal thickening and severity of inflammatory lesions upon imiquimod treatment. This was associated with lower expression of inflammatory markers as compared to littermates, such as antimicrobial peptides, inflammatory cytokines and chemokines. To further elucidate the underlying mechanisms, we evaluated the role of JNK1 in the epidermal and the hematopoietic compartment. In comparison to their WT littermates, $Jnk1^{\Delta EP}$ (K14-Cre $Jnk1^{fl/fl}$) mice displayed reduced imiquimod-induced epidermal thickening and proliferation, despite similar levels of inflammatory markers. Preliminary data further show that the response to rIL17A upon intradermal injection or upon *in vitro* stimulation of primary fibroblasts was reduced in absence of *Jnk1*. In sharp contrast, we observed that imiquimod-induced expression of inflammatory markers was decreased upon ablation of *Jnk1* in the hematopoietic compartment (Tie2-Cre $Jnk1^{fl/fl}$ mice). However, pathological features were not significantly affected in these conditions. These findings were recapitulated upon ablation of *Jnk1* in myeloid (LysM-Cre $Jnk1^{fl/fl}$ mice) and CD11c-expressing cells (CD11c-Cre $Jnk1^{fl/fl}$ mice).

Taken together, these data indicate that JNK1 plays a dual role in the context of psoriasis by regulating the production of inflammatory cytokines by myeloid cells, as well as the sensitivity of keratinocytes to these inflammatory signals. Our results suggest that JNK1 could represent a valuable therapeutic target in the context of psoriasis.

19. Towards a quality assurance for dosimetry in peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE

Marin G, Vanderlinden B, Karfis I, Guiot T, Wimana Z, Reynaert N, Vandenberghe S, Flamen P
Services de Radiophysique et de Médecine Nucléaire, Institut Jules Bordet, Bruxelles
Medisip, department of Electronics and Information systems (ELIS), Faculty of Engineering and Architecture (FEA), Ghent University (UGent)

Aim : Peptide receptor radionuclide therapy (PRRT) with Lutetium-177-DOTA-(Tyr3)-octreotate (177Lu-DOTATATE) has become a notable treatment modality in neuroendocrine tumours (NETs). However, in order to establish a reliable dose-response/-toxicity correlation for PRRT, a good precision on all measurements must be achieved. The aim of this work is to evaluate the precision of a clinically implemented dosimetry procedure.
Materials and methods : Twenty-seven patients with NETs underwent 3 to 5 177Lu-DOTATATE administrations. Three SPECT/CT images were acquired at 4, 24 and 144–192 h post-injection. Three blood samples were obtained together with the SPECT/CT acquisitions and 2 additional samples were obtained around 30 min and 1 hour post-administration. Cumulated activity in source volumes was calculated by multiplying specific activity (Bq/mL) and CT volume. A bi-exponential fit was used to compute the source organ time-integrated activity coefficients (TIACs). Dose computation was finally performed for each administration.
To compute intra-individual (inter-administration) dosimetry variability, dose per injected activity (D/A0) was first normalized by the mean value of all administrations for each patient. The coefficient of variation (CoV) of the normalized D/A0 was then computed for each patient. The mean CoV for all patients was finally used as an estimator for the variability of the dosimetry.
Results : Mean D/A0 CoV were 14% and 18% for right and left kidneys and 23%, 16% and 15% for spleen, remainder of the body and bone marrow respectively.
For liver, mean D/A0 CoV was 23%. Three patients showed a systematic dose decrease over 177Lu-DOTATATE administrations (corresponding to decreasing lesion uptake). When discarded from the evaluation, liver dose variability decreased to 16%.
Conclusion : As intra-individual variability includes both stochastic errors and physiological inter-administration modifications, the proposed methodology makes it possible to compute the maximum stochastic error committed on the computed absorbed dose. Such a process may help identify methodological sources of error requiring additional quality control. By introducing additional quality control, better precision on dose-toxicity correlations can be obtained.

20. Predisposition to pulmonary arterial hypertension in high risk populations: contribution of echocardiography

Asma Rimouche, Sergio Caravita, Laurence Dewachter, Céline Dewachter, Christian Mélot, Antoine Bondue, Jean-Luc Vachiéry.
Department of Cardiology, Hôpital Erasme.

Introduction: Systemic sclerosis (SSc) is a connective tissue disease that can be associated with pulmonary arterial hypertension (PAH) in 5-12% of patients. Screening for PAH in high risk populations is based mainly on resting echocardiography. Although exercise may unmask early abnormalities in pulmonary circulation, exercise echocardiography (Ex-Echo) is currently not recommended due to uncertainties about results interpretation. It was recently suggested that pulmonary circulation at exercise should be evaluated by the relationship between pulmonary artery pressure (PAP) and cardiac output (CO). Few data are available in SSc-patients using this new methodology. Cardiopulmonary exercise testing (CPET) provides important information about adaptation to exercise but was not extensively investigated in SSc-patients without cardiac or pulmonary disease. **Aims:** Define the role of Ex-Echo and CPET in screening of PAH in SSc-patients.
Methods: Prospective follow-up of SSc-patients without PAH in comparison with healthy controls, based on Ex-Echo and CPET.
Results: Forty-two patients and 47 healthy subjects were enrolled. There was no bias for PAP/CO relationship between baseline and repeated test in controls. Coefficient of variation was 9.8% and coefficient of repeatability

was 0.53 mmHg.min.L^{-1}. PAP/CO ratio (3.2±0.6 vs 2.6±0.5; p<0.001) and PAP/CO slope (2.34±0.71 vs 1.93±0.56 mmHg.min.L^{-1}; p=0.003) were higher in patients vs controls. CPET showed lower exercise capacity (84±42 vs 178±58 W; p<0.001) and oxygen uptake (17±6 vs 30±8 mL.min.Kg^{-1}; p<0.001) in patients than controls, with higher VE/VCO2 slope and lower PetCO2 at ventilatory threshold. Markers of right ventricular function at peak exercise were lower in SSc-patients compared with controls.
Conclusion: We tested for the first time the repeatability of PAP/CO relationship in healthy subjects and evaluated the variability of the method which should be considered in interpreting Ex-Echo. We showed that SSc-patients without overt lung or heart involvement have reduced exercise capacity with cardiovascular limitation. They also have different pulmonary hemodynamic response, and reduced RV function at exercise, which might be explained by occult heart involvement or latent pulmonary vascular disease.

21. An innovative approach to study the role of RNA epigenetics in cancer

Soares Da Costa C, de Bony de Lavergne E, Ma HL, Calonne E, Hassabi B, Putmans P, Bizet M, Dube G, Li A, Zhang B, Daniels D, Yang YG, Fuks F.
Laboratoire d'Epigénétique du Cancer, Faculté de Médecine, ULB.
ULB - Cancer Research Center (U-CRC)

To Histone modifications and DNA modifications a new pillar of epigenetics should be considered: "RNA epigenetics". RNA modifications, more than 100 kinds of which have been reported in different RNA species, are involved in diverse biological and physiological processes. Moreover, "RNA epigenetics" is a fast-evolving field and recent data highlighted the existence of RNA modification writers but also the presence of readers. Enzymes involved in methylation of adenosine in RNA have been shown to be elevated in tumours and to be associated with increased cancer risk. N6-Methyadenosine (m6A), the most abundant modification on higher eukaryote mRNAs, is recognized by YTHDF2 (YTH domain family 2), a specific m6A reader implicated in mRNA degradation. Recently, the association between YTHDF2, m6A deregulation and malignancy of hepatocellular carcinoma (HCC), has been reported. Besides the well-characterised m6A RNA modification, TET-mediated hydroxymethylation of cytosine has been identified not only in DNA but also recently in RNA, and our group has highlighted the key functional and biological roles played by RNA hydroxymethylation. It is well known that TET and DNA hydroxymethylation distribution are vastly altered during tumorigenesis; hence the recent emergence of a new function of TET in RNA hydoxymethylation (hmC-RNA), is bringing a whole new interest in the link between epigenetics and cancers. RNA epigenetic events are dynamic and reversible, providing attractive targets for the development of new anti-cancer therapies. Although the multiple layers of epigenetic regulation that result from modification of DNA and proteins have been intensely explored, RNA modifications are still an uncharted territory. Hence, we thought to get a full picture of RNA epigenetics and assess the role of readers in cancer. Through Btn-RNA pulldown assay followed by Mass Spectrometry analysis we have uncovered specific RNA modification readers. Unraveling the function of RNA modifications through the analysis and discovery of specific readers is of major importance for the development of new cancer treatment and diagnostic tools.

22. Aneurysm wall motion: optimization of dynamic CTA

Vanrossomme A E, Chodzynski K J, Corredor R A, Eker O F and Zouaoui Boudjeltia K.
Laboratory of Experimental Medicine (ULB 222 unit) – André Vésale Hospital

Objective: To propose a 4D-CTA acquisition protocol optimized to best detect the pulsation of intracranial aneurysms with the lowest achievable radiation dose. **Materials and Methods**: The acquisition protocol was optimized stepwise: 1°) We determined the smallest detectable pulsation in silicone phantoms mimicking aneurysms; 2°) we determined the 4D-CTA parameters able to detect this pulsation; these two steps being conducted in vitro on a test bench simulating blood flow; 3°) we recorded the radiation dose delivered by various acquisition protocols; and 4°) we tested the 4D-CTA parameters by verifying the detectability of aneurysm pulsation in seven human subjects. **Results**: This study shows that: 1°) in a simplified in vitro setting 4D-CTA allows for an effective and reproducible method to detect and quantify aneurysm pulsation with an inferior limit of 0.5 to 3 mm^3 below which pulsation cannot be detected; 2°) aneurysm pulsation can be detected in vivo but post-processing still needs to be optimized for appropriate detection and quantification; 3°) pulsation detection can be achieved with a radiation dose approximating 1.7 mSv. **Conclusion**: 4D-CTA can detect intracranial aneurysm pulsation at a low radiation dose but image post-processing remains challenging for pulsations of small amplitudes.