IREC

ACTIVITY REPORT 2019

« DISCOVERY CONSISTS OF SEEING
WHAT EVERYBODY HAS SEEN,
AND THINKING WHAT NOBODY HAS THOUGHT.»

Albert Szent-Gyorgyi,
1937 Nobel Prize for Medicine

INTRODUCTION BY THE PRESIDENT

The Institute of Experimental and Clinical Research is a Translational Research Institute. It conducts research in all areas of clinical and experimental medicine aiming at a better understanding of the mechanisms underlying diseases as well as discovery and development of new therapeutics.

The Institute gathers multidisciplinary researchers (clinicians, fundamentalists), technological platforms and a Clinical Trial Center, in close collaboration with the « Cliniques Universitaires Saint-Luc », thereby constituting a critical mass of expertise that meets the challenges of the medicine of tomorrow.

In June 2016, our Scientific Advisory Board composed of prominent international scientists visited the Institute on-site, heard presentations from the PI's and researchers from all the research Poles and elaborated a report with recommendations on our prospective research strategy.

Since then, several steps were taken to implement this strategic reorientation. The research Poles of the Institute were re-organized in Thematic groups, for improved collaborations within a critical mass of gathered expertise, better visibility and integration with clinical departments of excellence in the Cliniques Universitaires Saint-Luc.

In 2018, the new research building ("Tour Laënnec") was officially inaugurated, offering top-of-the-line research facilities, including dedicated space for animal experimentation fulfilling all latest regulatory requirements.

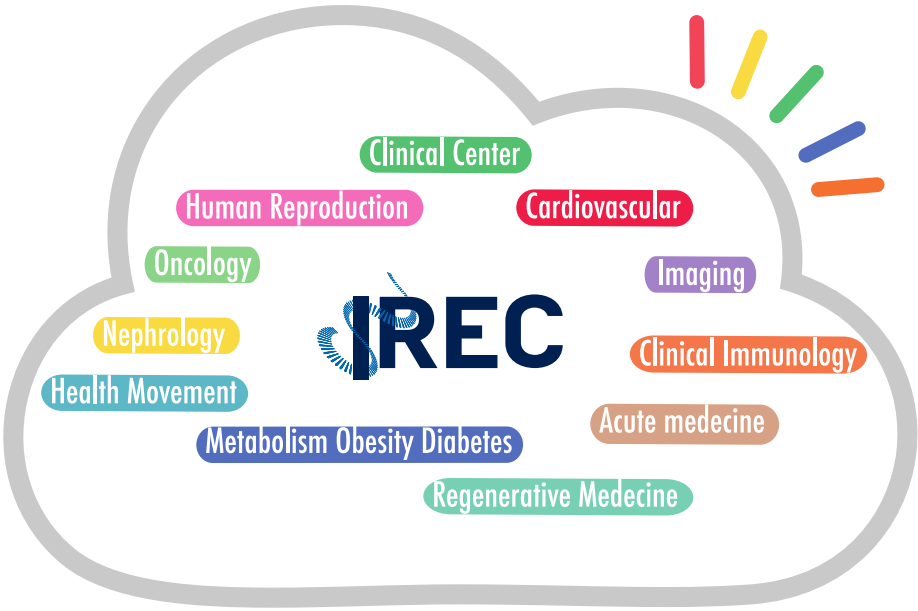
In this and other buildings of IREC, our technological platforms were further developed with the acquisition of state-of-the-art research tools accessible to our members, as well as external collaborators, thereby fostering intense exchanges of experimental protocols across disciplines and raising the technical level of our research output and publications.

As in past years, we enjoyed the visits of prominent national and international scientists at our monthly Seminars (now held in the new "G. Cori" Auditorium in the Laënnec building), and held highly praised networking events, such as the "IREC lunch" and "IREC PhD day".

Through this year 2019, we have enjoyed the company and collaboration of many international young scientists, a number of whom defended their PhD thesis, others competitively obtained research Fellowships and more senior ones were promoted to permanent -including academic- positions. An exceptionally high number of members of our technical and administrative staff were also promoted in their career tracks. This is a tribute to their, as well as their supervisors'dedication to our common mission: building knowledge together to combat diseases.

Jean-Luc Balligand

IREC President



UCLouvain

ADMINISTRATIVE STRUCTURE

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The Institute gathers multidisciplinary researchers (clinicians, fundamentalists), technological platforms and a Clinical Trial Center, in close collaboration with the « Cliniques Universitaires Saint-Luc », thereby constituting a critical mass of expertise that meets the challenges of the medicine of tomorrow.

President : *Professor Jean-Luc Balligand*

ADMINISTRATIVE COORDINATOR:

Veronica Curto

SCIENTIFIC COORDINATOR:

Nancy Van Overstraeten

LOGISTICS AND ACCOUNTS UNIT:

Maimouna Elmjouzi MBLG/PNEU/CTMA
Nadtha Panin LTAP
Myriam Goosse-Roblain MIRO
Deborah Morrens FATH/RUMA/2IP/Cytoflux
Dora Ourives Sereno GAEN/GYNE/CARD
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http://uclouvain.be/en/research-institutes/irec

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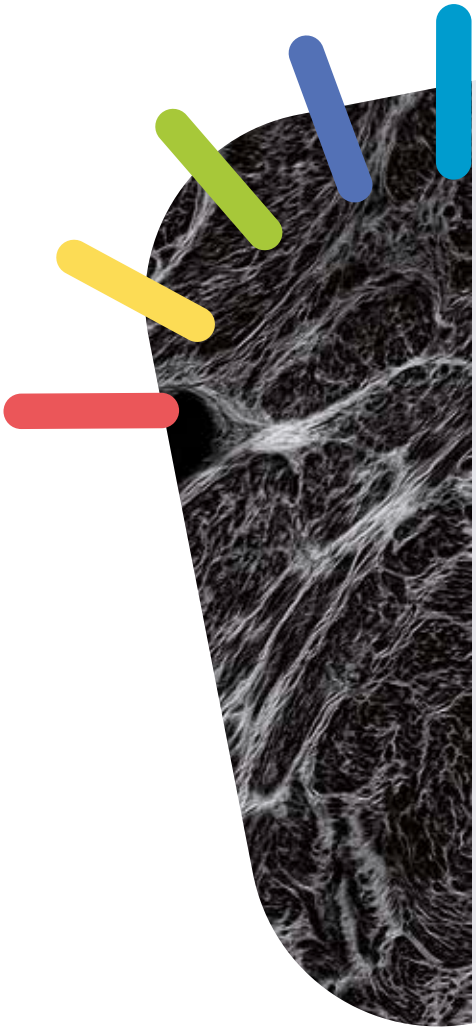
SCIENTIFIC ADVISORY BOARD

THE INSTITUTE HAS CONSTITUTED AN EXTERNAL SCIENTIFIC ADVISORY BOARD COMPOSED OF PRESTIGIOUS INTERNATIONAL SCIENTISTS FROM THE VARIOUS DISCIPLINES REPRESENTED WITHIN THE INSTITUTE.

THIS SCIENTIFIC ADVISORY BOARD WAS CHAIRED BY PROF. J. LOSCALZO, CHAIR OF THE DEPARTMENT OF MEDICINE AND HERSEY PROFESSOR OF THE PRACTICE OF MEDICINE AT BRIGHAM AND WOMEN'S HOSPITAL, HARVARD MEDICAL SCHOOL, BOSTON, USA, AND COMPOSED OF :



Prof. B. Vanhaesebroek,

Professor at the University College of London
London, UK

Prof. B. Wouters,

Executive Vice-President,
Science and Research at University Health Network,
Toronto, Canada

Prof. H. Vidal,

Professor at Claude Bernard University,
Lyon, France

Prof. P. Ferre,

Professor at the Faculty of Medecine Pierre et Marie Curie,
Paris, France

Prof. M. Goldman,

Institute for Interdisciplinary Innovation in healthcare,
ULB, Brussels, Belgium

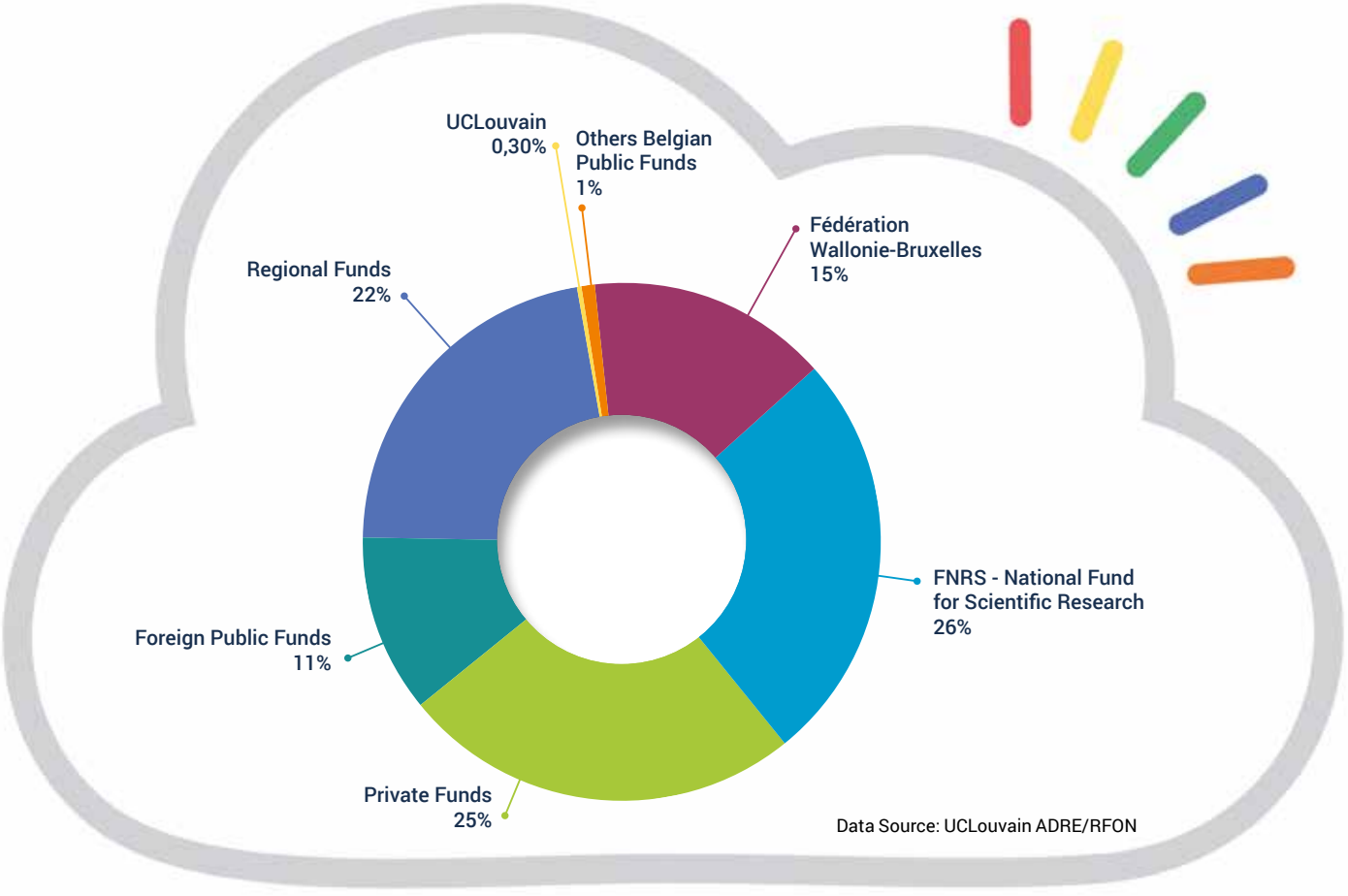
The Scientific Advisory Board visited the Institute on-site from 15 to 18 June 2016 and examined the scientific output of all the thematics of the Institute, and produced a critical report which guided the President and the governing board of the Institute to define a prospective scientific strategy for the next 5 years.

The SAB will regularly visit the Institute to monitor the progress and update the evaluation.

NEW RESEARCH AGREEMENTS AND CONTRACTS CONCLUDED 2019

Funding Sources	N. of agreements	Funding Amount
Foreign Public Funds	3	€ 1,318,460
Private Funds	20	€ 3,066,923
Fédération Wallonie-Bruxelles	14	€ 1,771,903
FNRS - National Fund for Scientific Research	64	€ 3,119,610
Regional Funds	5	€ 2,665,072
UCLouvain	1	€ 36,000
Others Belgian Public Funds	2	€ 90,000
TOTAL	**109**	**€ 12,067,968**

SIGNED FUNDING AGREEMENTS PER FUNDING SOURCE (%) 2019



CARDIOVASCULAR

The importance of cardiovascular disease in terms of public health is well established. Indeed, they are responsible for about 50% of deaths in western countries. Therefore, a better understanding of their pathophysiology is fundamental to improve therapeutic treatments.

The Cardiovascular Thematic Group has developed a wide expertise in translational research on cardiovascular pathologies, ranging from experimental to clinical approaches (bench to bedside). The research poles working collaboratively within the thematic group are the Pole of Cardiovascular Research (CARD) and the Pole of Pharmacology and Therapeutics (FATH). The basic and clinical research within the thematic group is conducted by principal investigators who are qualified researchers of the FNRS, cardiologists and/or cardiac surgeons.

Research Poles

POLE OF CARDIOVASCULAR RESEARCH (CARD)

Christophe Beauloye, MD, PhD

Bernhard Gerber, MD, PhD

Luc Bertrand, PhD

Sandrine Horman, PhD

Laurent De Kerchove, MD, PhD

Parla Astarci, MD, PhD

Joëlle Kefer, MD, PhD

Jean-Benoit le Polain de Waroux, MD, PhD

Agnès Pasquet, MD, PhD

Alexandre Persu, MD, PhD

Anne-Catherine Pouleur, MD, PhD

David Vancraeynest, MD, PhD

Jean-Louis Vanoverschelde, MD, PhD

Diego Castanares-Zapatero, MD, PhD

Members:

Gébrine El Khoury, MD, PhD
Marine Angé, MD, PhD student
Sylvain Battault, Postdoctoral Fellow
Laurent Bultot, Postdoctoral Fellow
Julien Cumps, PhD student
Evangelos Daskalopoulos, Postdoctoral Fellow
Julien De Poortere, PhD student
Justine Dontaine, PhD student
Cécile Dufeys, Postdoctoral Fellow
Laura Ferté, PhD student
Anais Gauthey, MD, PhD student
Coralie Georges, PhD student
Audrey Ginion, Research Scientist
Vincent Hanet, MD, PhD student
Laura Houard, MD, PhD student
Shakeel Kautbally, MD, PhD student
Pauline Krug, MD, PhD Student
Sibille Lejeune, MD, PhD student
Sebastian Marchandise, MD, PhD student
Sebastian Militaru, MD, PhD student
Marie Octave, PhD student
Edith Renguet, PhD student
Clotilde Roy, MD, PhD student
Alison Slimani, MD, PhD student
Delphine Thibou, Technician
Emmanuel Vandenhooft, Technician
Carole Verhaegen, PhD student

Pole Contact Persons

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For clinical research:

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Bernhard Gerber
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POLE OF PHARMACOLOGY AND THERAPEUTICS (FATH)

Chantal Dessy, PhD

Jean-Luc Balligand, MD, PhD

Members:

Emilie André, PhD student
Ramona Bella, Postdoctoral Fellow
Joël Cosse, Technician
Flavia Dei Zotti, PhD Student
Delphine De Mulder, Technician
Laurent Dumas, Postdoctoral Fellow
Hrag Esfahani, Research Scientist
Charlotte Farah, Postdoctoral Fellow
Virginie Joris, PhD student
Irina Lobysheva, Senior Scientist
Dorothée Marchand, PhD student
Lauriane Michel, Post-doctoral Fellow
Virginie Montiel, Postdoctoral Fellow
Lucie Pothen, PhD Student
Delphine Thibou, Technician
Nancy Van Overstraeten, Postdoctoral Fellow
Roxane Verdoy, Technician
Deborah Morrens, Grants and Contracts Administrator

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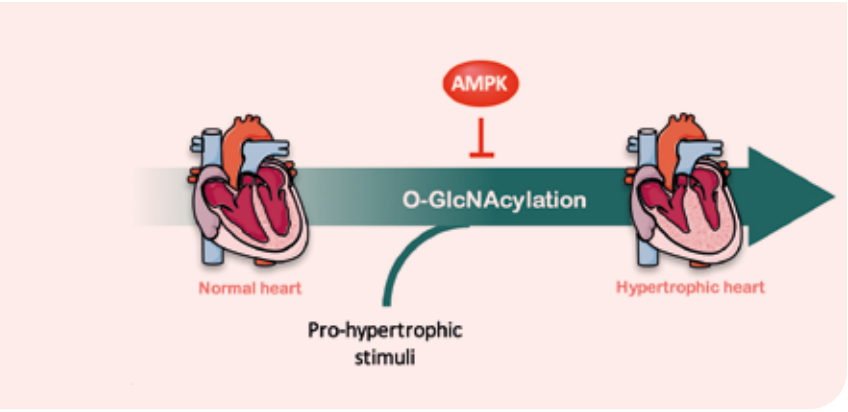
CARDIAC HYPERTROPHY

PK and O-GlcNAcylation, two partners intimately connected to prevent cardiac hypertrophy development

J. Dontaine, L. Bultot, S. Horman, C. Beauloye, L. Bertrand

AMPK was known to inhibit cardiac hypertrophy. However, the precise molecular mechanism involved in this action was unknown. Our recent study reveals that AMPK activation blocks cardiac hypertrophy by reducing a particular post-translational modification called O-GlcNAcylation. Using several models of cardiac hypertrophy, both in vitro than in vivo, we showed that a pharmacological activation of AMPK inhibits O-GlcNAcylation by controlling phosphorylation of GFAT, the rate limiting enzyme of O-GlcNAcylation pathway. Interestingly, reverting this inhibition by using O-GlcNAcylation inducers, prevents the anti-hypertrophic action of AMPK activators. Our study also identifies troponin T as being one of the protein O-GlcNAcylated during cardiac hypertrophy, AMPK activation reducing troponin T O-GlcNAcylation level. More recently, we established an unbiased mass spectrometry approach to identify O-GlcNAcylated proteins in heart with the goal to find new therapeutic targets.



Beta-3 Adrenoreceptors protect from hypertrophic remodelling through AMP-Activated Protein Kinase and Autophagy Dependent Signalling Pathways

E. Deruy, H. Esfahani, L.Bertrand, L. Michel, C. Dessy, C. Beauloye, J.-L. Balligand

We are expanding studies on the mechanisms of inhibition of hypertrophy by AMPK, e.g. downstream beta3-adrenergic receptors. We found that AMPK promotes the autophagic flux in cardiac myocytes submitted to a hypertrophic stress (Deruy et al.).

Aquaporin-1 (AQP1), microcardia and hypertropic remodelling

V. Montiel, H. Esfahani, D. De Mulder, O. Devuyst, J.-L Balligand

We have serendipitously observed a microcardia in mice with genetic deletion of the water channel, Aquaporin-1 (AQP1) *(Montiel et al.)*. Deletion or inhibition of this channel also attenuates the hypertrophic remodelling in vitro/vivo. Among underlying mechanisms, we found that AQP1 mediates the localized transport of H_2O_2, driving oxidant-dependent hypertrophic signaling in cardiac myocytes. AQP1 also regulates tissue fibrosis. Orally administered Bacopaside inhibitors of AQP1 prevent adverse remodeling in mice submitted to infusion of Angiotensin II, as well as oxidation of erythrocytes in human volunteers. In a translational endeavor, similar Bacopa extracts will be tested in a RCT in patients with structural cardiac disease presenting with heart failure with preserved ejection fraction (HFpEF), for which there is, as yet, no treatment with proven efficacy.

Endothelial function and cardiac hypertrophy

L. Pothen, R. Verdoy, J.-L. Balligand

We are undertaking an unbiased comparative RNAseq analysis of endothelial cells in a mouse model of cardiac remodelling, before and after stress removal, to identify putative genes involved in the maintenance of endothelial dysfunction despite regression of hypertrophy.

MiR-199a and the NOS/NO pathway.

V Joris, T Metzinger, L Dumas, E.-P. Daskalopoulos, D Marchand, S Horman, C Dessy

The major mechanism employed by endothelial cells to maintain vascular homeostasis is the release of NO. Exposure to pathological insults translates into reduced NO bioavailability setting the ground for cardiovascular diseases. We have identified the endothelial molecular targets of miR199a3p and -5p and showed that the mature products of miR-199a independently modulates the NOS/NO pathway by reducing NOS activity and NO bioavailability, adding a layer of regulation for endothelial (dys)function *(Joris et al.)*. Our recent work points to the miR-199a family as relevant regulators of cardiovascular functions in health and disease. Beneficial consequences of physical training on cardiac and endothelial phenotypes correlate with a down-regulation of miR-199a expression while the opposite is observed in a context of pathologic cardiac hypertrophy or hypertension. Our aim is now to gain deeper insights into the pathological implications of miR-199a.

From gut to the endothelium

V Joris, L Dumas, C Dessy

Lifestyle and food choices dramatically impact cardiovascular health. Our research focusses on the impact of inulin type fructans (an example of probiotics) enriched diet on endothelial dysfunction in a mice model of hypercholesterolemia *(Catry et al.)*. Our current work proposes to further document the mechanisms underlying the improvement in endothelial function.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Heart failure with preserved ejection fraction in Belgium: characteristics and outcome of a real-life cohort.

S. Lejeune, C. Roy, C. Beauloye, J.-L. Vanoverschelde, B. Gerber, A.-C. Pouleur

Heart failure with preserved ejection fraction (HFpEF) has been established as a major cause of cardiovascular morbidity and mortality, especially among the elderly and its prevalence is still increasing. Several mechanisms have been implicated in HFpEF, including advanced age and cardiovascular, metabolic, and pro-inflammatory comorbidities such as hypertension, diabetes, obesity, chronic obstructive pulmonary disease, coronary disease and renal failure. However, the exact pathophysiology of HFpEF remains unclear. Our research projects focus on phenotyping these patients and evaluating the role of cardiac fibrosis by biomarkers and ECV measurements in cardiac MR, the role of right ventricular function by strain echocardiography and the role of HbNO and endothelial dysfunction.

Animal model of HFpEF

C. Farah, H. Esfahani, C. Beauloye, J.-L. Balligand

We developed a mouse model of heart failure with preserved ejection fraction, with a echocardiographic phenotype recapitulating the features of the human disease. We are currently characterizing the expression/phosphorylation of key regulatory proteins mediating cardiac myocyte relaxation, as well as EC coupling and myofilament calcium sensitivity (skinned myocytes; collab. w/J. van der Velden, NL), as well as their putative regulation by beta3AR.

Future treatments, translational perspectives

J.-L. Balligand (coordinator), A-C Pouleur, B. Gerber, A. Persu, D. Gruson, R. Lhommel, N. Van Overstraeten

We are studying the effect of the beta3-adrenoceptor agonist, *mirabegron*, in patients with structural heart disease (Stage B, AHA) to prevent the progression of myocardial remodelling and development of heart failure with preserved ejection fraction. This investigator-initiated, European multicentric RCT, subsidized by a Horizon2020 grant, is coordinated at UCLouvain (Beta3-LVH).

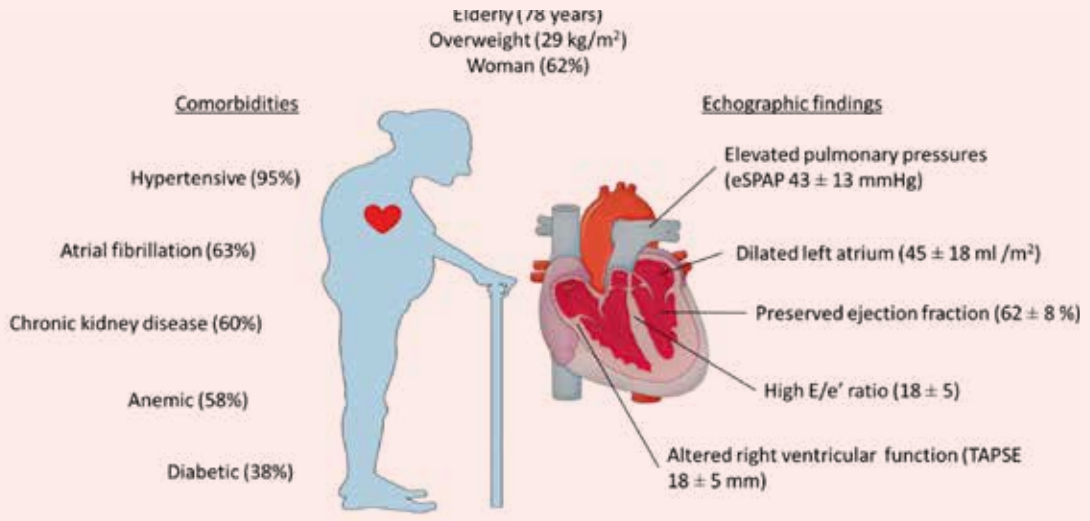
CARDIAC FIBROSIS

Cardiac fibrosis/oxidant stress

N. Hermida, H. Esfahani, J.-L. Balligand

Hemodynamic and neurohormonal stress induce the production of several reactive oxidant species. Using superfusion assays and shotgun proteomic analysis of cardiac cell secretomes, we found that oxidant stress in cardiac myocytes induces paracrine release of Connective Tissue Growth Factor (CTGF) that promotes myofi-

Clinical and echographic charactersitics of our HFpEF population

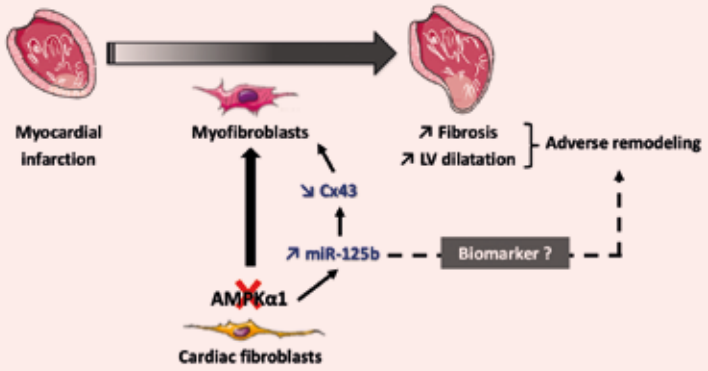


broblast differentiation and cardiac fibrosis. Conversely, activation of cardiac beta3-adrenergic receptors exerts anti-oxidant effects and protects against myocardial fibrosis and hypertrophy *(Hermida et al)*.

Fibrotic remodelling after myocardial infarction/AMPK signalling

C. Dufeys, E.-P. Daskalopoulos, D. Castanares-Zapatero, A. Ginion, L. Bertrand, C. Beauloye, S. Horman

Myofibroblasts (MFs) are crucial components of the fibrotic remodelling after myocardial infarction (MI). We have investigated the effects of MF-specific deletion of AMPKα1 on left ventricular adaptation following MI, and the underlying molecular mechanisms. We showed that MF-restricted AMPKα1 conditional knockout hearts exhibit exacerbated post-MI adverse LV remodelling and are characterized by exaggerated fibrotic response, compared to wild-type hearts. The deleterious effects of MF-specific AMPKα1 deletion are mediated via Connexin 43, and its post-transcriptional regulation by miR-125b *(Dufeys et al)*.



Contribution of SMIT1 and myo-inositol transport in cardiac fibroblast properties

J. Cumps, S. Battault, C. Dufeys, D .Castanares Zapatero, A.-C. Pouleur, L. Bertrand, C. Beauloye and S. Horman

Clinical studies reported a rise in plasmatic myo-inositol in patients with severe heart failure. Additionally, we showed that SMIT1 (Sodium Myo-Inositol Transporter 1) mRNA expression was increased in human failing hearts and correlated with fibrotic markers. We aim to evaluate the role of SMIT1 and myo-inositol in fibroblasts properties regulation. Using human CF (HCF) and mouse CF (MCF) isolated from SMIT1 wild type and knock-out mice, we demonstrated that SMIT1 controls myo-inositol uptake in CFs and influences proliferation, migration and myodifferentiation processes. We are currently investigating the underlying mechanisms, as well as the significance of these observations in *in vivo* models of cardiac fibrosis.

CARDIAC REGENERATION

Cardiac progenitor cells

E. Andre, L. Bertrand, J.-L. Balligand

We identified an epigenetic regulation of cardiac progenitor cells differentiation through miR-29 and Dnmt3a regulation of canonical Wnt. Implantation of cardiac progenitors with downregulated Dnmt3a around the infarcted myocardium resulted in improved contractility and reduced adverse remote remodelling.

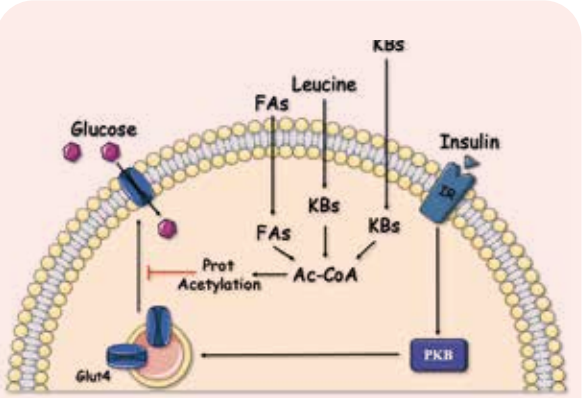
In collaboration with L. Bertrand, CARD, we also identified critical shifts in metabolic substrate utilization in CPC during their differentiation to cardiac myocytes, with concurrent regulation of mitochondrial content and oxidative metabolism *(André et al.)*.

CONTROL OF CARDIAC METABOLISM

Protein acetylation participates in the reduced glucose uptake induced by fatty acids

L. Bultot, M. De Loof, E. Renguet, S. Horman, C. Beauloye, L. Bertrand

Type 2 diabetes is characterized by elevated plasma levels of fatty acids, leucine and ketone bodies. We previously showed that both leucine and ketone bodies are catabolised into acetyl-CoA, inducing an increase in protein acetylation. They also inhibit glucose uptake by reducing translocation of glucose transporter Glut4. Pharmacological inhibition of protein acetylation prevents this decrease in glucose uptake. More recently, we showed that fatty acids act similarly, inhibiting cardiac glucose transport via protein acetylation events. This provides new clue in the elucidation of the molecular mechanisms involved in the metabolic inflexibility of the diabetic heart



Connection between beta3-AR and glucose uptake

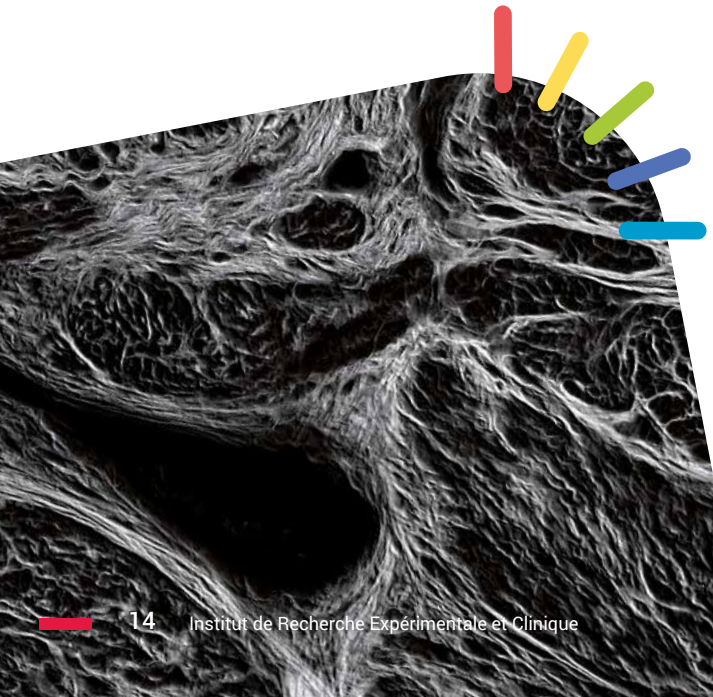
E. Dubois-Deruy, C. Beauloye, H. Esfahani, C. Dessy; L. Bertrand, J.-L. Balligand

We found that expression of the beta3-AR in cardiac myocytes promotes glucose uptake under stress in these cells in vitro and in vivo (FDG-PET) and reverses insulin resistance, together with attenuation of the hypertrophic response. We are expanding this line of research with other metabolic substrates (e.g. lipids) to better define the role of cardiac beta3 AR in metabolic flexibility.

Role of sodium glucose co-transporter SGLT-1 in cardiac glucose uptake

L. Ferté, S. Battault, L. Bultot, A. Ginion, S. Horman, L. Bertrand, C. Beauloye

Although sodium-glucose co-transporter 1 (SGLT1) has been identified as one of the major SGLT isoforms expressed in the heart, its exact role remains elusive. We have assessed the contribution of SGLT1 in cardiac glucose uptake using an SGLT1 knock-out mouse model. Our hypothesis was that SGLT1 barely influences overall glucose transport. Accordingly, glucose uptake was similar in cardiomyocytes isolated from SGLT1-deficient and control littermate mice, either under basal state, insulin, or hyperglycemia. Similarly, in vivo basal and insulin-stimulated cardiac glucose transport measured by micro-PET scan technology did not differ between the WT and SGLT1 KO mice. Micromolar concentrations of phlorizin had no impact on glucose uptake in either isolated WT or SGLT1 KO-derived cardiomyocytes. However, higher concentrations (1mM) completely inhibited insulin-stimulated glucose transport without affecting insulin signalling and GLUT4 translocation. More importantly, this effect was observed irrespectively of cardiomyocyte genotype. In conclusion, SGLT1 does not contribute to overall cardiac glucose uptake. The inhibitory effect of phlorizin on cardiac glucose uptake cannot be attributed to its action on SGLT1 and is more likely explained by GLUT transporter inhibition *(Ferté et al)*.



Role of cardiac glycogen content on ventricle remodelling after myocardial infarction

E. Daskalopoulos, C. Dufeys, L. Bertrand, C. Beauloye, S. Horman

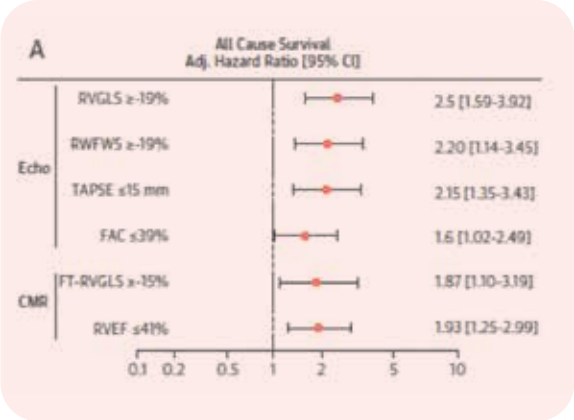
Glycogen is a double-edged sword for the myocardium. It supplies ATP when energy is depleted but high glycogen content is also known to be deleterious in prolonged ischemia. Our objective was to evaluate the impact of myocardial glycogen depletion on cardiac function after ischaemia/reperfusion (I/R) and during permanent myocardial infarction (MI).

We used transgenic mice (mutated glycogen synthase knock-in) where myocardial glycogen level is marginal. We demonstrated that glycogen genetic depletion does not reduce cardiac function recovery following I/R. It also improves survival compared to WT without however affecting the post-MI adverse LV remodelling progression. Further studies are required, in order to shed light onto the association between low glycogen content and cardioprotection.

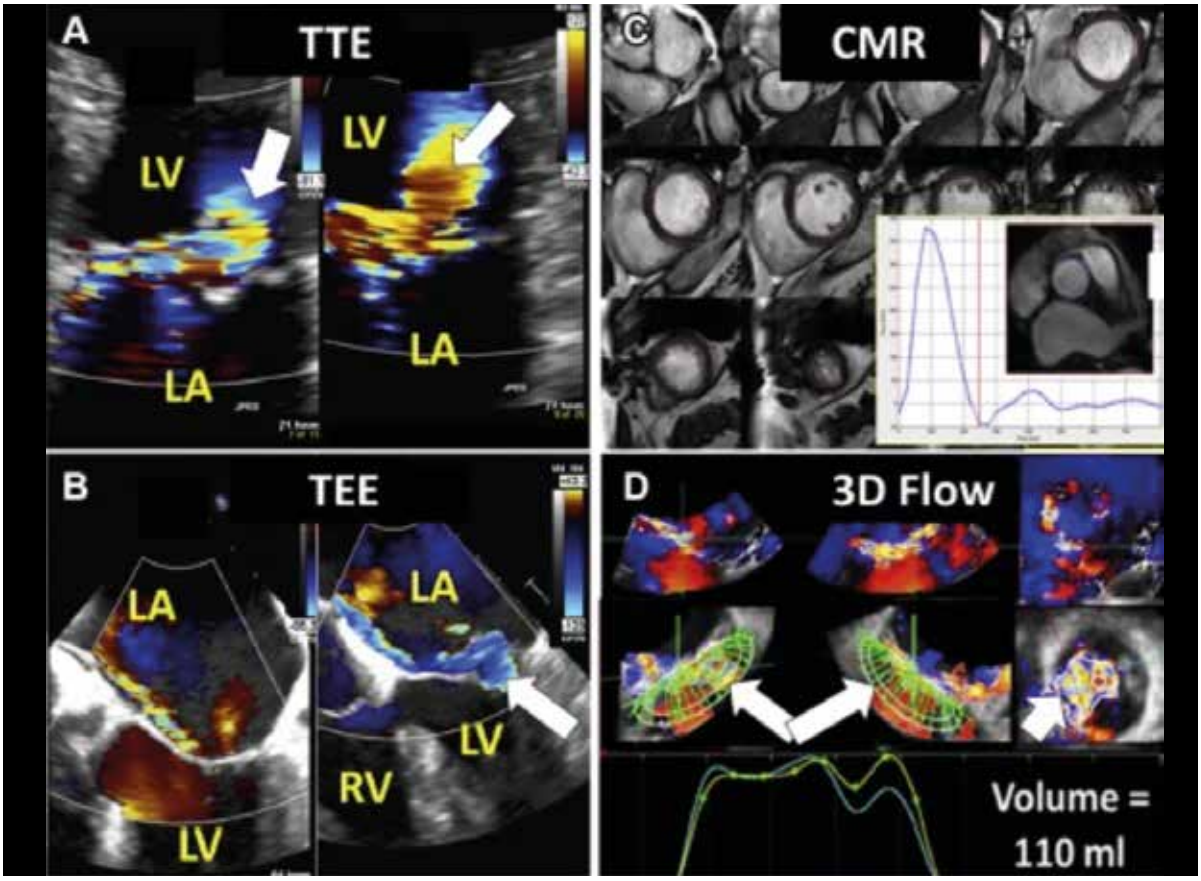
Non-invasive cardiac Imaging - heart function

B. Gerber, D Vancraeynest A Pasquet, J.-L. Vanoverschelde

Our work focuses on characterisation of myocardial deformation of the left and right ventricle using non-invasive imaging. Indeed, we performed cross modality comparison of myocardial strain measurements and validated 2D and 3D speckle tracking echocardiography myocardial strain measurements by different software. We also recently evaluated the test-retest reproducibility of these methods and evaluated the prognostic value of right ventricular strain for heart failure with both preserved and reduced ejection fraction. Further we performed multivendor comparison of feature tracking strain MR and comparison of feature tracking vs speckle tracking strain.



Other works focused on development and validation of new echocardiographic methods for quantification of regurgitant flow. We evaluated a new 3D color flow technique for quantification of mitral regurgitation using Navier Stokes equations vs cardiac MR as reference technique.



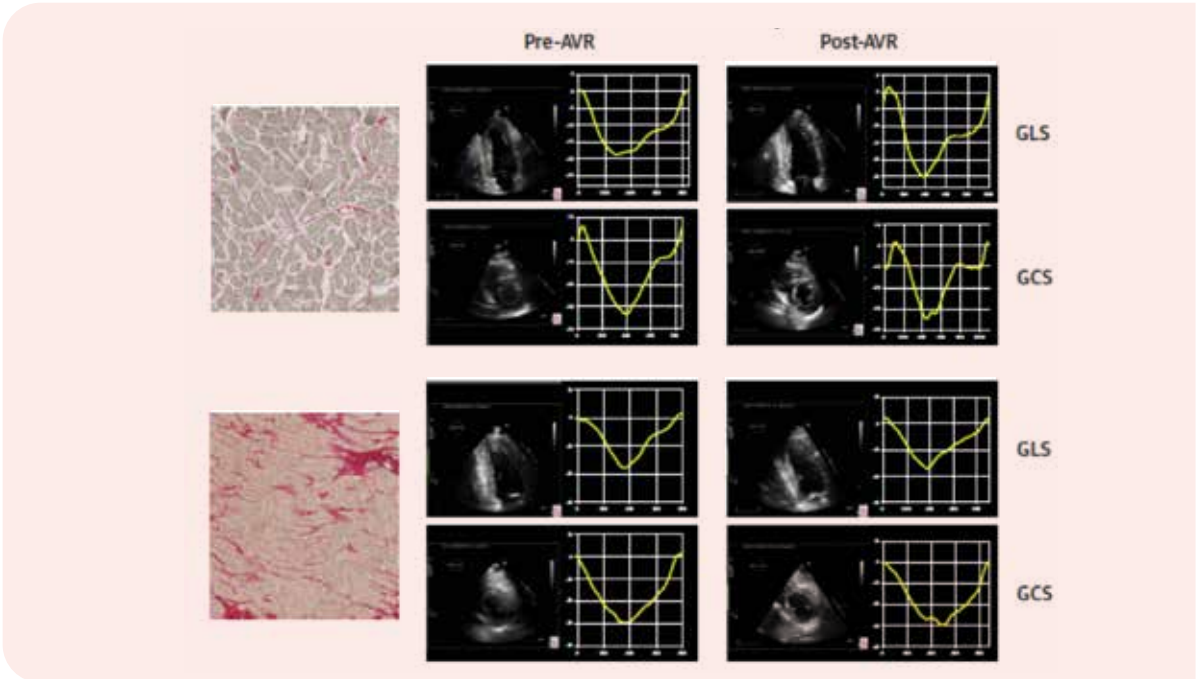
We also performed studies validating pulmonary transit time as measurement for pulmonary congestion in heart failure and evaluated the prognostic value of this parameter on outcome of patients with heart failure.

Valvular heart disease

A. Slimani, V. Hanet, A. Pasquet, D Vancraeynest, J.-L. Vanoverschelde, BL Gerber

Our research aims at studying the pathophysiology and prognosis of different valvular heart diseases. In particular we studied low flow low gradient aortic stenosis, where we evaluated the role of LV afterload mismatch and myocardial fibrosis on deformation measurements.

In mitral and aortic valve regurgitation, we studied prognostic markers and guideline criteria for surgery. Ongoing research focuses on studying the development of myocardial fibrosis relative to myocardial remodelling by cardiac imaging in mitral and aortic regurgitation before and after surgery.



Cardio-Oncology

P. Krug, A-C. Pouleur, BL. Gerber

Ongoing research focuses on determining the consequences of radiation exposure during radiotherapy for breast cancer on the heart on development of coronary artery disease, valvular heart disease and myocardial fibrosis.

Cardiac Rhythm Disorders

A. Gauthey, S. Marchandise, JB Lepolain de Waroux, B. Gerber

Research consists in determining the role of modulation of vagal tone on atrial fibrillation development, on pacing sites and ECG timings on left ventricular reverse remodeling after CRT implantation. Ongoing research focuses on characterization of atrial fibrosis and metabolism by PET and MRI in patients with atrial fibrillation.

Resistant Hypertension and Fibromuscular Dysplasia

M. Pappaccogli, S. Di Monaco, S. Ciurica, A. Persu

Resistant hypertension: research consisted in looking for the influence of drug adherence on outcome of renal sympathetic denervation (1); identifying predictors of blood pressure control in patients with resistant hypertension after intensive management in expert centres (2- Figure 1 A); investigating safety and efficacy of alcohol-mediated renal denervation in patients with difficult-to-treat hypertension (3 - Figure 1 B).

Fibromuscular Dysplasia (FMD): in the wake of the First International Consensus dedicated to the diagnosis and management of FMD, co-chaired by H. Gornik (Cleveland) and A. Persu (4), research consisted in revisiting the interest and quantification of arterial tortuosity in FMD and beyond (5); establishing the prevalence and characteristics of renal FMD in middle-aged hypertensive women (6); and identifying clinical phenotypes (Figure 2 A) (7) and predictors of arterial complications (Figure 2 B), based on in-depth analysis of the first 1000 patients enrolled in the European/International FMD Registry (8).

Figure 1 A

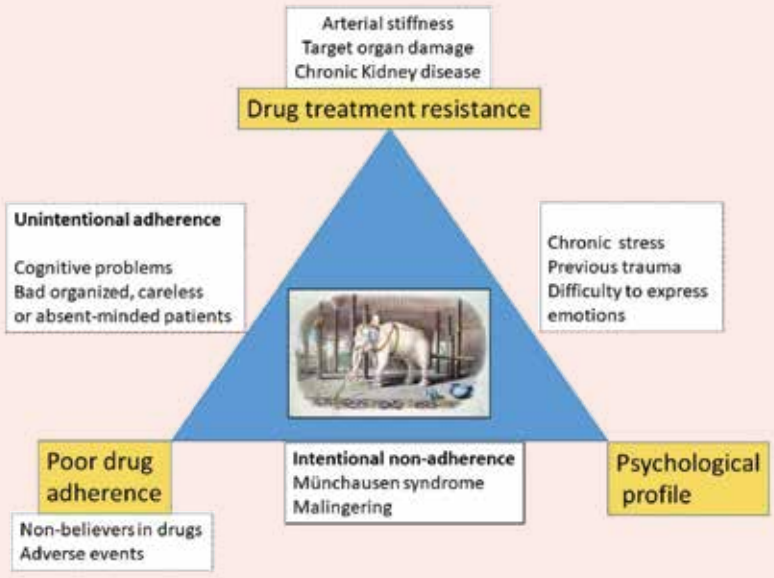


Figure 1 B

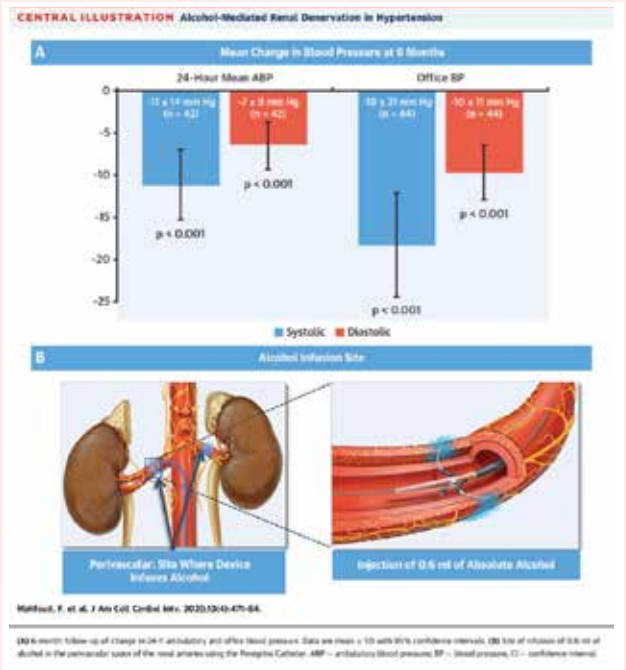


Figure 2 A

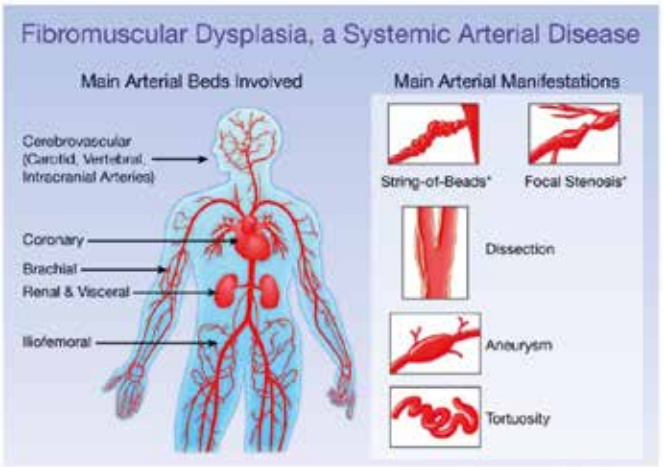
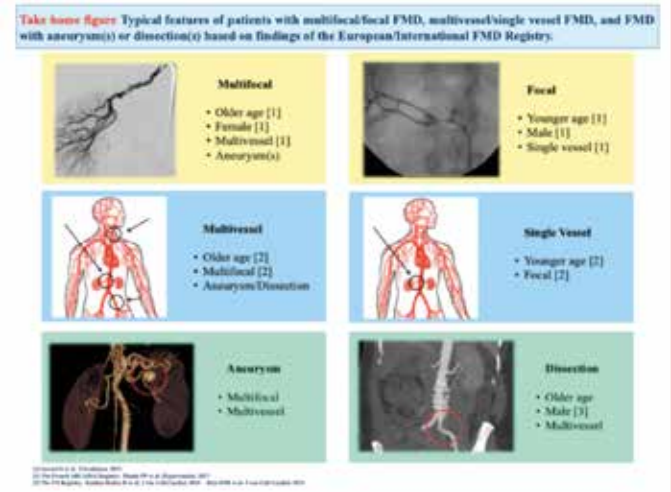


Figure 2 B



ENDOTHELIAL FUNCTION

MiR-199a and the NOS/NO pathway

V. Joris, T. Metzinger, C. Dessy

The major mechanism employed by endothelial cells to maintain vascular homeostasis is the release of NO. Exposure to pathological insults translates into reduced NO bioavailability setting the ground for cardiovascular diseases. We have identified the endothelial molecular targets of miR199a3p and -5p and showed that the mature products of miR-199a independently modulates the NOS/NO pathway by reducing NOS activity and NO bioavailability, adding a layer of regulation for endothelial (dys)function. Our aim is now to gain deeper insights into the pathological implications of miR-199a *(Joris et al)*.

From gut to the endothelium

L. Dumas, V. Joris, C. Dessy

Lifestyle and food choices dramatically impact cardiovascular health. Our research focusses on the impact of inulin type fructans (an example of probiotics) enriched diet on endothelial dysfunction in a mice model of hypercholesterolemia *(Catry et al)*. Our current work proposes to further document the mechanisms underlying the improvement in endothelial function.

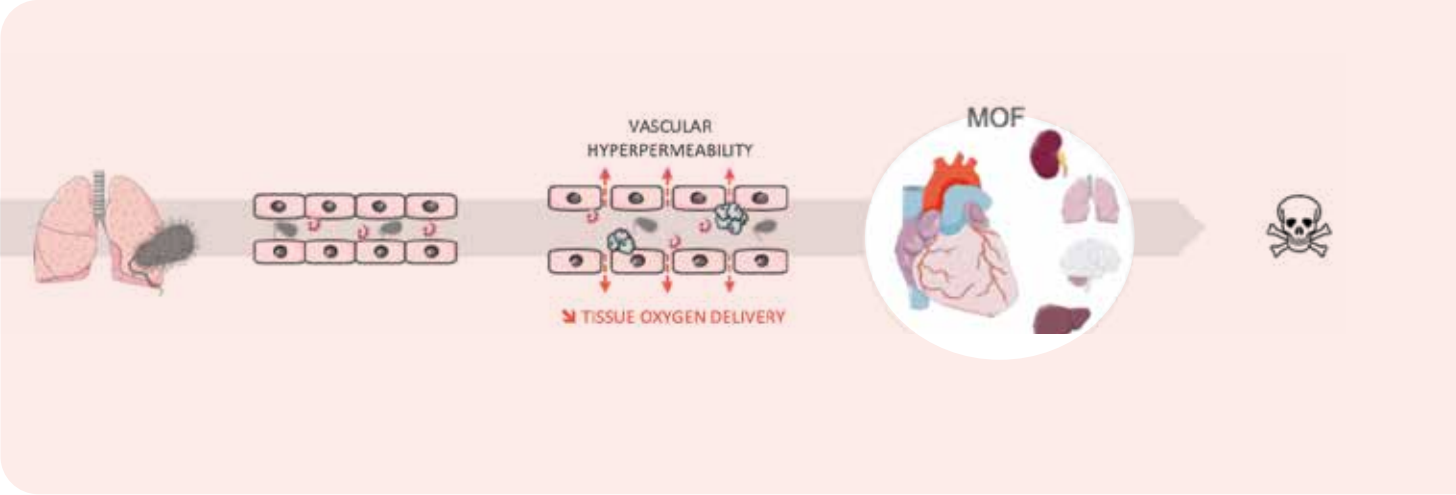
Clinical assessment of endothelial (dys) function

J.-L. Balligand, F. Dei Zotti, C. Beauloye, I. Lobysheva, N. Van Overstraeten

We also correlated endothelial function, measured by digital microtonometry (ENDO-PAT) with circulating concentrations of nitrosylated hemoglobin (HbNO) measured by Electron Paramagnetic Resonance spectroscopy (EPR) in red blood cells. We established that this HbNO signal mainly originates from endothelial NO, supporting its use as surrogate biomarker of NO-dependent endothelial function. We demonstrated its applicability for the detection of endothelial dysfunction in young women taking contraceptive pills.

This biomarker is being validated in prospective clinical studies in patients with hypercholesterolemia and correlated with classical cardiovascular risk factors to evaluate its interest to refine risk stratification *(Dei Zotti et al)*.

This line of research generated funding by the "Region Wallonne" to develop a new spin-off (SPINOVIT) specializing in the development of cardiovascular biomarkers.



Control of endothelial barrier/AMPK signalling

M. Angé, J. De Poortere, C. Dufeys, A. Ginion, L. Bertrand, C. Beauloye, D. Castanares-Zapatero and S. Horman

Sepsis is a major health problem worldwide, defined as a dysregulated host response to an infection. Its evolution toward multi-organ failure, known as a crucial predictor of survival, directly relies on the microcirculatory function. The latter is highly dependent on the regulation of vascular extravasation, while the maintenance of the intravascular volume remains one of the most important challenges of the clinical support in septic patients. Dysregulation of the transendothelial paracellular permeability is the main determinant of sepsis-induced vascular extravasation. It results from interendothelial junctions disruption and actin cytoskeleton disorganisation. Our data showed that AMPK regulates expression and localization of interendothelial junctions. Moreover, its activation protects against lipopolysaccharide induced endothelial barrier disruption by reinforcing the cortical actin cytoskeleton. It results in a drastic decrease of the LPS-induced hyperpermeability. Our work thereby provides strong arguments to further consider AMPK activation as a new therapeutic approach of sepsis-induced vascular leakage (*Angé et al.* 2019; *Angé et al,* 2020).

Vascular dysfunction and haemostatic disorders during sepsis/AMPK signalling

J. De Poortere, M. Angé, M. Octave, L. Bertrand, S. Horman, C. Beauloye and D. Castanares-Zapatero

In addition to vascular hyperpermeability, haemostasis impairment also plays a key role in the onset of organ failure during sepsis. Using tissue-specific knockout models, we are currently investigating the role of AMPK from endothelium, platelets and neutrophils in haemostatic defects associated to sepsis.

PLATELETS AND THROMBOSIS

Metabolic signalling and protein acetylation

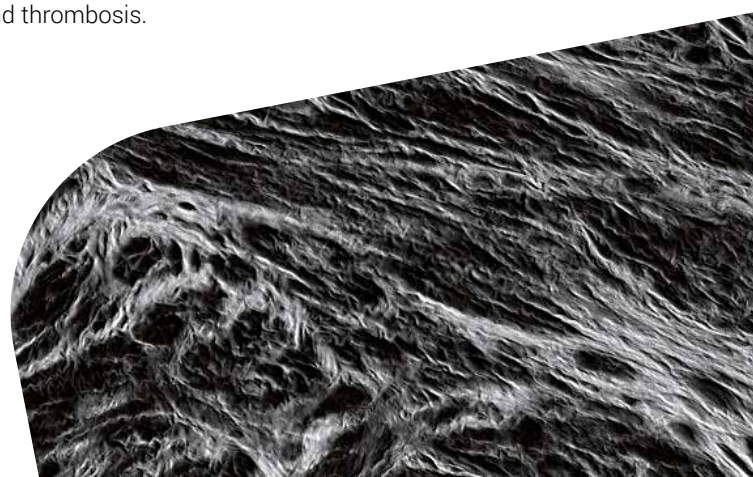
M. Octave, A. Ginion, L. Bertrand, C. Beauloye, S. Horman

We previously showed that acetyl-CoA carboxylase (ACC) promotes platelet activation and thrombus formation by increasing platelet phospholipid content. ACC carboxylates acetyl-CoA into malonyl-CoA, the precursor of de novo lipogenesis. Inhibition of its activity decreases lipogenesis. The concomitant increase in acetyl-CoA can serve as a substrate for protein acetylation. This posttranslational modification may play a key role in the regulation of platelet functions, especially on platelet aggregation, shape change and spreading. We are currently testing this hypothesis, using pharmacological and genetic approaches to invalidate ACC activity.

Platelet phosphoACC: A witness of platelet-lipid interaction in CAD

S. Kautbally, M. Octave, A. Ginion, L. Bertrand, S. Horman, C. Beauloye

We showed that AMPK-ACC signalling is activated by atherogenic lipids and can be considered as a metabolic signature in high-risk coronary artery disease (CAD) patients. Lipidomic analysis revealed that increased phosphoACC led to a down-regulation of intraplatelet triglycerides (ACCTHEROMA, NCT03034148) *(Kautbally et al; Horman et al)*. We are currently investigating how increased ACC phosphorylation may affect platelet functions and thrombosis.

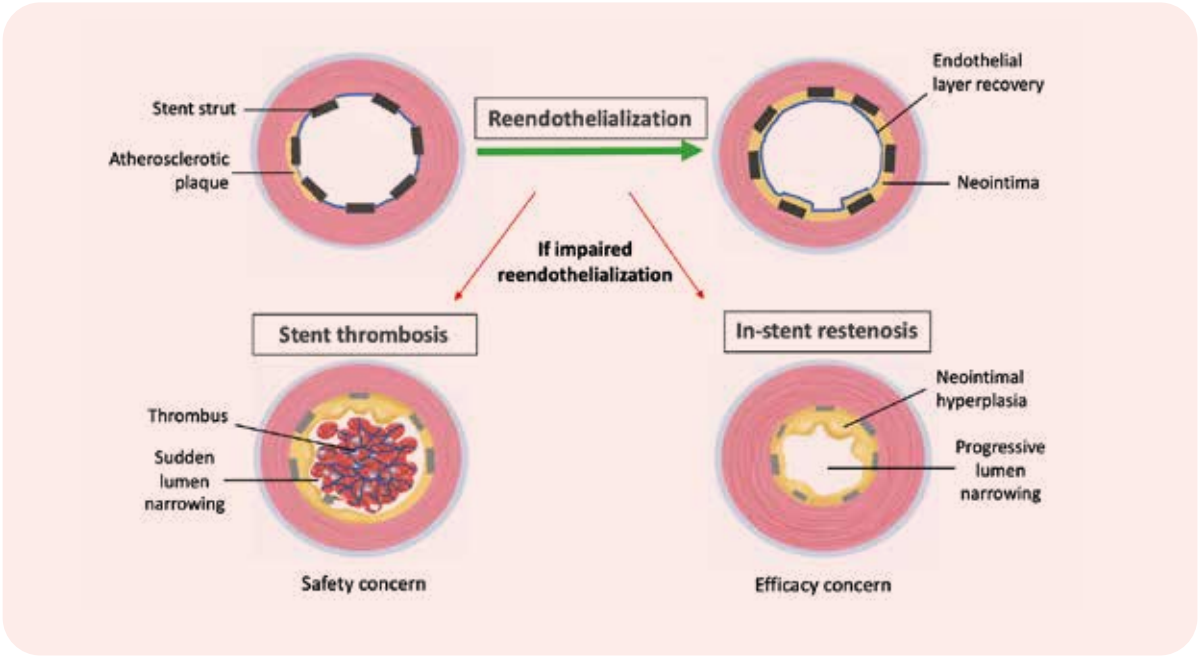


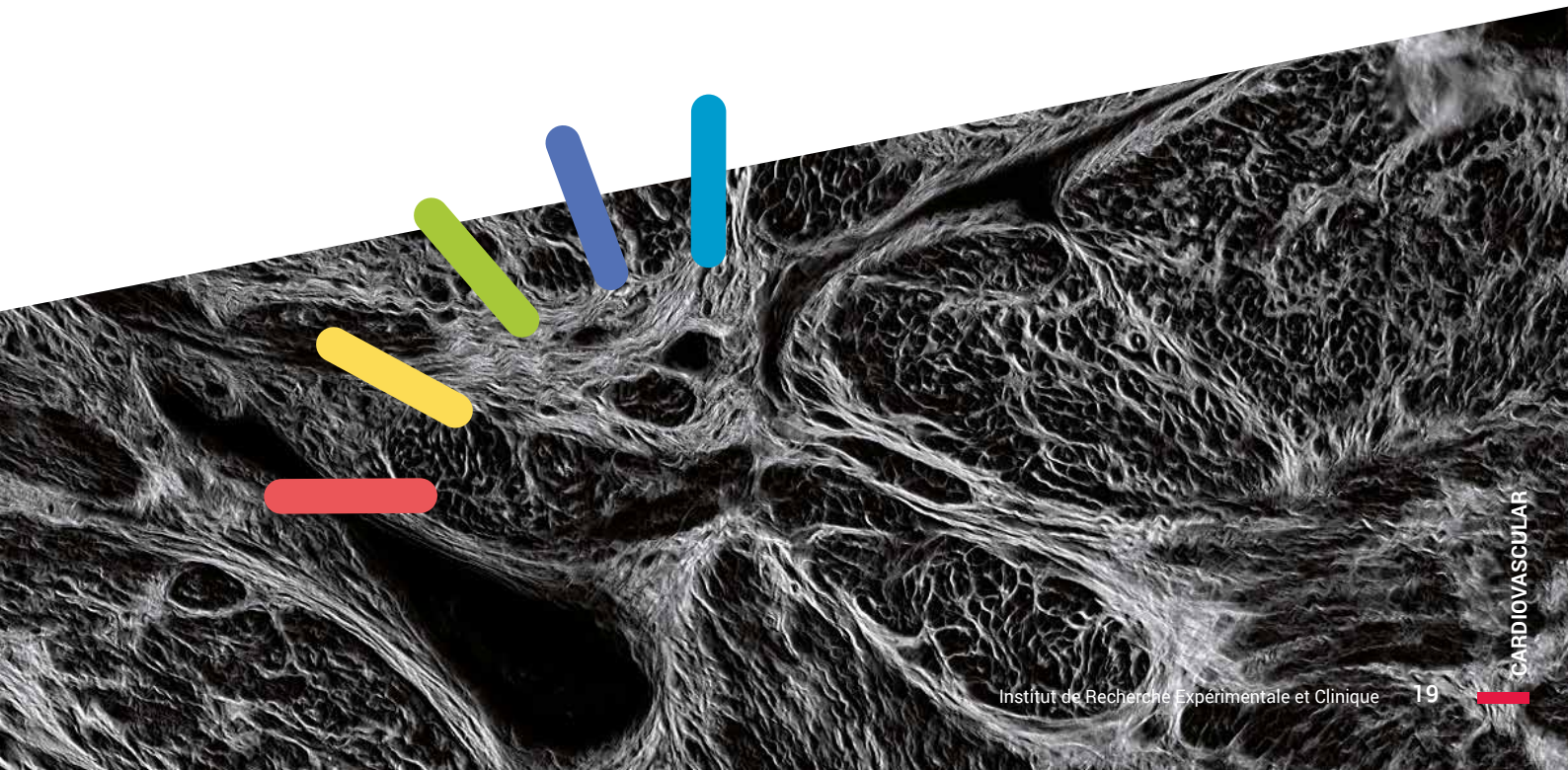
New degradable biomaterials for Endovascular Stents : evaluation of thrombogenicity

C. Verhaegen, L. Bertrand, C. Beauloye, S. Horman and J. Kefer

This global project aims to investigate the thrombogenic responses to new degradable biomaterials for cardiovascular stents. Although 1-month dual antiplatelet therapy (DAPT) in patients treated with bare metal stents (BMS) is well established, the optimal duration of DAPT after implantation of a drug-eluting stent (DES) is still a matter of debate. The safety of shortened DAPT is under investigation due to concern about the risk of stent thrombosis. Data on platelet activation and prothrombotic response in vivo following bioresorbable polymer sirolimus-eluting stent (BP-SES) implantation are scarce. The objective of our study was to compare the early thrombogenicity of BP-SES with that of BMS in an aortic rat model. Our data demonstrate the low early thrombogenicity of a BP-SES implanted in an aortic rat model, which does not differ from a BMS. These results support the safety of a shortened 1-month DAPT duration following BP-SES implantation in the human coronary artery *(Verhaegen et al, 2020)*.

Developing new bioresorbable stents that combine optimal mechanical properties and biodegradation rates with limited thrombogenicity remains an important challenge. In this context, twinning-induced plasticity (TWIP) steels are good material candidates. Using an in vitro approach, we have demonstrated the relative hemocompatibility of a new bioresorbable TWIP steel, compared to traditional stent materials *(Verhaegen et al, 2019)*. However, as in vitro tests are unable to reproduce physiological environments, in vivo compatibility evaluation will be necessary to confirm our encouraging findings.





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IMAGING

IMAG is the medical imaging research group of the Université Catholique de Louvain originating from and embedded within the Radiology Department of the Cliniques Universitaires Saint-Luc.

IMAG support active research programs in Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Ultrasound Imaging (US) in relying on state-of-the-art facilities and by getting involved together physicists, radiologists, MD residents, PhD students and staff technologists. By the diversity of expertise of its investigators, IMAG can rely on knowledge in several fields such as neuroimaging, abdominal and thoracic imaging, musculoskeletal imaging, pediatric imaging, women's imaging, vascular and interventional imaging, animal experimentation, physics, signal and image processing, and data mining. Research axes within IMAG are therefore numerous. Among these axes, a privileged area of research is the development of MRI as a non-invasive morphologic and functional imaging tool for the diagnosis, staging, treatment monitoring and follow-up of oncological and rheumatological disorders.

The main lines adopted by IMAG can be summarized as follows:

To develop, optimize and translate advanced imaging technologies into clinical practice and patient care, and contribute to shape the future of radiological imaging.

To constitute an open technical platform, offering the opportunity to work with research groups within the UCL and beyond, and favor innovation in biomedical research.

Additional activities of IMAG include the participation in multicenter trials (with other universities, EORTC, pharmaceutical industry) and the collaboration on technological tests and optimization with major imaging companies (GE, Siemens, Philips). IMAG investigators also provide expert advice in the various fields of medical imaging techniques.

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ONCOLOGY

MRI vs CT performance in detecting lymph node metastasis in patients with testicular cancer.

Pasoglou V

PURPOSE: To assess the diagnostic accuracy of an optimized Whole-Body Magnetic Resonance Imaging (WB-MRI) with diffusion weighted imaging (DWI) for the detection of metastasis in patients with testicular cancer. To develop an optimal WB-MRI protocol for the detection of lymph node metastasis in these patients.

MATERIAL AND METHODS : In this prospective study, 31 patients diagnosed with testis germ cell tumors were imaged with contrast enhanced computed tomography (CT) and WB-MRI for detection of metastasis. A follow up-pair of studies was performed 3-12 months after the initial study. Two independent observers have reviewed CTs and WB-MRIs. The location and number of metastasis were recorded. In every reading the best sequence for the detection of the metastasis was also recorded.

RESULTS: For the detection of abnormal retroperitoneal lymph nodes (RPLN) the sensitivity and specificity of both CT and WB-MRI was 100% for both readers. For the detection of abnormal supra-diaphragmatic LN (SDLN) the sensitivity of CT was 71.4% for both readers when specificity was 100% for the first reader and 95.8% for the second. The sensitivity of WB-MRI for the detection of abnormal SDLN was 100% for both readers when specificity was 100% for the first and 95.8% for the second reader.

Before treatment, the DWI was the most useful sequence for the detection of RP and SD LN. After treatment, the abnormal LN were much more easily detected by the anatomic axial T2 sequence.

Shortening the acquisition time of whole-body MRI: 3D T1 gradient echo Dixon vs fast spin echo for metastatic screening in prostate cancer.

Lecouvet FE, Pasoglou V, Van Nieuwenhove S, Van Haver T, de Broqueville Q, Denolin V, Triqueneaux P, Tombal B, Michoux N.

PURPOSE: To compare 3D T1-weighted fast spin echo (FSE) and 3D T1-weighted gradient echo (GE) mDixon as morphologic sequences to complement diffusion-weighted imaging (DWI) for the metastatic screening in prostate cancer (PCa) patients.

MATERIALS AND METHODS: Thirty PCa patients at high risk of metastases prospectively underwent both a 3D T1 FSE (14 min) and a rapid 3D T1 GEmDixon (1 min 20 s) sequences within a WB-MRI protocol. Two readers assessed the diagnostic performance of the FSE/Fat/in-phase (IP)/IP+Fat sequences in detecting bone and node metastases. The reference standard was established by a panel of four physicians on the basis of all baseline and follow-up imaging, biological and clinical information. The reproducibility of readings, predictive accuracy (Acc) from ROC curves analysis, and contrast-to-reference ratio (CRR) in lesions were assessed for each sequence.

RESULTS: In bone and lymph nodes (per-region analysis), reproducibility was at least good for all sequences/readers, except for nodes in the common iliac/inguinal regions. In bone (per-organ analysis), Acc of FSE was superior to that of mDixon (difference + 4%, $p < 0.0083$). In nodes (per-organ analysis), Acc of Fat was superior to that of other sequences (difference + 4% to + 6% depending on reader, $p < 0.0083$). In the per-patient analysis, Acc of FSE was superior to that of mDixon (difference + 4% to + 6% depending on sequence, $p < 0.0083$). Fat images had higher CRR compared with FSE in the thoracic spine, the bony pelvis and lymph node metastases ($p < 0.025$).

CONCLUSION: 3D T1 GEmDixon may replace 3D T1 FSE to complement DWI in WB-MRI for metastatic screening in PCa. It demonstrates an Acc ranging from + 4% to + 6% (nodes) to - 4% to - 6% (bone and patient staging) compared with FSE and considerably reduces the examination time, offering the perspective of acquiring WB-MRI examinations in less than 20 min.

Bone marrow MRI versus 18F-FDG-PET/CT for detecting multiple myeloma lesions: diagnostic performance and clinical relevance.

Lecouvet FE, Boyadzhiev. D, Collette L, Berckmans M, Michoux N, Triqueneaux P, Pasoglou V, Jamar F, Vekemans MC

PURPOSE : To compare the diagnostic performance of MRI and 18F-FDG-PET/CT in detecting bone marrow involvement (BMI) in patients with multiple myeloma (MM).

MATERIALS AND METHODS : This retrospective study was approved by our Institutional Review Board. Two radiologists and two nuclear medicine specialists independently and blindly reviewed 84 pairs of MRI and PET/CT scans obtained in 73 MM patients. Readers assessed the presence and patterns of BMI. The best valuable comparator (BVC) for BMI was established by a panel review of all baseline and follow-up imaging, biological and pathological information. Intra- and inter-reader agreement and correlation between MRI and PET/CT were assessed using the prevalence-adjusted bias-adjusted kappa (k) coefficient. Diagnostic performance of MRI and PET/CT in detecting BMI was evaluated from ROC characteristics. Association between imaging and biological, pathological and clinical findings was assessed using Wilcoxon rank-sum and chi-square tests.

RESULTS : Intra- and inter-reader agreement was very good for MRI (k = 0.90 [0.81; 1.00] and 0.88 [0.78; 0.98]). Intra- and inter-reader agreement was substantial for PET/CT (k = 0.80 [0.69; 0.91] and 0.71 [0.56; 0.86]). The sensitivity of MRI to detect BMI (97% [90%; 100%]) was significantly superior to that of PET/CT (76% [64%; 85%]). The specificity of MRI (86% [57%; 98%]) was lower than that of PET/.CT (93% [66%; 100%]), without reaching statistical significance. There was a strong correlation between decisions regarding patient management and PET/CT findings.

CONCLUSION: WB-MRI is significantly more sensitive than PET/CT to detect BMI in MM. Patient management is more strongly correlated with PET/CT findings.

OSTEOARTICULAR

Value of CT to detect radiographically occult injuries of the proximal femur in elderly patients after low-energy trauma: determination of non-inferiority margins of CT in comparison with MRI.

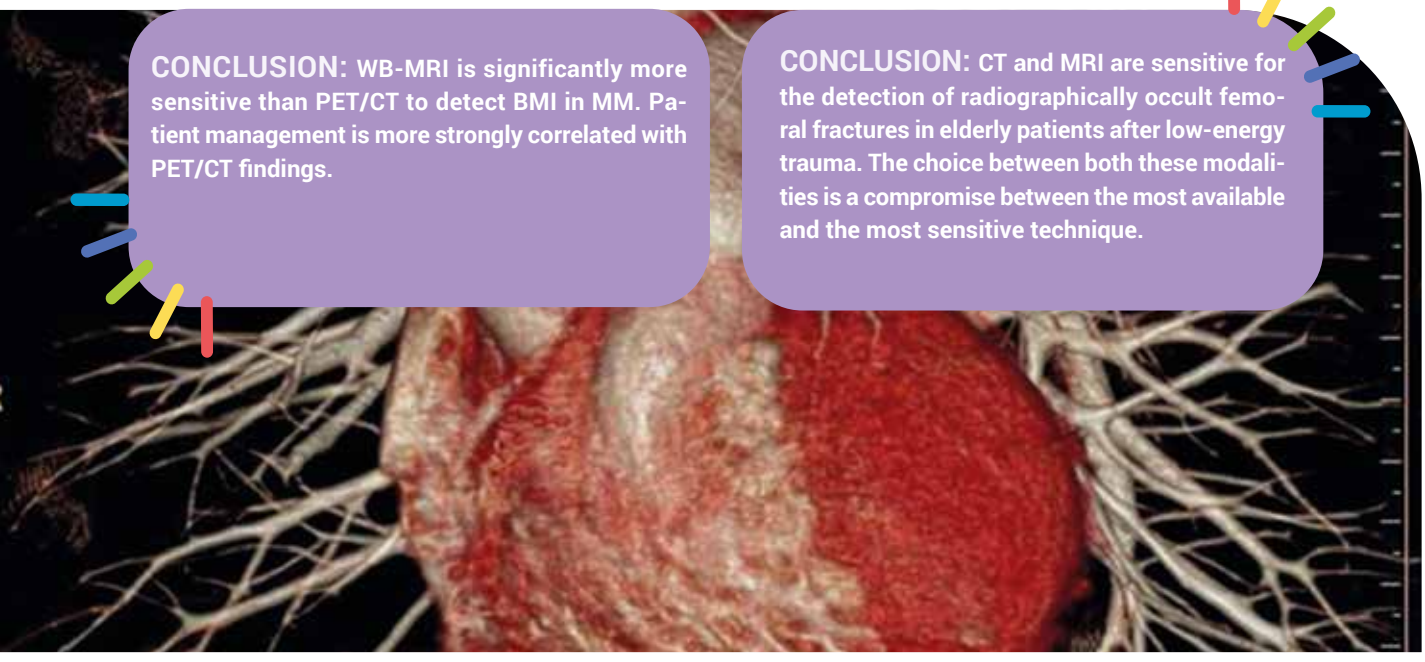
Lanotte SJ, Larbi A, Michoux N, Baron MP, Hamard A, Mourad C, Malghem J, Cyteval C, Vande Berg BC

PURPOSE: To determine the margins of non-inferiority of the sensitivity of CT and the sample size needed to test the non-inferiority of CT in comparison with MRI.

MATERIAL AND METHODS : During a 2-year period, elderly patients with suspected radiographically occult post-traumatic bone injuries were investigated by CT and MRI in two institutions. Four radiologists analyzed separately the CT and MRI examinations to detect post-traumatic femoral injuries. Their sensitivities at CT (SeCT) and MRI (SeMRI) were calculated with the reference being a best valuable comparator (consensus reading of the MRI and clinical follow-up). ROC analysis followed by an exact test (Newcombe's approach) was performed to assess the 95% confidence interval (CI) for the difference SeCT-SeMRI for each reader. A sample size calculation was performed based on our observed results by using a one-sided McNemar's test.

RESULTS: Twenty-nine out of 102 study participants had a post-traumatic femoral injury. SeCT ranged between 83 and 93% and SeMRI ranged between 97 and 100%. The 95% CIs for (SeCT-SeMRI) were [- 5.3%, + 0.8%], (pR1 = 0.1250), [- 4.5%; + 1.2%] (pR2 = 0.2188), [- 3.4%; + 1.1%] (pR3 = 0.2500) to [- 3.8%; + 1.6%] (pR4 = 0.3750) according to readers, with a lowest limit for 95% CIs superior to a non-inferiority margin of (- 6%) for all readers. A population of 440 patients should be analyzed to test the non-inferiority of CT in comparison with MRI.

CONCLUSION: CT and MRI are sensitive for the detection of radiographically occult femoral fractures in elderly patients after low-energy trauma. The choice between both these modalities is a compromise between the most available and the most sensitive technique.



ONCOLOGY AND MRI TECHNIQUE

Insights into tissue microstructure using a double diffusion encoding sequence on a clinical scanner: Validation and application to experimental tumor models.

Duchêne G, Abarca-Quinones J, Leclercq I, Duprez T, Peeters F.

PURPOSE: To present a double diffusion encoding MRI sequence on a clinical scanner to analyze micro-structure and micro-vasculature of tumors.

METHODS: The sequence was tested on phantoms, asparaguses, and 2 tumors allografts in a rodent. Results were analyzed using an adapted VERDICT model to estimate microstructural parameters. The technical feasibility of the sequence on a 3T clinical system was assessed on a water phantom. The accuracy of cell size estimation was assessed on asparaguses by comparison with light microscopy. Cell size estimations were also validated when limiting relative angles of diffusion encodings to 0 and 180°. Sensitivities to restricted diffusion and incoherent flow from the vasculature were investigated in experimental tumor models. Values of microstructural parameters in viable and decaying tumor tissue were compared with those obtained from histological analysis.

RESULTS: Measurements on the water phantom revealed no significant sequence artifacts and accurate apparent diffusion coefficient values within a 4% relative error. In asparaguses, quartiles and medians of pore size distributions typically deviated less than 6% from light microscopy regardless of whether the full or reduced set of relative angles was used. Signal analyses in tumors showed mixed effects of both blood flow and diffusion restriction. Microstructural parameter estimations in tumors were consistent with histology and allowed clear and histology-proven distinctions between decaying and viable tumor tissue.

CONCLUSION: Double diffusion encoding with clinical gradients and scan times allows characterization of restricted diffusion and micro-circulation flow in tumors. Our estimated microstructural parameters are promising for further investigations in assessing microstructural evolutions in tumors.

Double diffusion encoding for probing radiation-induced microstructural changes in a tumor model: a proof-of-concept study with comparison to the apparent diffusion coefficient and histology

Duchêne G, Abarca-Quinones J, Feza-Bingi N, Leclercq I, Duprez Th and Peeters F.

BACKGROUND: Microstructure analyses are gaining interest in cancer MR imaging as an alternative to the conventional Apparent Diffusion Coefficient (ADC) of which determinants remain unclear.

PURPOSE: To assess the sensitivity of parameters calculated from a Double Diffusion Encoding (DDE) sequence to changes in tumor's microstructure early after radiotherapy and to compare them with ADC and histology.

STUDY TYPE: Cohort study on experimental tumors.

ANIMAL MODEL: Sixteen WAG/Rij rats grafted with 1 rhabdomyosarcoma fragment in each thigh. Thirty-one were imaged at days 1 and 4, of which seventeen tumors received a 20 Gy radiation dose after the first imagery.

FIELD STRENGTH/SEQUENCE: 3T. Diffusion weighted imaging, DDE with flow compensated and non-compensated measurements.

ASSESSMENTS: (i) To compare, after irradiation, DDE-derived parameters (intracellular fraction, cell size and cell density) to their histological counterparts (fraction of stained area, minimal Feret diameter and nuclei count, respectively). (ii) To compare percentage changes in DDE-derived parameters and ADC. (iii) To evaluate the evolution of DDE-derived parameters describing perfusion.

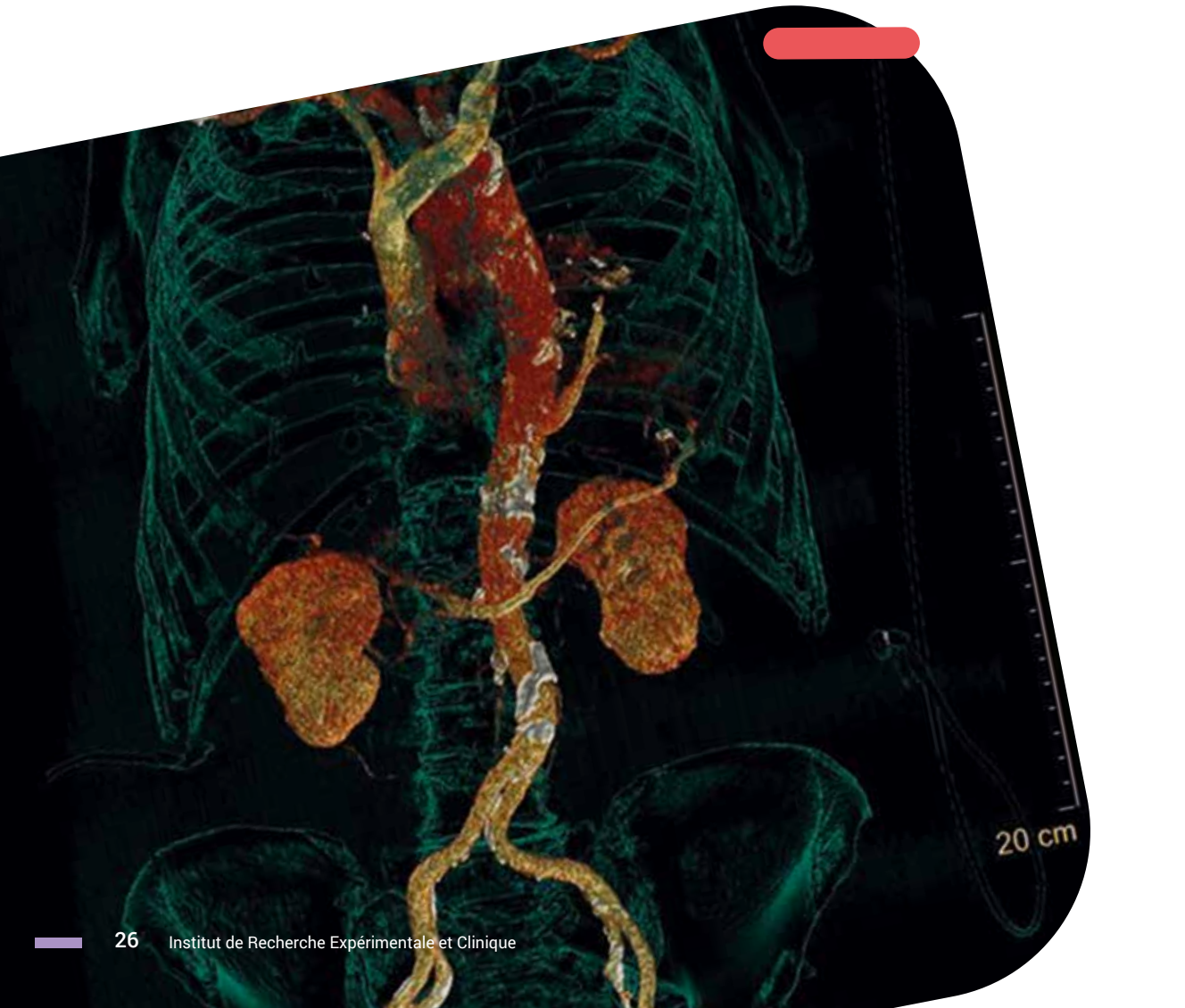
STATISTICAL TESTS: Wilcoxon Ranksum test.

RESULTS: (i) Intracellular fraction, cell size and cell density were respectively lower (-24%, p<0.001), higher (+7.5%, p<0.001) and lower (-38%, p<0.001) in treated tumors as compared to controls. Fraction of stained area, minimal Feret diameter and nuclei count were respectively lower (-20%, p<0.001), higher (+28%, p<0.001) and lower (-34%, p<0.001) in treated tumors. (ii) The magnitude of ADC's percentage change due to irradiation (16.4%) was superior to the one of cell size (8.4%, p<0.01) but inferior to those of intracellular fraction (35.5%, p<0.001) and cell density (42%, p<0.001). (iii) After treatment, the magnitude of the vascular fraction's decrease was higher than the increase of flow velocity (33.3%, versus 13.3%, p<0.001).

DATA CONCLUSION: The DDE sequence allows to quantitatively monitor effects of radiotherapy on tumor's microstructure whereas ADC only reveals global changes.

EQUIPMENTS

New MRI research magnet: Availability of the new advanced MRI research magnet, dedicated to translational and clinical research, within the IMAG pole, with all interested IREC's poles and external partners, optimized for research in all medical fields



CLINICAL AND TRANSLATIONAL IMMUNOLOGY

Tissue-specific or systemic dysregulation of the immune system leads to several diseases or disease complications across all fields of medicine. Auto-immune or auto-inflammatory disorders, hypersensitivities/allergies, inflammatory responses, and graft rejection represent major clinical manifestations indicative of a disruption in the homeostasis of the innate and/or adaptive immune system.

Clinical care of patients with such disorders requires the intervention of qualified rheumatologists, pulmonologists, nephrologists, and others according to the affected system. By contrast, understanding mechanisms of disease and finding innovative strategies in order to stratify patients (and thereby personalize medical decisions) takes advantage of pooling diverse scientific and technological expertise in a translational platform that aims at scaling up ambitions and results.

In this context, the scientific competitiveness of the IREC clinical and translational immunology platform is promoted by specific strengths. In particular, access to large collections of biological samples from well-characterized patients with immune-related disorders, shared high-throughput and imaging technological platforms, development of appropriate animal models and, last but not least, numerous interactions in national and international research networks gave rise to significant advances in the field, as described below.

Research Poles

POLE OF RHEUMATOLOGY RESEARCH (RUMA)

Patrick Durez, MD

Bernard Lauwerys, MD, PhD

Frédéric Houssiau, MD, PhD

Christine Galant, MD, PhD

Gaëlle Tilman, PhD

Farah Tamirou, MD, PhD

Aurélie De Groof, PhD

Laurent Méric de Bellefon, MD
Maria Stoenoiu, MD, PhD
Adrien Nzeusseu Toukap, MD
Pauline Montigny, PhD Student
Clément Triaille, PhD Student
Joëlle Marchandise, laboratory assistant
Caroline Gabrys, laboratory assistant
Tatiana Sokolova, Clinical Research Coordinator
Isabelle Faille, Clinical Research Coordinator
Charlène Mouafo, Clinical Research Coordinator
Séverine Nieuwland, Study Nurse
Aleksandra Avramovska, Study Nurse
Marie M'Zoughui, Trial Coordinator
Samira El Hajjami, Administrative Assistant
Kenza Berbit, Administrative Assistant

Research Projects

Our research interests are in line with our clinical expertise in the field of systemic and inflammatory rheumatic disorders, in particular RA, SLE and SSC. Our recruitment of large numbers of patients and the use of a validated clinimetry and imaging to characterize disease activity and response to therapy are a unique ressource supporting clinical and translational research projects aimed at improving quality of care in these severe disorders. One of our main hypotheses is that target tissues in these disorders (e.g. the kidney in lupus nephritis, the joint in rheumatoid arthritis) are not mere passive victims of systemic autoimmunity, but host specific inflammatory mechanisms that determine disease progression independently of the systemic first hit. From April 2020, our research unit will be chaired by Patrick Durez, who will further develop a strong translational research program in the field of inflammatory and systemic rheumatic disorders.

Mechanisms of disease severity in lupus nephritis

Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE). It is caused by the deposition of anti-chromatin antibodies in the glomerular basement membrane, where they activate complement and recruit inflammatory cells resulting in glomerulonephritis. Despite the use of corticosteroids and other immunosuppressive agents, 15% LN patients still develop end-stage renal disease, and up to 30 % have an impaired renal function after 10 years of evolution, a major issue in a population of mainly young women (1).

Type I interferons play an important role in the pathogenesis of SLE. By increasing the ability of antigen-presenting cells to stimulate autoreactive T and B cells, they contribute to the loss of tolerance to chromatin and the production of antinuclear antibodies. We demonstrated that IFN displays direct effects on B cell activation and differentiation. In SLE B cells, IFN induces the phosphorylation of STAT3, rather than STAT1/2, which results in cell proliferation and survival, instead of apoptosis (2). While TLR9 and TLR7 are known inducers of type I interferons, we found that TLR3 is overexpressed in the SLE skin and mediates the activating effects of UV irradiation on antigen-presenting cell functions (3). A few years ago, we had demonstrated that IFN-kinoid was able to induce the production of polyclonal anti-IFN antibodies in SLE patients, resulting in decreased expression of IFN-induced transcripts in patients' PBMC. The therapeutic efficacy of IFN-kinoid was tested in a phase II study that recruited SLE patients with mild to moderate disease activity worldwide. Although the study did not reach the very stringent pre-determined primary endpoint, secondary endpoints (lupus low disease activity score, reduction in corticosteroids intake) were met, confirming the therapeutic effect of IFN neutralization using IFN-kinoid (4).

In 2018, we had performed high-throughput transcriptomic experiments on kidney biopsies from LN patients and controls, resulting in the identification of second wave adaptive immune effectors, in particular CD8 T cells, in the renal interstitium as a significant contribution to disease progression. In collaboration with P. Coulie, from the DDUV Institute, we are presently running a WelBio-funded project aiming at characterization of intra-renal CD8 T cells in LN, using single cell RNASeq and cell cloning.

Our work in vitro is paralleled by experiments performed in a mouse model of the disease. B6.Sle123 mice are C57Bl/6 mice congenic for three lupus susceptibility loci found in NZW lupus prone animals. We are currently studying the role of PRKR (double stranded RNA-dependent protein kinase) in the amplification of the IFN response and B cell differentiation using PRKR -/- B6.Sle123 animals. The use of B6.Sle123 animals is also central in collaborative projects run in the context of an Action de Recherche Concertée focusing on SLE and systemic sclerosis at UCL.

Response to therapy in rheumatoid arthritis

We are active in many clinical trials in RA in order to develop and validate targeting therapies. Our large recruitment of RA patients allow us to analyze the predictive factors for severity and therapy responses. Using synovial biopsies (Figure 1) from patients with RA at different stages of the disease, we identified several molecular pathways associated with disease activity and disease severity, and described how they are impacted by the use of specific drugs. We are presently recruiting patients in large scale multi-centric prospective studies aiming at the formal validation of specific synovial markers for the prediction of response to therapy in RA. In parallel, prospective recruitment of patients in sponsored and national / international academic clinical trials (in particular the Cap48 cohort, including young patients with new-onset arthritis, and WelBio) provides us with additional clinical, biological and imaging data in order to develop novel patients' stratification algorithms (5-7). Our expertise in the field led to the signature of a 2M€ research contract with a pharmaceutical company, in order to generate single cell RNASeq data from RA synovial biopsies.

Pathogenesis of systemic sclerosis

We performed high-throughput transcriptomic studies on skin biopsies (affected versus unaffected skin) from patients with systemic sclerosis (SSc). As expected, SSc skin is characterized by a strong overexpression of TGFβ-induced and fibrosis-associated transcripts. We also reported overexpression of a large group of TGFβ-induced deubiquitinases, a novel observation pointing at the importance of post-translational modifications in the pathogenesis of fibrosis in SSc. Protein deubiquitination

inhibits their degradation by the proteasome. Thus, we demonstrated that overexpression of USP15 amplifies TGFβ signaling in cultured fibroblasts, through SMAD3 deubiquitination, thereby contributing to a pro-fibrotic amplification loop (8). In vivo experiments (bleomycin-induced fibrosis) in USP15-KO versus wild-type mice are being conducted (in collaboration with F. Huaux, IREC, UCLouvain) in order to further validate USP15 as a therapeutic target in SSc.

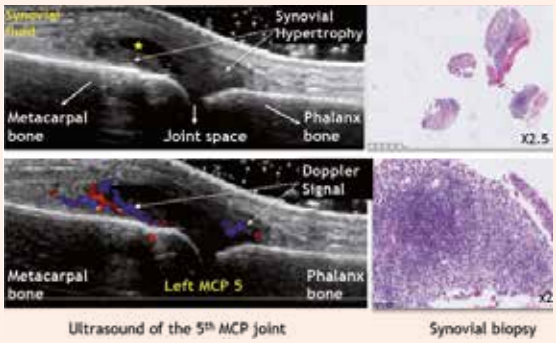


Figure 1: Ultrasound-guided synovial biopsies deliver material for a better stratification of RA patients based on the identification of specific molecular profiles in the tissue.

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LOUVAIN CENTRE FOR TOXICOLOGY AND APPLIED PHARMACOLOGY (LTAP)

François Huaux, PhD

Riccardo Leinardi, PhD

PhD Student : *Micaela Orsi*

Technicians : *Francine Uwambayinema, Yousef Yakoub, Amandine Pochet*

Research Projects

Our group has developed a specific expertise in the respiratory toxicity of micrometric- and nanometric-materials such as asbestos, silica and carbon nanotubes. We investigate the immune mechanisms by which certain fibers and particles induce alveolitis, lung fibrosis and cancer. Over recent years, we have accumulated experimental evidence that not only inflammation but also immunosuppression contribute to the development of particle-induced fibrosis, cancer or alveolar proteinosis (PAP). Immunosuppression is thought to represent an endogenous mechanism limiting excessive immune responses, thereby preventing immunopathology. In the context of lung responses to particles, we have newly proposed that this regulatory mechanism has deleterious consequences, as suppressive immune responses and mediators promote fibroblast activation and tumor expansion. Immunosuppressive pathways may thus become attractive targets for therapeutic intervention.

Immune suppression during particle-induced diseases

Fibrosis, cancer, and autoimmunity developing upon particle exposure have been exclusively linked with uncontrolled inflammatory processes. The critical role of inflammation is now challenged by several contradictory observations indicating that the emergence of these chronic disorders may result from non-inflammatory events. A growing number of studies reveals that micro- and nano-particles can cause exaggerated and persistent immunosuppression characterized by the release of potent anti-inflammatory cytokines (IL-10 and TGF-β), and the recruitment of major regulatory immune cells (M2 macrophages, T and B regs, and MDSC). This persistent immunosuppressive environment is initially established to limit early inflammation but contributes later to fibrosis, cancer, and infection. Immunosuppression promotes fibroblast proliferation and matrix element synthesis and subverts innate and adaptive immune surveillance against tumor cells and microorganisms. This review details the contribution of immunosuppressive cells and their derived immunoregulatory mediators and delineates the mutual role of inflammatory vs. immunosuppressive mechanisms in the pathogenesis of chronic diseases induced by particles (Figure 1). The consideration of these new results explains how particle-related diseases can develop independently of chronic inflammation, enriches current bioassays predicting particle toxicity and suggests new clinical strategies for treating patients affected by particle-associated diseases.

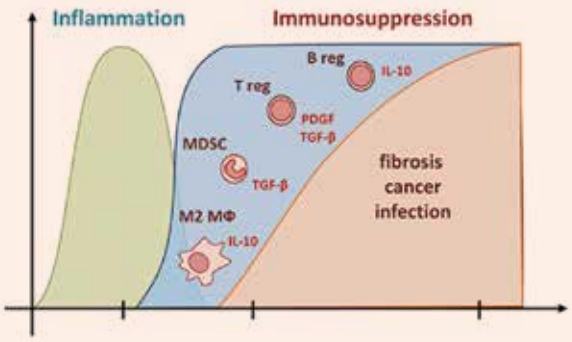

Figure 1: ***Pathological functions of persistent immunosuppressive cells and mediators during long-term responses to particles.*** Unresolved Immunosuppression (in blue) represents an alternative event during the responses to particles. According to this new pathological pathway, fibrogenesis, and carcinogenesis are governed by a persistent accumulation of immunosuppressive myeloid (M2 and MDSC) and lymphoid (T and B regs) cells and a sustained production of their related cytokines (IL-10 and TGF-β). These immunoregulatory components limit both the recruitment of inflammatory cells and the activity of pro-inflammatory mediators (in green). The high amount of immunosuppressive cytokines produced can, in addition to their anti-inflammatory action, also act as profibrotic mediators, conceivably by stimulating mesenchymal cells to overproduce collagenase inhibitors and ultimately matrix elements under non-inflammatory conditions. The persistence of immunosuppressive cells and mediators is also incriminated in carcinogenesis and infection by preventing host immune responses directed against transformed cells and microorganisms.

Publication: Huaux F. Emerging Role of Immunosuppression in Diseases Induced by Micro- and Nano-Particles: Time to Revisit the Exclusive Inflammatory Scenario. Front Immunol. 2018 Nov 19;9:2364.

The sensing arsenal of phagocytes capable of recognizing inhaled particles

Major progress has been achieved in recent years to elucidate mechanisms driving the early response of pulmonary innate immune cells to inhaled micrometric and nanometric particles. Mononuclear phagocytes promptly categorize particles, alert immune network and engage crescendo responses for particle clearance and homeostasis restoration. Negatively charged particles directly interact with scavenger receptors A and B (SR-A and SR-B) and consequently activate specific signaling pathways, resulting in the production of TNF and IL-1 family members, which coordinate effective innate immune responses. Cytokine secretion also arises after a simple contact between particle-associated radicals and cell membranes. Reactive particles engage the passive release of constitutive alarmins, ensuing particle- or TNF-α-induced cell death and membranolysis. Finally, the inflammasome machinery represents the decisive intracellular platform that finely tune immune pathways engaged after SR activation, alarmin release, TNF-α production and cell homeostasis perturbations (Figure 2). Disturbance of these collective recognition processes prolongs particle persistence and innate immune responses that generate long-lasting adaptive immunity and cause chronic lung diseases.

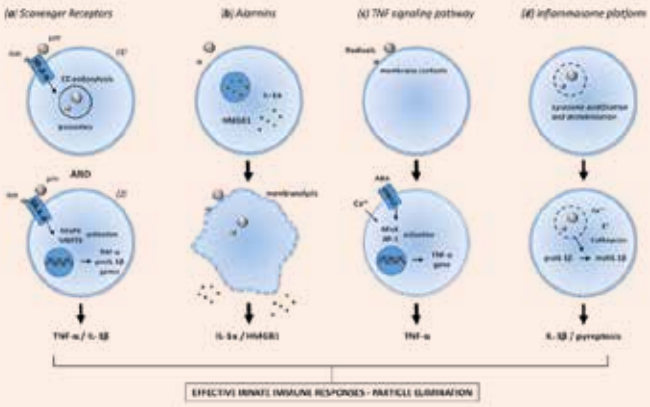

Figure 2: ***Early sensing and alerting processes are combined and mutually linked in response to inhaled particles.*** (a1) Micrometric (µm) and nanometric (nm) particles are internalized by phagocytes through the scavenger receptors (SR) A and B and clathrin-dependent (CD) endocytosis. (a2) Particle sensing by these subclasses of pattern recognition receptors (PRRs) also results in the activation of MAPK and MerTK signal transduction leading to TNF-α and IL-1β secretion, which instruct innate immune responses and inflammasome platform (see d). (b) Endocytosis of particles can result in cell death and membranolysis, permitting the passive release of alarmins (subclass of danger-associated molecular patterns, DAMPs) in the tissue environment. Beside their direct activity on innate immune cell recruitment and stimulation, alarmins are also powerful stimulators of immature proIL-1β production and mature (mat) IL-1β secretion (d). (c) Radical groups on particle surface induce plasma membrane peroxidation, calcium flux perturbation, abscisic acid (ABA) release and LANCL2 receptor activation that consequently result in TNF-α release. In addition to its own innate immune activity, TNF-α is known to actively increase the pool of proIL-1β available for the inflammasome machinery (d) and to induce cell death and membranolysis (b). (d) Reactive particles which are taken up by phagocytes (see a1) induce perturbations in cytoplasmic homeostasis (homeostasis-altering molecular processes, HAMPs such as ion concentration modifications and lysosomal leakage of cathepsin K and S) that are sensed by the intracellular PRR-related inflammasome complex (NLRP) and cause NLRP engagement and mature IL-1β release from inactive proIL-1β. Inflammasome engagement results in a cell death termed pyroptosis that can contribute to alarmin release (b). The stepwise engagement of PRRs with the progressively increase of serial cytokine secretion coordinates effective immune responses and promotes particle elimination.

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New models of skin and lung fibrosis

Mouse models of fibrosis have been central to our understanding of disease mechanisms. In collaboration with the clinical immunology groups of Bernard Lauwerys and Charles Pilette, we have improved version of the bleomycin-inducible mouse model of systemic sclerosis and lung diffuse fibrosis, in which bleomycin is delivered via subcutaneously implanted osmotic pumps or repeatedly injected by pharyngeal instillation into the lungs. This results in a pattern and severity of lung and skin fibrosis that is strikingly similar to that observed in sclerodermic and IPF patients, respectively. We are able to assess key pathologic events such as inflammatory cell infiltration, vascular destabilization, Th-immune polarization, fibroblast activation and tissue fibrosis in these models.

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POLE OF PULMONOLOGY, EAR-NOSE-THROAT AND DERMATOLOGY RESEARCH (PNEU)

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Research Projects

The importance of respiratory and skin diseases for public health is increasingly recognized. This ranges from lethal disorders such as lung cancer or severe COPD which continue to increase despite current treatments, to chronic diseases that affect a large part of the population - such as asthma, sleep apnea, rhinitis or atopic dermatitis (WHO predicts allergy will affect 50% of the population by 2020) - and to orphan diseases such as idiopathic pulmonary fibrosis. Our research pole has been focusing on the study of the physiology and pathology of breathing and sleep; mucosal immunology and inflammation/fibrosis of the lungs and skin; and biology of lung cancer.

Physiology and pathology of breathing and sleep: pitfalls of CPAP treatment in sleep apnea.

Obstructive sleep apnea (OSA) represents the paradigm of the complex interactions between breathing and sleep. Some people develop asphyxia when asleep, resulting in sleep destructuration and reduced survival. Treatment with continuous positive airway pressure applied all and every night normalizes sleep and breathing as well as survival. However, a third of patients is unable to accept/tolerate the treatment.

Firstly, the predictors of compliance with CPAP should be better assessed. We have evaluated the influence of the purchasing Cpap in Belgium social security system. We have found that the absence of reimbursement without micro-arousals criteria is a factor which negatively influences the acquisition of this treatment. We also found that the onset of periodic leg movements under CPAP therapy was a poor predictor of long-term compliance. Currently neuropsychological determinants of compliance with CPAP in patients with OSAS are studied.

Secondly, new treatments are needed for patients with obstructive sleep apnea intolerant to CPAP. Recent advances in OSA pathogenesis using upper airway and respiratory phenotyping techniques have identified four key causes of OSA. Impairment in upper airway anatomy is the primary cause. However, the anatomical contribution to OSA varies substantially. Indeed, impairment in pharyngeal anatomy can be modest and in many patients (~20%), pharyngeal anatomy is not different to people without OSA. Thus, non-anatomical factors or 'phenotypes' that modulate pharyngeal patency are crucial determinants

of OSA for many people. These include impairment in pharyngeal dilator muscle control and function during sleep, increased propensity for awakening during airway narrowing (low respiratory arousal threshold) and respiratory control instability (high loop gain).

Each phenotype is a potential therapeutic target. Impairment in pharyngeal dilator muscle control and function during sleep could be treated by Electro-stimulation of the hypoglossal nerve or has been assessed in our center (IMTHERA III). Currently a Phase III trial is ongoing. Specific training of oropharyngeal muscles on OSA syndrome has also been evaluated, and results show a significant improvement in a majority of patients unfortunately compliance to these exercises was poor of compliance to specific measures in postural OSA. We are also studying a prosthetic device allowing a muscles tongue training in order to counteract the bad compliance to the exercises.

We are also being assessed phenotype of OSA by using polysomnography. This would allow predictive classification of patients for the treatment of sleep apnea syndrome.

Third, interactions between non-invasive ventilation and sleep are studied, in patients with respiratory failure due to restrictive or obstructive disorders and in obese patients with hypoventilation syndrome. Both the effects of sleep on respiratory failure and the effects of non-invasive ventilation on breathing and sleep are assessed.

Physiology of exercise and airway deposition.

The research projects of the group « Exercise, aerosol and physiotherapy » were based on the deposition of nebulized particles in the lung and in the nasal area. New tools for functional exercise capacity and for comorbidities related to lung diseases evaluation were also investigated. Studies were mainly performed in neuromuscular patients and in children to validate these new tools. The dysphagia was one of the main topics this last year. Exercise training programs and telemedicine were tested in new indications (cancer, congenital heart disease, sleep apnea, Ehlers-Danlos). Rehabilitation in cancer and exercise during radiotherapy were investigated. Physiological effects of airway clearance techniques were also studied by the group including original tools of evaluations (electrical impedance tomography, lung clearance index). Moreover, the oxygen delivery was recently included in the thematic of the group with studies about high flow and way of delivery.

Mucosal immunology and inflammation in the airways and the skin: multi-layered alterations of the respiratory epithelium and underlying signalling pathways.

Asthma and chronic inflammatory diseases of the airways (chronic rhino-sinusitis, COPD) or skin (dermatitis) are very common conditions that affect many people usually throughout lifetime, although with a highly variable clinical expression.

Our first focus was the bronchial epithelium and studying its integrity during chronic lung diseases, including expression of the pIgR (polymeric immunoglobulin receptor), the receptor transcytosing into secretions IgA the main immunoprotein protecting mucosal surfaces against inhaled materials. We showed that the impaired bronchial expression of the pIgR in COPD correlates with disease severity and recapitulates ex vivo, in the bronchial epithelium cultured upon air/liquid interface, as a result of a global dysprogramming of the the bronchial epithelium (Figre 1). This IgA/pIgR axis is now studied in cystic fibrosis and pulmonary fibrosis. We have there implemented in our pole, in collaboration with F. Huaux (LTAP), a new animal model of chronic pulmonary fibrosis that mimicks the features observed in human IPF, following repeated instillation of bleomycin. This model enables to study (1) the role of the IgA system and epithelial pIgR in vivo, using PIGR and IGA KO mice, during the development of lung fibrosis, and (2) the determinants of lung epithelial changes.

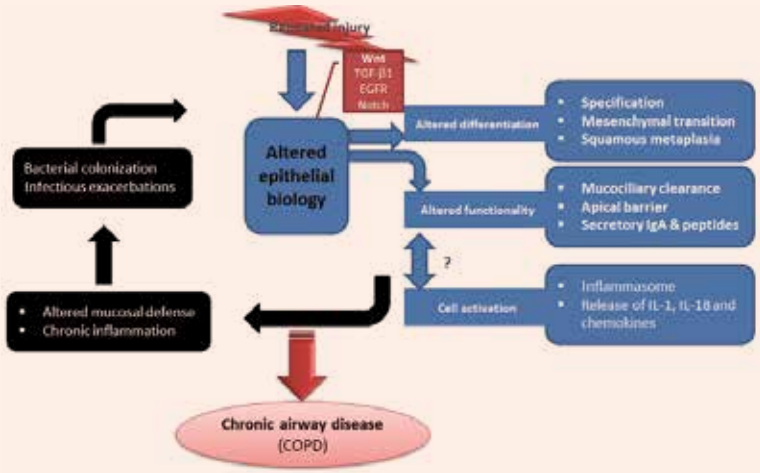

Figure 1. Hypothesis of airway epithelial cell dysregulation in COPD. The epithelium, repeatedly activated by cigarette smoke may become persistently dysregulated through aberrant signalling, with altered differentiation and functionality. This leads to impaired frontline defense against pathogens, further amplifying epithelial inflammation and damage that underlie the development/progression of this disease.

Patients with allergic contact dermatitis are fully characterized and explored through dedicated research projects. Tissue immunophenotyping is carried out in collaboration with L. Dumoutier (DDUV), who showed that skin infiltration is dominated by Th2-biased T cells and includes IL-4 producing γδ T cells. This unique observation is the ground of further investigations with other contact allergens.

Novel biological targets in lung cancer: the FAK pathway in SCLC.

Small cell lung cancer (SCLC) is the most aggressive subtype of lung cancer, with a five-year overall survival <5%. Molecular determinants of SCLC behaviour are still poorly understood and this deficiency has translated into the absence of targeted therapies, as opposed to NSCLC.

In a previous work, we found that Focal Adhesion Kinase (FAK), a non-receptor tyrosine kinase regulating cell proliferation, survival, migration, and invasion, was amplified and commonly expressed in SCLC tumors (Fig. 3) and constitutively phosphorylated in SCLC cell lines. PF-573,228, a FAK small-molecule inhibitor, decreased FAK phosphorylation at Tyr397 without modifying its total expression, leading to decreased adhesion and expression of focal adhesions in SCLC cell lines.

In a work submitted for publication, we also showed that PF-573,228 increased apoptosis, induced cell cycle arrest in G2/M phases, and decreased proliferation, DNA synthesis, and motility in SCLC cell lines. We then evaluated the effects of FAK genetic inhibition through stable transduction with FAK shRNA and/or FAK-related non-kinase (FRNK), a splice variant lacking the N-terminal and kinase domains. While FAK shRNA transduction decreased total and phospho-FAK (Tyr397) expression, it did not affect proliferation, DNA synthesis, or progression through cell cycle. However, restoration of FAK-targeting (FAT) domain (attached to focal adhesion complex where it inhibits pro-proliferative proteins such as Rac-1) by FRNK transduction inhibited proliferation, DNA synthesis, and induced apoptosis. Moreover, while FAK shRNA transduction increased active Rac1 levels, FRNK re-expression in cells previously transduced with FAK shRNA decreased it. From this work, we concluded that FAK is central in SCLC biology and that targeting its kinase domain may have a therapeutic potential, while targeting its FAT domain should be avoided to prevent Rac1-mediated pro-tumoral activity.

Currently, we attempt to further investigate the role of FAK and address its potential as a targeted therapy in SCLC by pursuing the following specific aims. 1/ To evaluate the antitumoral potential of FAK inhibition in an orthotopic SCLC mouse model. 2/ To investigate signaling events downstream of FAK contributing to its pro-tumoral functions.

3/ To quantify the expression/activation of proteins involved in the FAK pathway in human SCLC tissues and establish correlations with clinical outcomes. 4/ To identify and characterize the role of FAK mutations in tissues from SCLC patients. Understanding the role of FAK in SCLC may provide greater insight into the molecular steps leading to SCLC progression and, ultimately, may justify the development of FAK-targeted therapeutic strategies to reduce mortality from SCLC.

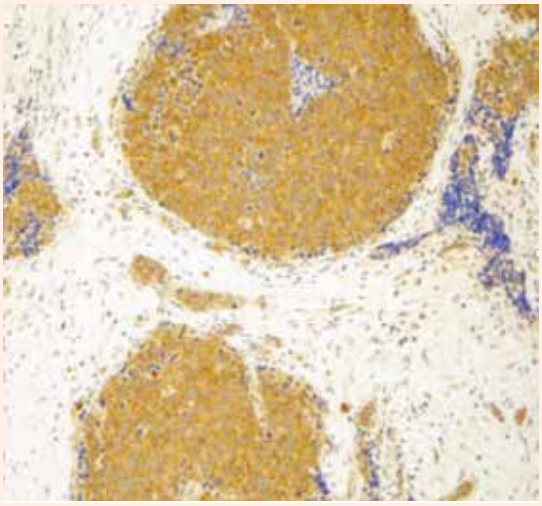

Figure 2. ***Total FAK expression in a small-cell lung cancer tissue.*** Two tissue microarrays consisting of SCLC tissues coming from 85 patients were incubated with an antibody against total FAK (A-17). In this figure is displayed a representative image of SCLC tumor with moderate total FAK expression. Magnification, x200.

Novel therapies in nasal, lung and skin diseases: clinical research programs.

A great energy is devoted to develop clinical research, in order to provide patients with innovative therapies and to participate to medical developments at the bedside. The participation of our clinical teams to early phase pharma trials (in lung cancer, asthma & COPD, rhinitis, dermatitis) is allowed by the implication in research of the IREC-PNEU physicians and research coordinators.

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ACUTE MEDICINE

The "acute medicine theme" comprises physicians conducting research in the three acute medicine units of the UCL Cliniques Universitaires Saint-Luc and CHU UCL Namur site Mont-Godinne: anesthesiology, intensive care, and emergency medicine. Our primary research work is devoted to clinical research, from local original studies to international multicenter studies, either academic or industry-sponsored. Our research pole does not currently have its own experimental lab, so that some acute medicine themes are shared with IREC poles (CARD and PNEUMO) according to a translational research.

The research is primarily focused on the six following topics: (1) sepsis and septic shock; (2) pulmonary embolism and new anticoagulant drugs; (3) peri-operative management; (4) cardiovascular and hemodynamic failure; (5) lung protection of critically-ill patients; (6) acute intoxication and poisoning.

Most of the researchers of this group belong to international collaborative groups, resulting in national or European leading board coordination and some co-authoring studies published in the highest impact factor journals. One of the challenges of this research sector focused on acutely-ill patients is developing fundamental aspects of clinical studies, participating in preliminary phases of drug developments, and including patients outside working hours (at nights and weekends)

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Improvement of the understanding of sepsis

SEPSIS is characterized by the inflammatory response of the organism following a microbial attack. This very complex reaction has adverse effects on the function of many organs, and leads to mortality in 30 to 60% of cases. Sepsis in its severe form is therefore a major concern for any intensive care unit. Our service develops a field of clinical and fundamental research aiming at the improvement of the understanding of sepsis as well as its treatment by various approaches.

PF. Laterre co-authored a study devoted to selepressin, a selective vasopressin type 1a receptor agonist which increases arterial pressure and has the potential to reduce vascular leakage and pulmonary edema. This trial showed promising results for selepressin by rapidly replacing norepinephrine while maintaining adequate blood pressure, and by improving fluid balance and shortening the time of mechanical ventilation (1). He also improved the knowledge on the field of combatting hospital-acquired infections with a vaccine : a new, recombinant vaccine against the opportunistic pathogen Pseudomonas aeruginosa has been tested in a phase-II randomized, placebo-controlled, study in mechanically ventilated ICU patients. This vaccination produced a significant immunogenic effect without safety or mortality concerns (2). The ICU team also measured the impact of early exercise on signaling pathways in muscle metabolism in patients with sepsis: the objective of this project was to demonstrate that maintaining muscle activity at an early stage in patients with severe sepsis, restored the balance of skeletal muscle protein (3).

Management of pulmonary embolism in outpatients and monitoring the new oral anticoagulants (DOAC)

For many years, pulmonary embolism has been the subject of clinical research in our center, this potentially life-threatening disease represents a significant diagnostic, therapeutic and prognostic challenge for emergency physicians and for the 60,000 new patients diagnosed each year in Belgium.

F. Verschuren participated in a new international phase 1b, randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of a new Thrombin-activatable fibrinolysis inhibitor (TAFI) in subjects with acute pulmonary embolism. He also co-authored a study on the rationale for using Dabigatran (one of the DOAC) early after the diagnosis of intermediate-risk pulmonary embolism (4).

Monitoring and managing the Anticoagulation (DOAC) during the perioperative anesthetic period

This area of clinical research is targeted by several local, national and international prospective studies focusing on the tricky perioperative management of patients using oral anticoagulants.

S. Lessire and M. Gourdin published several papers on the validation of bedside guidelines for help during the anesthesiology consultation for the perioperative management of DOACs, on the monitoring of hemorrhagic and thromboembolic events, on the validation of biological tests in cases involving low DOAC concentrations, and on the validation of the interruption of DOAC prior to loco-regional anesthesia (5,6,7,8).

Finally, F. Verschuren participates in a large international study on antidotes to DOAC-type anticoagulants: The Cliniques Universitaires Saint-Luc (CUSL) are one of the only hospitals in the world currently involved in the prospective evaluation of those antidotes used for severe bleeding for patients taking anticoagulants of DOAC type (9).

Improvement of the perioperative management

Anesthesiology research aims to improve the quality of perioperative management of patients from the preoperative phase to the postoperative phase. We develop a clinical research activity in various anesthetic fields: neuromuscular blockade during the surgical procedure, the surveillance and management of anticoagulation induced by direct thrombin inhibitors (DOAC), the education for intubation and airway protection techniques, the impact of the patient's nutritional status on post-surgical morbidity, the fragility of elderly patients during cardiac surgery.

Ph. Baele published an original paper on twenty years of collaboration between Belgium and Benin in training anesthesiologists for Africa: he explained how this collaboration allowed 123 graduates from 15 African countries to succeed in reversing the trend of a decreasing anesthesiology workforce in those countries, thus improving the quality of anesthesia and patient safety (10).

Cardiovascular and hemodynamic failure

Sepsis is one of the world's 10 leading causes of death. The cardiovascular system is directly affected by the occurrence of sepsis. On one hand, a myocardial depression, defined as a reversible impairment of cardiac function, occurs in 50% of cases, on the other hand, an endothelial dysfunction, characterized by an increase of the permeability of the vessels and an increase in the expression of adhesion and coagulation molecules, induces a prothrombogenic state.

Pr Diego Castanares-Zapatero participates in collaborative and transversal research activities between the two IREC poles CARD and MEDA, devoted to acute medicine thematic. He is associate head of clinic in the ICU, and is a post PhD researcher in the cardio-vascular pole of IREC.

Management of lung and respiratory parameters

The lung, and more generally the respiratory system, is very frequently failing in patients admitted to the intensive care unit. However, the physiopathological mechanisms involved in this failure are not completely known. Research in respiratory pathology in acute patients is currently articulated over several axes, through fundamental and translational research.

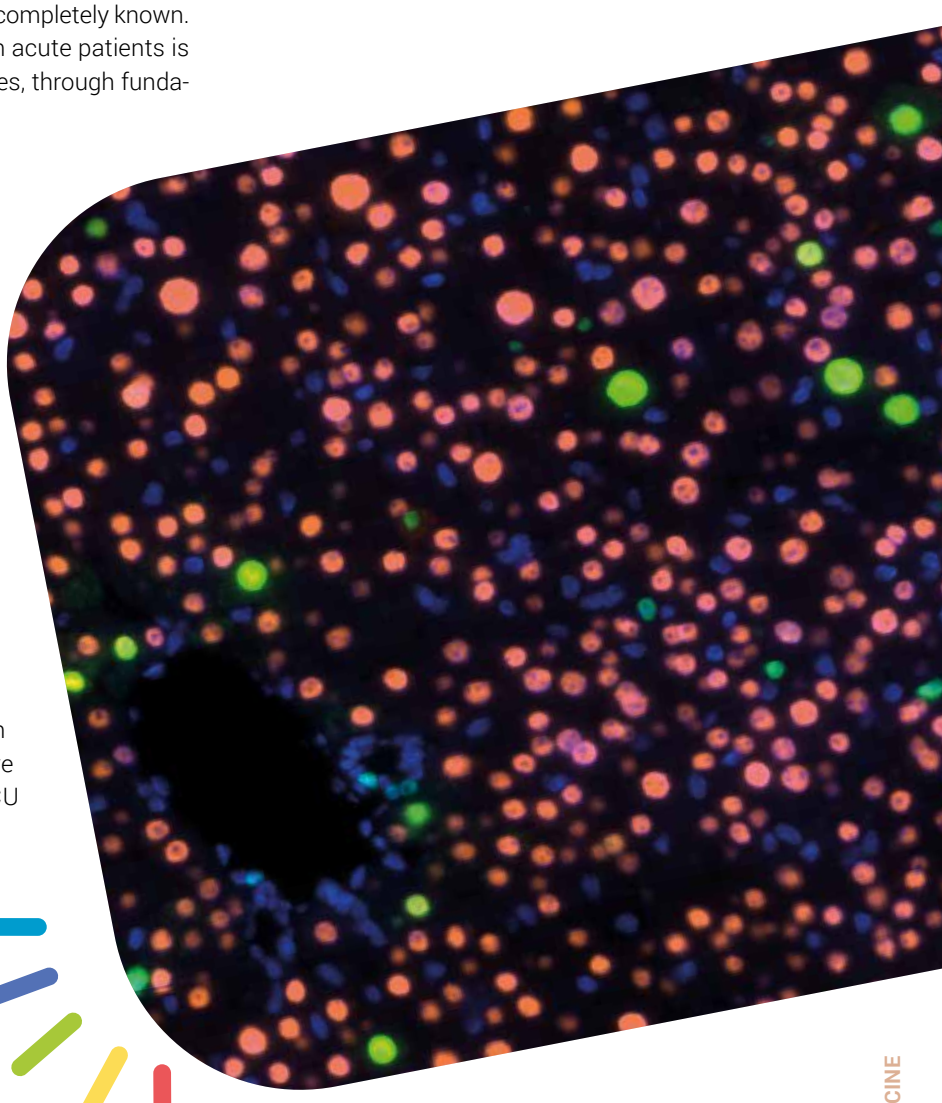
A. Dive, P.Bulpa and X. Wittebole participated in a Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE). In particular, they showed that the use of noninvasive ventilation in patients with ARDS was associated with higher ICU mortality when the patient is severely hypoxemic (11). The St-Luc ICU team reviewed the effect of aerosol delivery during mechanical ventilation, by performing a systematic review. They showed that lung deposition was as low as 20% (12). P. Bulpa was leader in the reflexion on which algorithm diagnoses invasive pulmonary aspergillosis best in ICU patients with COPD (13).

Ludovic Gerard also participates in collaborative and transversal research activities between the two IREC poles PNEUMO and MEDA, devoted to acute medicine thematic. Ludovic is a resident in the ICU and current PhD student. He has recently published a paper on the interest of open lung biopsy to identify a steroid-sensitive pathology in case of non-resolving acute respiratory distress syndrome patients (14).

Managing acute life-threatening poisoning

The intensive care unit is responsible for treating individual intoxications and evaluating potential new treatments in cases of rare and life-threatening poisonings.

Ph. Hantson and X. Wittebole confirmed their expertise in the management of severe poisoning with calcium channel blocker allowed us to be part of an international consensus experts panel for establishing a management consensus. We offered recommendations for the stepwise management of calcium channel blocker toxicity. For all interventions, the level of evidence was very low (15,16).



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REGENERATIVE MEDICINE

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Improving ovarian tissue transplantation using adipose tissue-derived stem cells

L. Cacciottola, D.D. Manavella, M-M. Dolmans

There is now sufficient evidence to support the feasibility and efficacy of ovarian tissue (OT) cryopreservation and transplantation for both fertility preservation and restoration purposes. However, there are still issues to address regarding the grafting procedure itself, since transplanted tissue suffers massive follicle loss in the early post-grafting period. To improve follicle survival after transplantation, our group recently developed a two-step transplantation technique for OT transplantation in a xenografting model using adipose tissue-derived stem cells (ASCs). ASCs were used in a model of xenotransplantation, were they were embedded in a fibrin scaffold and transplanted to the peritoneum of immunodeficient mice two weeks prior to transplantation of frozen-thawed human ovarian tissue. At 7 days post-transplantation significantly higher pO2 levels and greater human and murine CD34-positive endothelial areas, significantly higher primordial follicle survival rates and lower numbers of apoptotic follicles compared with the control group were observed. Our research model demonstrates that by adding ASCs to a fibrin scaffold before OT transplantation, faster and better graft reoxygenation and revascularization may be obtained, resulting in increased follicle survival and reduced follicle apoptosis.

Isolation and characterization of human ovarian cell populations

P. Asiabi, M.C. Chiti, C.A. Amorim

To support survival and growth of follicles, the transplantable artificial ovary should mimic the original organ, offering physical (3D matrix) and biological (cells) support. In order to replicate ovarian cell populations, we need to know the proportions of stromal and endothelial cells residing in the ovarian cortex. To this end, ovarian biopsies were obtained from six women (mean age: 49 years). The epithelial layer and medulla were carefully removed. The cortex was then finely minced and enzymatically digested and isolated cells were fixed. For cell characterization, immunostaining was performed for CD31 (endothelial cells) and inhibin-α (granulosa cells). Positive cells for each marker were counted and proportions of different cell populations were estimated from the total number of isolated cells.

Spatiotemporal changes in mechanical matrisome components of the human ovary from prepuberty to menopause

E. Ouni, D. Vertommen, M.M. Dolmans, C.A. Amorim

Fertility preservation research in women is increasingly taking advantage of bioengineering techniques to develop new biomimetic materials and solutions to safeguard ovarian cell function and the microenvironment in vitro and in vivo. However, available data on the human ovary are limited. We previously used proteomics before turning to quantitative image analysis to provide a readout of its characteristics. The ovary is among the most dynamic tissues in the human body, undergoing repeated cycles of growth and involution throughout a woman's life. It achieves this plasticity mainly thanks to its extracellular matrix (ECM) components. We investigated quantitative spatiotemporal changes in collagen, elastin, EMILIN-1, fibrillin-1 and glycopsaminoglycans (GAGs) from prepuberty to menopause, before conducting a closer analysis of the ECM surrounding follicles from primordial to secondary stages in both prepubertal and reproductive-age tissue. Our results revealed ECM deposition and remodeling in an age- and follicle stage-related manner. More precisely, our findings pointed to a more elastic ECM around reproductive-age follicles compared to the less compliant perifollicular ECM of prepubertal tissue. This work may offer a novel molecular basis to develop biomimetic scaffolds tailored to each follicle stage and age, bringing us one step closer to constructing an artificial ovary, or even discovering new mechanisms associating fertility preservation with ECM remodeling.

Creation of a bioengineered testicular organoid (TO) as in vitro model of male infertility, with a perspective to develop a transplantable human TO

M. Vermeulen, F. Del Vento, J. Poels, MG. Giudice, C. Wyns

We aim to elaborate a porcine bioengineered testicular scaffold to incorporate sorted and propagated human testicular cells with a view to increase knowledge on the spermatogonial stem cells (SSC) niche in vitro, and to achieve in vivo differentiation of SSCs after transplantation. By comparing different decellularization protocols of pig immature testicular tissue (ITT), we produced a testicular tissue scaffold allowing human Sertoli cell attachment and functionality. As testicular cells did not organize properly when cultured onto solid scaffolds, we produced a hydrogel from solubilized scaffolds that allowed proper seminiferous tubule-like structure with functional Sertoli and Leydig cells during culture. The TOs' behavior after transplantation is currently under investigation.

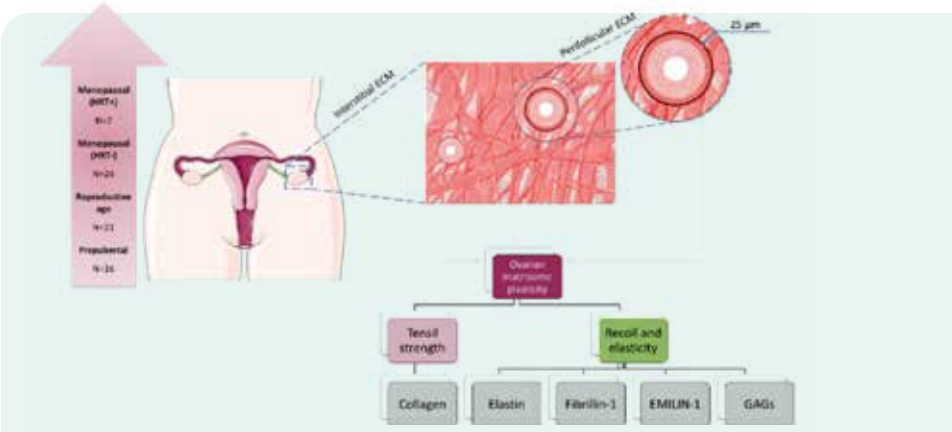

Figure1. Spatiotemporal follow-up of mechanical matrisome components of the human ovary from prepuberty to menopause.

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VASCULARIZED COMPOSITE TISSUE ENGINEERING RESEARCH GROUP (VCE)

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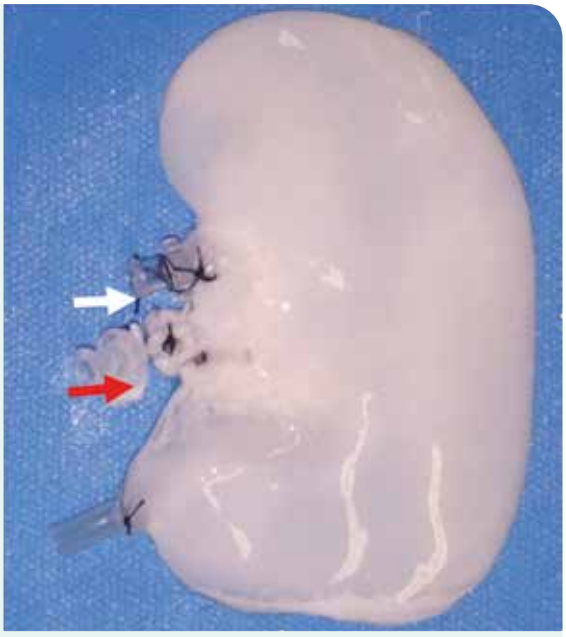
For two decades, Vascularized Composite tissue Allotransplantation (VCA) has represented a true revolution in the field of reconstructive surgery. However, the indications for such transplants remain very limited (fewer than 200 cases for limbs, less than 40 years for the face, worldwide) because of the need for an immunosuppressive treatment, burdened with significant systemic complications. In addition, recent results from long-term follow-up have shown a limited life-span of the graft, due to chronic vascular rejection. Aiming to overcome these limitations, tissue engineering applied to VCA, in a new reconstructive approach we called Vascularized Composite tissue Engineering (VCE), could represent a whole new alternative. Conventional decellularization technique, already used for simple tissues, such as the dermis or the valves, allows to remove cells and antigens from a native tissue by physical and/or chemical agents, while preserving the extracellular matrix and associated growth factors, the complexity of which is currently impossible to be reproduced, even with the most advanced synthesis techniques (i.e. 3D bioprinting). The major limitation here is the size and complexity of the treated tissues, restricted by the passive diffusion of the products, and the absence of an accessible vascular tree. The so-called "perfusion-decellularization / recellularization" (PDR) technique, previously described for solid organs (i.e. heart, kidney, lung), represents a variant of conventional bath-stirring techniques: by infusing the products directly by the arterial pedicle, it thus enables the production of very complex matrices, with a preserved, accessible and transplantable vascular system. In a new paradigm, the approach is to take the graft from the donor, transfer it to the laboratory where it will be decellularized, then recellularized into a bioreactor, partially or totally, with the recipient's cells. Thus, transplantation in the recipient will be performed with a totally immunologically compatible graft, removing current allotransplantation barriers. Our work initially hypothesized that the PDR technique could be applied to composite tissues, despite their great variability and tissue associations, characteristic of the body parts grafts. This required the development of a multi-purpose protocol, with recellularization-specific strategies and necessary bioreactors.

Vascular tree characterization, decellularization and recellularization

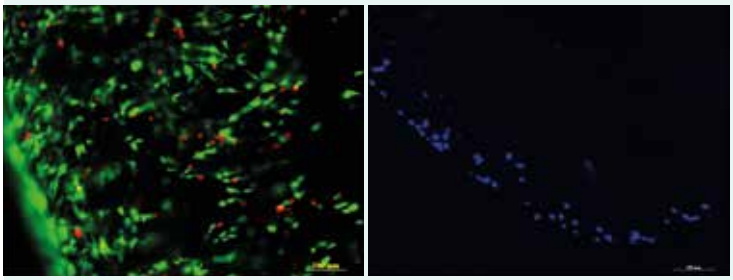
Louis Maistriaux, Jérôme Duisit, Catherine Behets, Greet Kerckhofs, Benoît Lengelé

Decellularized vascularized composite tissues such as face, ear, nose, hand or finger, have shown cytocompatibility with NIH3T3 and C2C12 cells as well as biocompatibility after implantation in animal model (rats or pigs). Complete and functional regeneration of the vascular network of the graft remains however the limiting step which can guarantee the complete recellularization of bioconstructed organs or composite tissues, either in vitro or in vivo. In continuation of the previous work on tissue engineering, we aim to study precisely the characteristics of vascular tree on native, decellularized and recellularized grafts in order to re-establish a physiological blood circulation, without thrombogenesis while restoring a capillary barrier preventing edema formation or interstitial hemorrhages into the matrix.

To this end, we developed a decellularized vascularized pig stomach graft in addition to the human finger model. We demonstrated the surgical harvest of stomachs and their decellularization process. Despite its low clinical applicability in patient, this model appears suitable for tissue engineering experiments including the study of the biological sequence of vascular tree regeneration, the elementary reendothelialization and the more complex goal of bi-compartment recellularization of both external and internal wall sides, in parallel to the human vascularized finger.



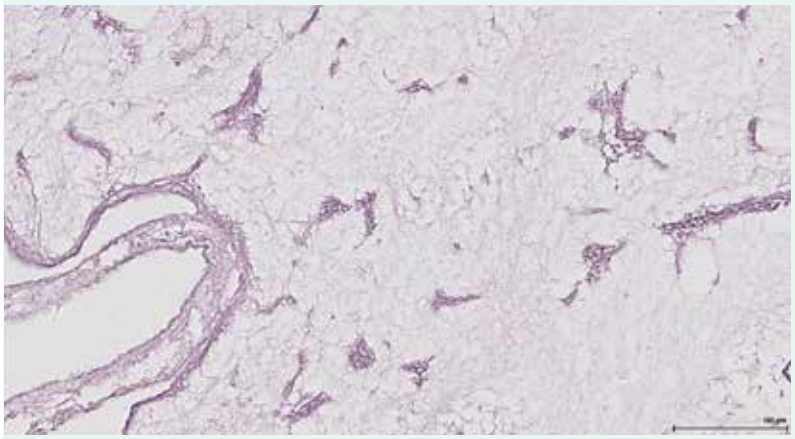
Decellularized pig stomach ECM with its vascular pedicle (red arrows) (with arrow = esophagus).



In vitro cytocompatibility test of gastric decellularized matrix with NIH3T3 after 9 days of static cell culture. Left: Live/dead staining (10x). Right: DAPI staining (10x).

In parallel of the vascular tree regeneration, we are also studying the use of a decellularized vascularized spleen matrix as a cell support of interest cells like endocrine cells (pancreatic, thyroid, adrenal cells).

Upper left: native rat spleen before decellularization
Upper right: rat spleen after decellularization



Lower: histological assessment of cell clearance and preservation of the extracellular matrix (H&E staining)

Perfusion-decellularization of vascularized bone matrix: application to porcine forelimb and human cranio-maxillo-facial subunits

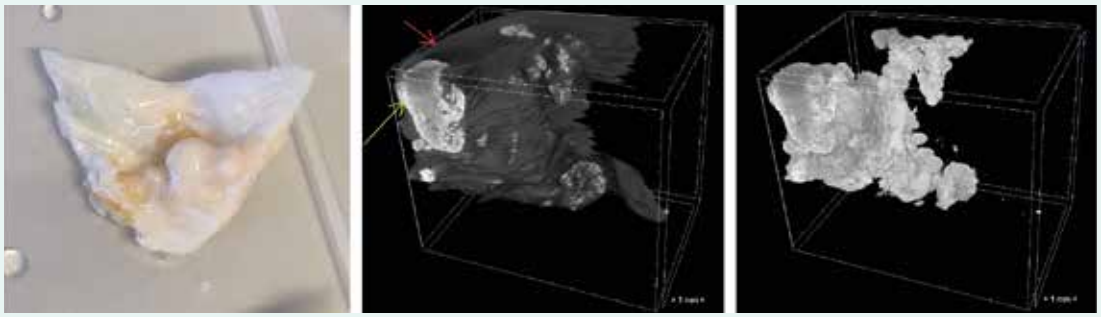
Guillaume Rougier, Louis Maistriaux, Jérôme Duisit, Catherine Behets, Greet Kerckhofs, Raphaël Olszewski, Benoît Lengelé

We here develop a protocol for perfusion-decellularization applied to vascularized porcine forelimb bone shafts and human cranio-maxillo-facial bone units. Porcine forelimbs including radius and ulna are harvested as free flaps based on the interosseous vascular pedicle and decellularized using a detergent-based perfusion protocol. Accordingly, unilateral human maxilla-mandibular complexes and calvarias based on the external carotid artery vasculature are decellularized, contralateral bones being tested as native. Histological analysis shows global disappearance of nuclei. DNA quantification results in 97% clearance for the surrounding muscle and periosteum and 100% for the cortical bone and bone marrow. Preliminary results of extracellular matrix proteins quantifications in decellularized scaffolds highlight different concentrations in GAGs and collagen according to the specific tissues (muscle, periosteum, bone marrow, cortical bone). pQCT attests an increase of Bone Mineral Density, whereas CBCT and nano-CT acquisitions show preservation of both vascular tree and micro canals. Such matrices could sort out in the future many issues in reconstructive bone surgery.

Micro-CT characterization of structural and functional properties of composite tissues

Camille Pestiaux, Greet Kerckhofs, Christophe Beauloye, Benoît Lengelé

Body parts (e.g. face, limbs, trunk) are made of composite tissues, which are organized in assembled tissue layers (e.g. skin, fat and cartilage for the ear) with an intertwining vascular and nervous network. Each of the layers is structured by its extracellular matrix (ECM) that provides physical and biochemical cellular support. By using advanced imaging techniques, such as contrast-enhanced microfocus X-ray computed tomography (CE-CT), the aim is to visualize and characterize, in an unprecedented way, the full 3D morphology and organization of the different types/layers of ECM and, if present, the intertwining vascular and nervous network in composite tissues. For this, both native and decellularized tissues will be used. The PhD of Camille Pestiaux will focus on heart valves, and her aim is to characterize the microstructure and the mechanical behavior of heart valves using CE-CT. For the first work, calcified aortic heart valves were used. MicroCT allowed to highlight the density variation inside calcified aortic valves (see figure 1). The next step will be to optimize CE-CT imaging to visualize the composition and organization of the soft tissues around the calcifications, to assess the tissue disorganization and better understand the progress of valve calcification.



Human aortic heart valve. Left - image of a thawed leaflet of an aortic heart valve. Middle - 3D rendering of a CE-CT dataset (using Hf-WD POM as staining agent) of the heart valve. The red arrow shows soft tissues and the yellow arrow shows the calcifications. Right - 3D rendering of the same CE-CT dataset, but only showing the calcifications (the brighter the color, the denser the calcification).

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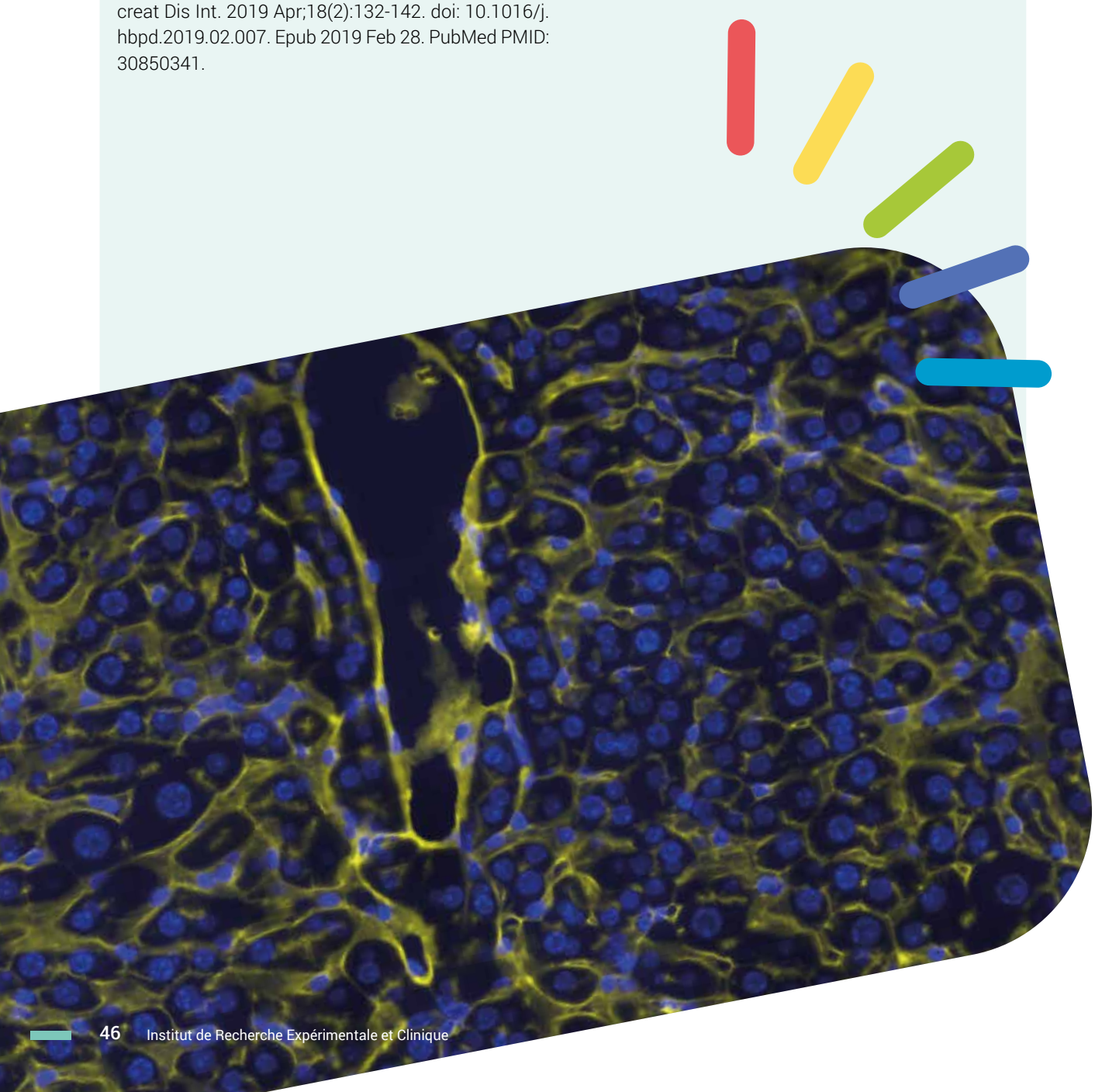

METABOLISM, OBESITY AND DIABETES

This theme brings together MD and PhD scientists from different IREC Poles who are active in two lines of research («Hormones and Metabolism» and "Cancer and Metabolism") with fundamental, translational and clinical aspects.

The Pole of Endocrinology, Diabetes and Nutrition (EDIN), the team of Philippe Lysy at the Pole of Pediatrics (PEDI), the Pole of Hepato-Gastroenterology (GAEN), the team of Pierre Gianello at the Pole of experimental surgery (CHEX) and the team of Marie-Christine Many at the Pole of Morphology (MORF) focus on the mechanisms of action of hormones and their therapeutic use in human diseases, with a large array of research on the causes and consequences of obesity and diabetes mellitus in different tissues.

The teams of Olivier Feron, Pierre Sonveaux and Cyril Corbet at the Pole of Pharmacology and Therapeutics (FATH) are dedicated to the study of cancer metabolism, including the metabolic plasticity of cancer cells with respect to fluctuating microenvironmental conditions (e.g., hypoxia and acidosis), tumor progression to metastasis, cancer-host cells relationships and resistance to treatments. Most research programs include translational aspects, with the aim of identifying new anticancer approaches targeting tumor metabolism. The team of JP Thissen at the EDIN Pole is currently investigating the mechanisms of cancer cachexia, with the aim to identify new targets to mitigate muscle atrophy and to develop new biomarkers for its diagnosis.

The central role of metabolism in human diseases, including cancer, and the ever-growing prevalence of obesity and diabetes worldwide generate a lot of research interest in other institutes of the Health Sciences Sector and in other Sectors of the University. The « OMEDIAB@UCLouvain.be » research center animated by Jean-Christophe Jonas and Philippe Lysy from the IREC institute has established close connections with these research teams and organizes quarterly scientific meetings confronting the views of clinicians and bench-scientists on specific questions.

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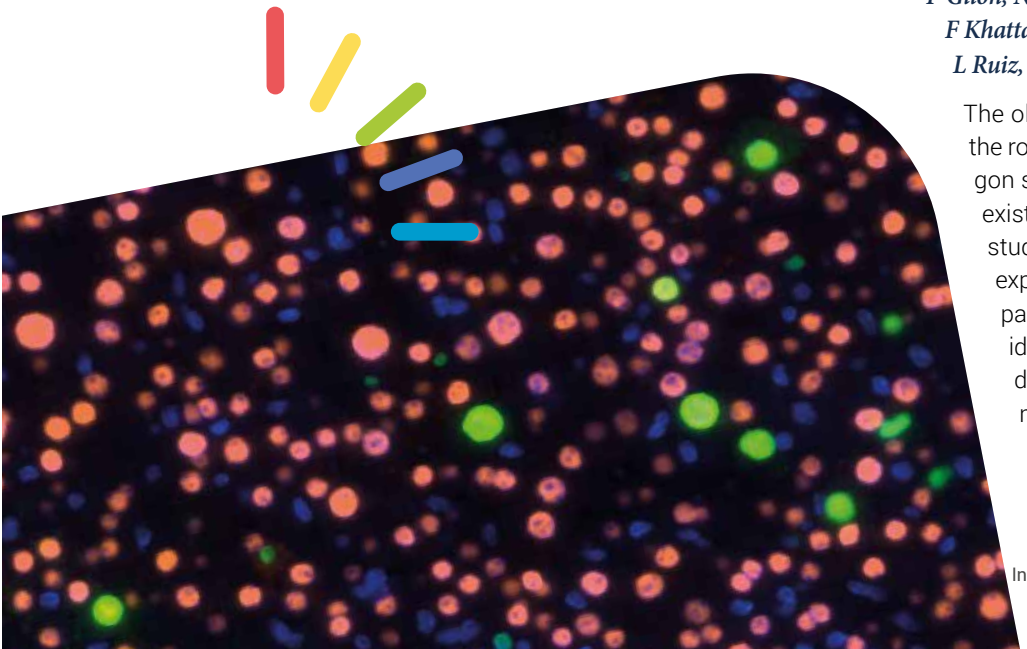
Research Projects

HORMONES AND METABOLISM

Several teams focus their research on the role of different organs in the pathophysiology of obesity and diabetes. Other teams investigate how to improve the diagnostic and treatment of patients suffering from a variety of endocrine diseases and collaborate on translational projects with teams from UCLouvain and outside.

ENDOCRINE PANCREATIC ISLET CELLS IN HEALTH AND DISEASE

Glucose homeostasis is mainly controlled by the endocrine pancreas organized in islets containing β-, α- and δ-cells that respectively secrete insulin, glucagon and somatostatin (SST). Our aim is to better understand how the secretion of these hormones is regulated under normal conditions and dysregulated in diabetes, and to improve cell replacement strategies to treat type 1 diabetes.



Study of intrinsic cellular mechanisms and of the crosstalk between islet cells in the control of pancreatic hormone secretion, and search for the causes of their defects in diabetes

P Gilon, N Antoine, F Belhaj-Aïssa, HY Chae, F Khattab, F Knockaert, E Gatineau, BK Lai, L Ruiz, B Singh

The objectives of this project are: (a) to study the role of β- and δ-cells in the control of glucagon secretion by glucose, and investigate the existence of a control intrinsic to α-cells; (b) to study the glucotoxic alterations of α-cell gene expression in models that recapitulate the impaired glucagon secretion of diabetes; (c) to identify how glucagon secretion is altered in diabetes and how we could restore a normal secretion; (d) to study the influence that α-cells exert on β- and δ-cells.

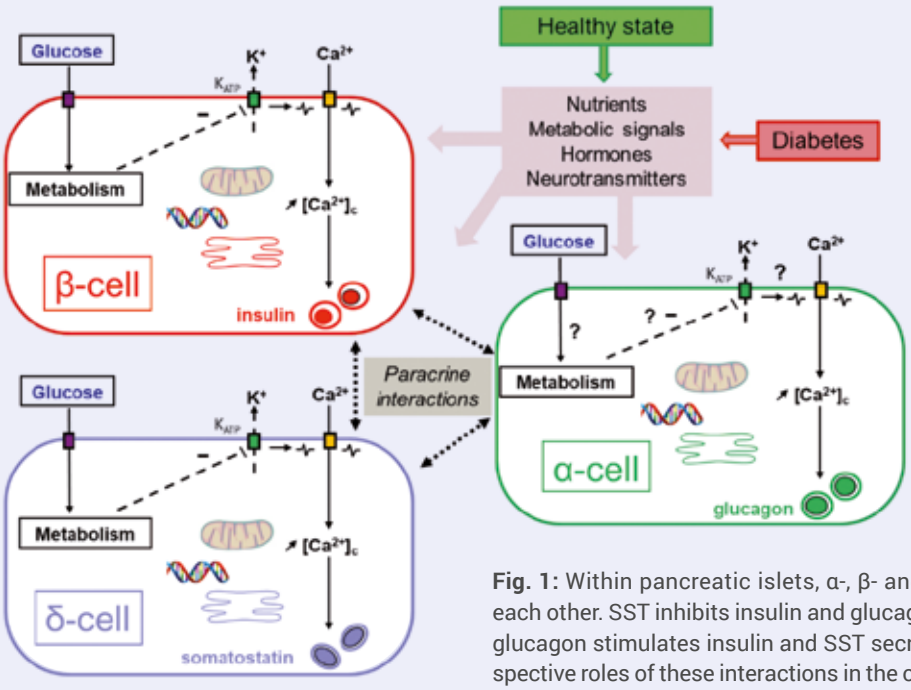


Fig. 1: Within pancreatic islets, α-, β- and δ-cells interact with each other. SST inhibits insulin and glucagon secretion, whereas glucagon stimulates insulin and SST secretion. However, the respective roles of these interactions in the control of islet hormone secretion by nutrients is only partly understood. In diabetes, the secretion of all islet hormones is altered.

Role of metallothioneins in mouse β-cell function and survival under normal and metabolic stress conditions

M Bensellam, AF Close, JC Jonas

Metallothionein 1 and 2 are among the top ten glucose-regulated genes in cultured rat islets. These proteins interact with Zn2+, a metal involved in insulin crystallization in the β-cell secretory granules. We have shown that metallothionein expression inversely correlates with glucose-stimulated insulin secretion in vivo and in vitro. While the reduced expression of metallothionein could play a role in the adaptation of insulin secretion in non-diabetic obese mice, its increased expression could contribute to the alteration of insulin secretion in type 2 diabetes.

Control of the subcellular redox state in pancreatic β-cells

AF Close, M Craigie, JC Jonas

We use protein-based fluorescent redox probes targeted to specific subcellular compartments to measure the acute and long-term effects of nutrients on β-cell subcellular redox state, and we test their role in the stimulation of insulin secretion and its alterations in diabetes. This project led to several publications, including a review written together with Leticia P Roma from Universität des Saarlandes (Homburg/Saar).

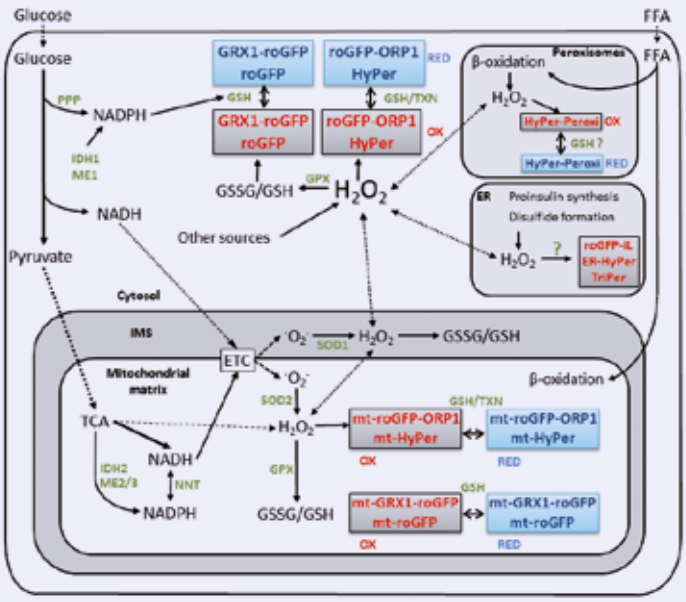


Fig. 2: Compartmentalized redox reactions and the genetically encoded probes used to measure the impact of nutrient metabolism on β-cell subcellular redox state. Schematic representation of the pathways by which nutrients affect NADH, NADPH, and GSH. Enzymes are shown in green, oxidized (OX) probes in red font, and reduced (RED) probes in blue font. Solid lines, enzymatic reaction, stimulation, inhibition; dashed lines, reaction by-product, or indirect effect; dotted line, transport, diffusion, or substrate shuttle; (?), unclear effect.

iPSCs-derived islet cells as a "disease in a dish" model

HY Chae, AF Close, P Gilon, JC Jonas, M Tariq

In collaboration with the group of Miriam Cnop at ULB, we study the function of iPSCs-derived β-cells from patients with rare monogenic forms of diabetes (e.g. Friedreich ataxia frataxin-deficient patients) and test the effect of antidiabetic drugs to improve their treatment.

Decreasing inflammation within islets of Langerhans

P Lysy, O Polle, S Welsch

Inflammation is a critical factor in the triggering of T1D. Cytokine antagonist therapies failed to improve long-term β-cell survival. To improve β-cell survival during T1D onset, we aim to specifically downregulate islet inflammation without affecting general immunity. We so far used the CRISPR/Cas9 system to downregulate IL1 and IFNY signaling in primary β-cells.

Improved secretory function of transgenic InsGLP-1Ser8M3R porcine islets

P Gianello, N Mourad, M Ramirez

The team of P Gianello has a long-term research program on the use of functionally-enhanced porcine pancreatic islets for xenotransplantation.

PATHOGENESIS OF LIVER DISEASES

The activities of the laboratory of hepato-gastroenterology (GAEN) are divided into 4 main themes devoted to the study of the pathogenesis of liver diseases. The ultimate objectives are to identify bio-markers to diagnose the disease, predict and follow the response to treatment and to identify new targets amenable to therapeutic manipulation.

The study of non-alcoholic steatohepatitis (NASH) and its progression to liver fibrosis and cirrhosis with a specific interest for the cross-talks between the liver and peripheral organs in the context of metabolic syndrome

I Leclercq, N Lanthier, B Delire, M Nachit, J Gillard, C Pichon, S Bott, N Feza-Bingi, S Meurice, M Beka,

This project explores several aims: (1) to better understand the mechanisms for steatosis and for inflammatory recruitment in a dysmetabolic context; (2) to explore the inter-organ crosstalk in NASH: In the one hand, we analysed the changes in the skeletal muscle compartment in NASH natural history. In the other hand, we demonstrated that failure to activate the brown adipose tissue in response to calorie overload contributes to NASH. We now explore the mechanistic role of bile acids in the process (see figure3).

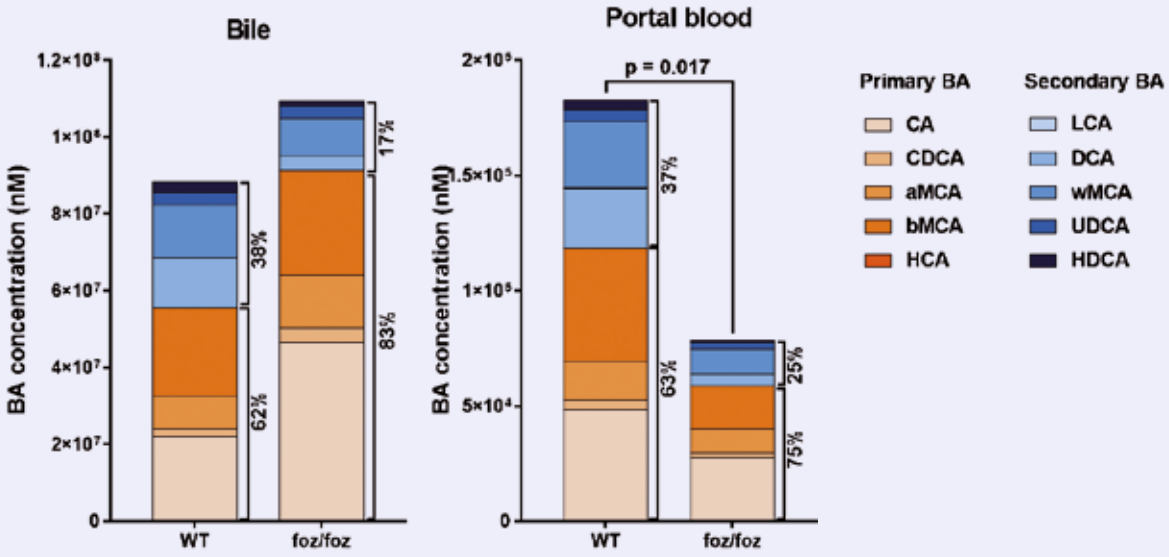


Fig 3: In high fat diet-fed foz/foz mice, an experimental model of non-alcoholic steatohepatitis, the pool of bile acids is altered with decreased absolute amount and relative proportions of secondary bile acids, reduced portal bile acid pool size and low hydrophobicity and TGR5 affinity of the bile acid pool compared to controls.

Alterations of the gut-brain-liver axis in the context of alcohol consumption: contribution to liver disease progression

P Starkel, N Lanthier, L Maccioni, B Pirlot

The aim of this collaborative project is to better understand the interrelation between alcohol consumption, gut microbiome, intestinal barrier dysfunction and immunity in alcohol-induced liver disease and damage of other target organs (e. g. the brain) associated with chronic alcohol abuse and alcohol dependence.

Progenitor-driven regeneration and ductular reaction in the context of chronic liver injury

I Leclercq, R Manco, N Lanthier, M De Rudder, B Pirlot, S Meurice, N Feza Bingi

Chronic liver diseases are characterized by expansion of the small immature cholangiocytes - a mechanism named ductular reaction - which have the capacity to differentiate in hepatocytes. We demonstrated that such newly formed hepatocytes are protected from carcinogenic transformation.

How to prevent liver insufficiency after extended liver resection: lesson learned from the ALPPS, a new surgical technique

I Leclercq, A Dili, R Manco, M De Rudder, B Pirlot, S Meurice

Portal hyperperfusion and "dearterialization" of the liver remnant are the main pathogenic mechanisms for Small For Size syndrome (SFSS). ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) induces rapid remnant hypertrophy. We demonstrated that ALPPS hemodynamically differ from SFSS by a much lower arterial flow in ALPPS's future liver remnant. We show that the ensuing hypoxic response is essential for the function of the regenerating liver by preserving sinusoidal morphology.

The study of pancreatic and neuro-endocrine malignancies

I Borbath

Pancreatic adenocarcinoma (PDAC) is a disastrous disease with a very poor prognosis and deceptive treatment efficacy. We bring new elements identifying the cell of origin of PDAC, and of intraductal papillary and mucinous neoplasm. In clinical work, we show the value of confocal endomicroscopy for PDAC diagnosis and participate in prospective multicentric international trials in the field of neuroendocrine tumor, hepatocellular carcinoma and biliary tract cancers.

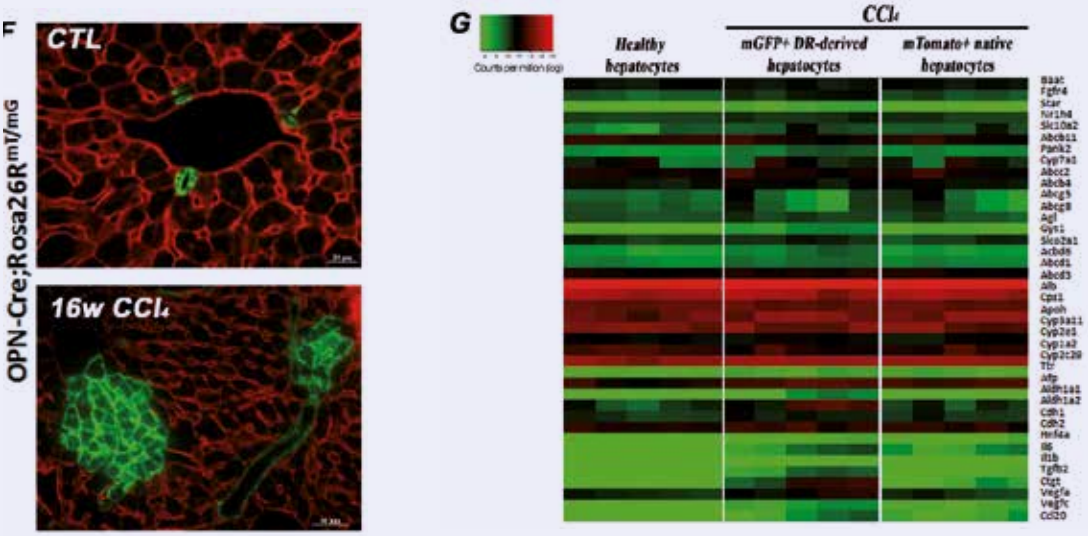
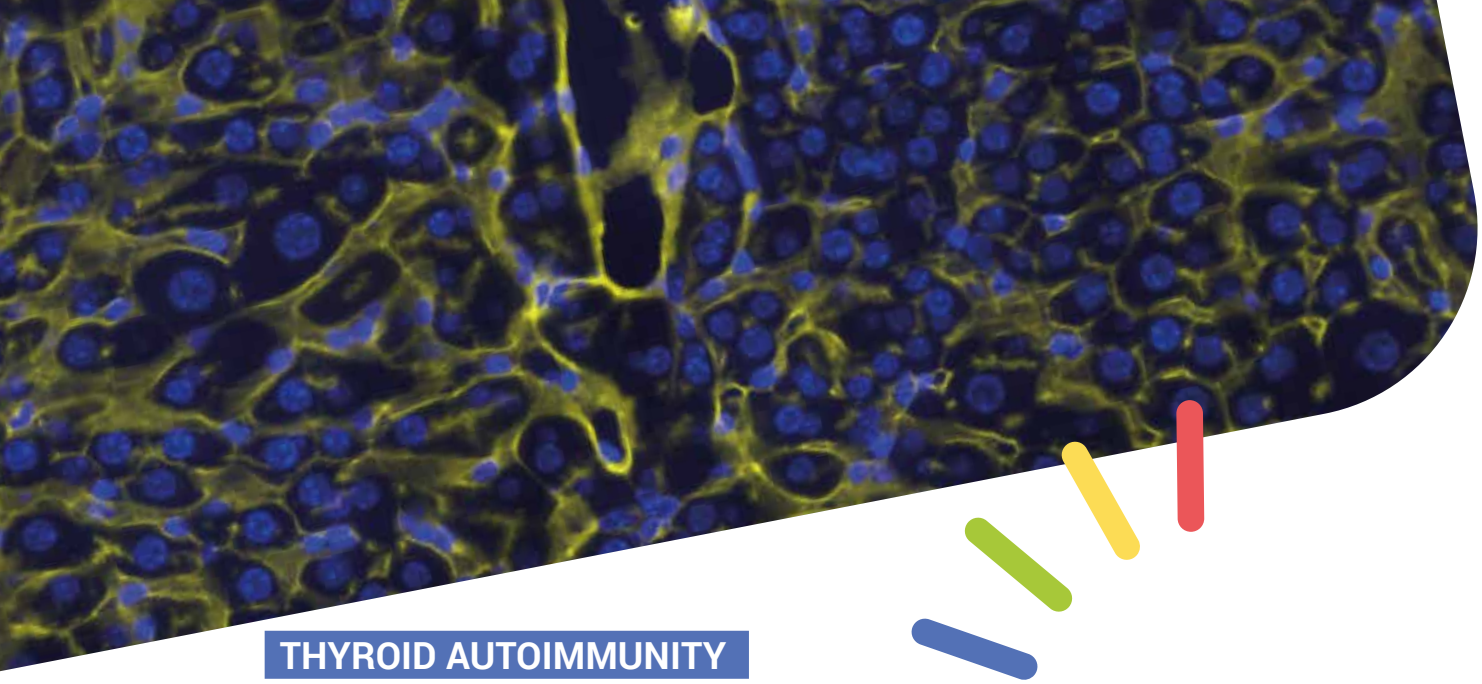


Fig. 4: In the chronically injured liver, biliary cells (green cells in controls) proliferate and differentiate in young fully mature hepatocytes (green cells in 16w CCl4) undistinguishable from native hepatocytes as demonstrated by RNA seq analysis on sorted cell populations.



THYROID AUTOIMMUNITY

Oxidative stress, epigenetic regulation, Graves' disease and associated orbitopathy

MC Many, J Craps; collaboration with C Dessy and V Joris (FATH), A Boschi and L Baldeschi, Saint-Luc Hospital, Ophthalmology Department, MC Burlacu (EDIN), and M Mourad (CHEX).

The main objective of the team is to unravel the mechanism(s) underlying Graves' disease. The aim of this project is to evaluate the potential impact of microRNA 199a family on oxidative stress and angiogenesis and their role in the development of clinical symptoms and systemic effects of Graves' disease, namely thyroid orbitopathy and pretibial myxoedema.

CLINICAL RESEARCH IN ENDOCRINOLOGY AND NUTRITION

Diabetes in children and adolescents

P Lysy, P Gallo, O Polle, S Welsch

The team of P Lysy focuses on the natural evolution of Type 1 diabetes in children and the production of tailored treatment algorithms to avoid dysglycemia during sports in these children. Furthermore, the team is thoroughly studying rare forms of diabetes to better understand the genetic grounds of these diseases and to establish diagnosis-centered treatment protocols.

Research by the division of endocrinology and nutrition, Saint-Luc University Hospital

D Maiter, O Alexopoulou, C Burlacu, M de Barsy, R Furnica, M Hermans, A Loumaye, L Orioli, V Preumont, B Vandeleene

The Division of Endocrinology and Nutrition at Saint-Luc University Hospital is conducting several clinical studies on type 2 diabetes, metabolic syndrome, bariatric surgery, rare thyroid diseases and Grave's ophthalmopathy, and adrenal and pituitary tumors. The Division is a recognized center in the European Network of Rare Endocrine Diseases (ENDO-ERN)

Research by the Service of Endocrinology and Diabetes at the CHU UCL Namur

J Donckier, E Delgrange, C Jonas

The Service currently focuses its research on clinical fields including thyroid cancer, diabetes complications, pituitary and adrenal diseases. This is achieved through case reports, review of clinical series and observational studies.

Emerging Biomarkers and mobile Health

D Gruson, V Cardone, Z Denamur, P Rousseau

We are investigating the added value of biomarkers and neurohormones for diagnosis and risk stratification of chronic diseases. The assessment of point of care assays for measuring their circulating levels is also one of our priorities. We are also investigating the value of mobile Health technologies (point of care testing and digital applications) for the management and empowerment of patients with chronic diseases.

Role of myokines in the remission of type 2 diabetes caused by bariatric surgery

JP Thissen, L Orioli, P Lause, C Verheyden

Over the past decade, bariatric surgery has been recognized as a therapeutic modality for obesity, but also for type 2 diabetes. We currently characterize the modifications in muscle secretome induced by bariatric surgery and determine their role in the improvement of insulin sensitivity of skeletal muscle and insulin secretion by the B cell.

ADIPOKINES IN METABOLIC AND INFLAMMATORY DISEASES

Adiponectin and its mimics on skeletal muscle

SM Brichard, M. Abou-Samra, N. Dubuisson, C. Selvais and L. Noel

The team of S Brichard is mainly involved in the study of hormones secreted by the adipose tissue (adipokines) in metabolic and inflammatory diseases. Their recent discovery that adiponectin receptor activation is beneficial in a model of Duchenne's muscular dystrophy has been recently awarded prizes for the therapeutic perspectives it offers to the patients. Adiponectin receptor agonists are now also tested in ageing and age-related sarcopenia.

Human obesity disrupts circadian clock function

E. Maury, L. Noel and SM Brichard

Clock function is particularly vulnerable to direct triggers of NF-κB activation in adipose tissue from obese subjects. Disruption of these clock oscillators may lead to abnormal chemokine production and low-grade inflammation in obesity.

Proposed model for the protective effects of adiponectin/AdipoRon on the dystrophic muscle.

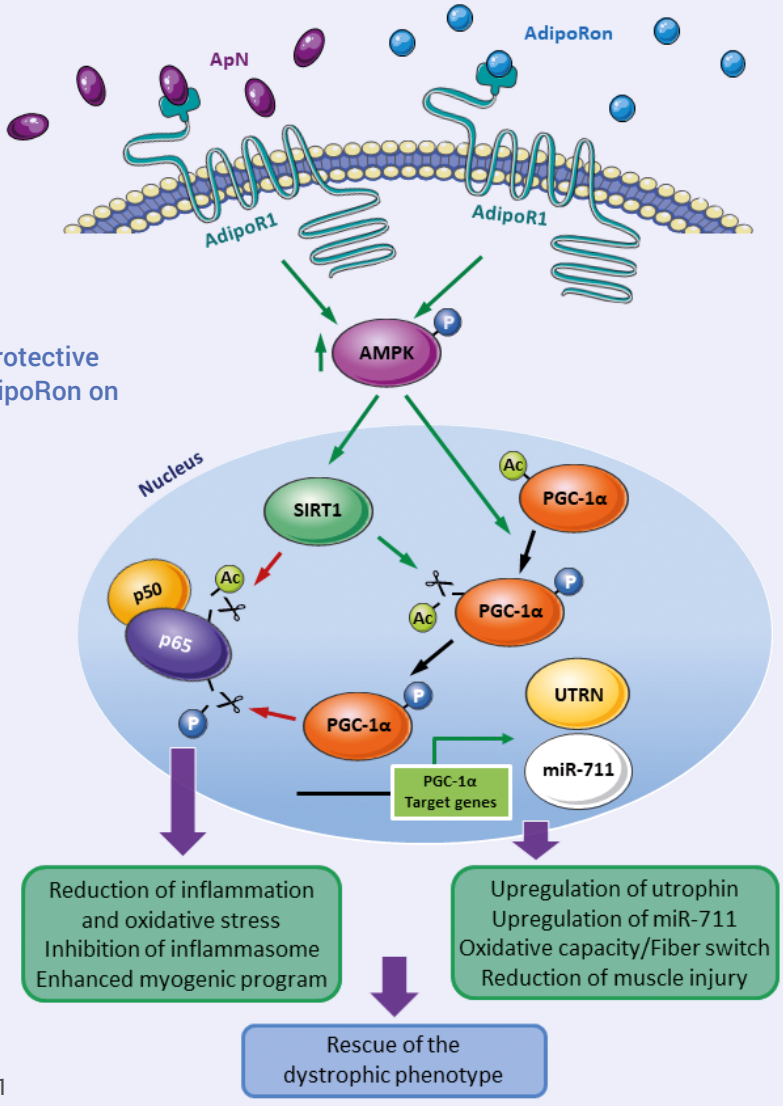


Fig. 5: Signal transduction mediating ApN and AdipoRon protection on dystrophic skeletal muscles: binding to AdipoR1 activates the AMPK/SIRT1/PGC-1α pathway. Briefly, ApN (AdipoRon) leads to AMPK phosphorylation/activation. P-AMPK then phosphorylates PGC-1α and indirectly increases the expression of SIRT1. SIRT1 in turn deacetylates and fully activates PGC-1α. Next, PGC-1α represses NF-κB activity by de-phosphorylation of the p65 subunit, while SIRT1 represses it by deacetylation. This results in upregulation of miR-711 and reduction of inflammation/oxidative stress and muscle injury, improved myogenic program, as well as enhanced utrophin expression, all processes helping rescue the dystrophic phenotype. Green arrow, stimulation; red arrow, inhibition.

CANCER AND METABOLISM

Identification of new biomarkers and molecular pathways involved in muscle atrophy caused by cancer cachexia

JP Thissen, A Loumaye, I Massart, N Pelet, P Lause

The team of JP Thissen is currently investigating the regulation of skeletal muscle mass by hormones, with the aim to identify new targets to mitigate muscle atrophy, and develop new biomarkers for its diagnosis. Animal and cellular models are developed in the lab to gain deep understanding of the observations that we made in human cancer cachexia.

Tumor metabolism and anticancer drug resistance

C. Corbet

The group of C. Corbet aims to characterize the metabolism of therapy-resistant cancer cells (incl. cancer stem cells) and the interplay thereof with the tumor microenvironment in order to develop new targeted therapies overcoming conventional treatment escape.

Tumor microenvironment and metabolism

O Feron

Current research topics of the team of O. Feron include the study of different aspects of the tumor metabolism impacting on, or influenced by, the tumor microenvironment, in particular hypoxia and acidosis. The lab has also implemented a technological platform to identify and validate new chemical entities targeting tumor metabolism and stimulating anticancer immunity, as well as innovative prognostic cancer biomarkers.

Tumor metabolism and metastases

P Sonveaux

The team of P Sonveaux currently investigates metabolic remodeling during metastasis and metabolic changes associated with acquired radio- and chemoresistance in cancer. It also collaboratively develops new drugs targeting the oxidative pathway of lactate in cancer.

EQUIPMENTS

- **Cell culture and molecular biology**
- **Construction and generation of defective adenovirus (biosecurity level 2)**
- **Evaluation of islet cell biology (dynamic hormone secretion in perifusion)**
- **Hormone RIA, ELISA and HTRF assays (automatic pipetting, Y and β counters)**
- **Clariostar multifunction plate reader with gas and temperature control (absorbance, luminescence, fluorescence, HTRF)**
- **Live-cell imaging systems (excitation and emission fluorescence ratio, highly sensitive EMCCD cameras)**
- **Confocal microscopy (spinning disc), TIRF**

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HEALTH AND MOVEMENT

Physical activity is included in the WHO main recommendations for health. Exercising regularly, every day if possible, is the single most important thing you can do for your health. In the short term, exercise helps to control appetite, boost mood, and improve sleep. In the long term, it reduces the risk of heart disease, stroke, diabetes, dementia, depression, and many cancers.

"Health and movement" is an interdisciplinary research topic assessing human movement in relationship with biological problems. It aims to better understand the mechanisms of disorders impacting patient's autonomy and physical activity, to improve the quality of treatment and reduce the cost of health care. It includes fundamental research regarding musculoskeletal pathophysiology and bone biomaterials, assessment of neuro-musculoskeletal system in rehabilitation, orthopedic, cranofacial and neurological patients, as well as assistive technologies for surgery and new standards for surgical accuracy measurements.

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HUMAN BIOMECHANICS

Biomechanics of human movement can be defined as the interdisciplinary which describes, analyzes, and assesses human movement to explore biological problems. Biomechanics, as an outgrowth of both life and physical sciences, is built on the basic body of knowledge of physics, chemistry, mathematics, physiology, and anatomy. Under the banner of interdisciplinary complementarity and especially around the very privileged between clinicians and researchers' link, the new research group is dedicated to human Biomechanics: the study of neuro-musculoskeletal system in orthopaedics (1) and neurologic patients (2), the assistive technologies for surgery and new standards for surgical accuracy measurements (3). Engineers, orthopaedic and maxillo-facial surgeons, physiotherapists and Physical Medicine & Rehabilitation therapists are found in a common scientific area to better understand the mechanisms of orthopaedics and neurologic disorders to improve the quality of care and reduce the cost of health care. In addition, the investigators associate the harvesting of all medical and computer data collected by high-precision tools in the surgical treatments, to better define the surgical precision.

Activity tracker, sensors to better assss patients in walking and freeliving conditions

C Detrembleur, P Mahaudens, J Lebleu, R Hage

Rationale, aims, and objectives Consumer-based activity trackers aim at quantifying physical activity in a wide range of contexts. Nevertheless, they need to be validated before they are confidently used. This study assessed the concurrent validity of the Nokia®Go against reference devices, according to different sensor locations, in two measurement conditions: during a walking task and during a 24-hour free-living condition. Methods We examined the agreement between devices and between locations in the number of steps and total sleep time by using intra-class correlation coefficient and Bland-Altman method. Results In the walking task, the agreement is good to excellent for steps between the Nokia®Go and the reference device. In the free-living condition, there is a systematic underestimation of steps in comparison to the ActiGraph. Excellent agreement was found between locations. The device worn at the hip indicated the lowest number of steps and the device located at the dominant wrist, indicated the greatest number of steps. Conclusions There are high discrepancies in step count between devices due to the different type of activities in daily life. The Nokia®Go may be confidently used for step counting during pure walking tasks, at different locations. However, the lack of concurrent validity with ActiGraph call for caution regarding their use in daily living conditions.

Development of a robotic upper limb assessment to configure a serious game

T Lejeune, G Stoquart, S Dehem, G Everard, A Lheureux

BACKGROUND: TheROBiGAME project aims to implement serious games on robots to rehabilitate upper limb (UL)motor function in children with cerebral palsy (CP). Serious game characteristics (target position, level of assistance/resistance, level of force) are typically adapted based on the child's assessment before and continuously during the game (measuring UL working area, kinematics and muscle strength).

OBJECTIVE: This study developed an UL robotic motor assessment protocol to configure the serious game.

METHODS: Forty-nine healthy children and 20 CP children participated in the study. The clinical assessment consisted of the child's UL length and isometric force. The robot assessment consisted of the child's UL working area (WA), the UL isometric and isokinetic force in three directions and the UL kinematics during a pointing task toward targets placed at different distances.

RESULTS: Results showed that WA and UL isometric force were moderately to highly correlated with clinical measures. Ratios between the UL isokinetic force generated on three directions were established.Thevelocityandstraightnessindexes of all children increased when they had to reach to targets placed more distant.

CONCLUSIONS: This protocol can be integrated into different serious games in order to continuously configure the game characteristics to a child's performanc.

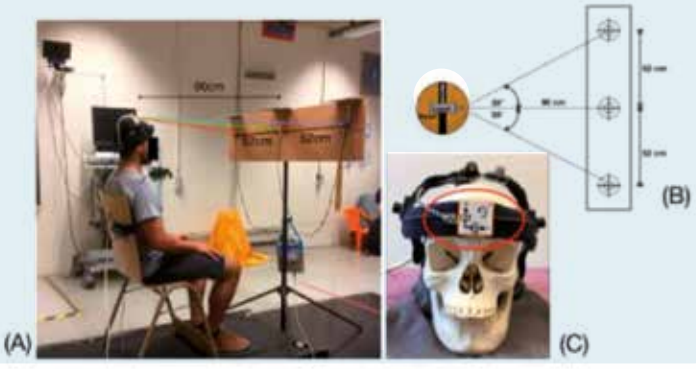

Figure 1. (A) DidRen Laser Test installation device. (B) Schematic view from above. The passage from one target to another induces an axial rotation of the head of 30° either to the left or to the right sides of the bodyline. (C) The Helmet worn by the participant with the Laser on the top. The DYSKIMOT sensor can be seen (red circle) at the front of the helmet.

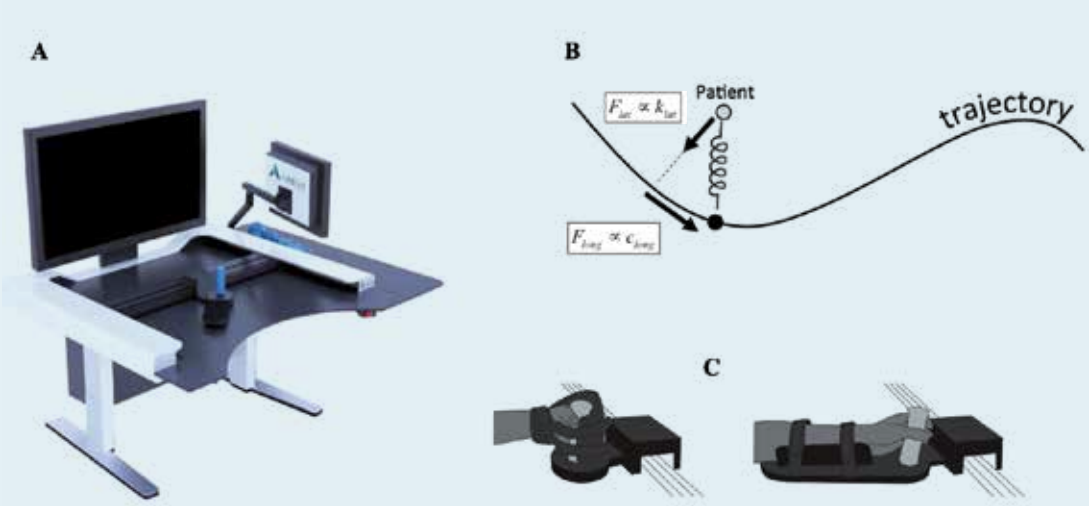

Figure 2. Illustration of (A) the REAplan® robot, (B) the assistance as needed and (C) the positioning of the hand in the glove and the forearm in the gutter.

Anatomical evidence supporting the revision of classical landmarks for genicular nerve ablation

O Cornu, C Detrembleur, L Fonkoue, E Kouassi

Despite their emerging therapeutic relevance, there are many discrepancies in anatomical description and terminology of the articular nerves supplying the human knee capsule. This cadaveric study aimed to determine their origin, trajectory, relationship and landmarks for therapeutic purpose. METHODS: We dissected 21 lower limbs from 21 cadavers, to investigate the anatomical distribution of all the articular nerves supplying the knee joint capsule. We identified constant genicular nerves according to their anatomical landmarks at their entering point to knee capsule and inserted Kirschner wires through the nerves in underlying bone at those target points. Measurements were taken, and both antero-posterior and lateral radiographs were obtained. RESULTS: The nerve to vastus medialis, saphenous nerve, anterior branch of obturator nerve and a branch from sciatic nerve provide substantial innervation to the medial knee capsule and retinaculum. The sciatic nerve and the nerve to the vastus lateralis supply sensory innervation to the supero-lateral aspect of the knee joint while the fibular nerve supplies its infero-lateral quadrant. Tibial nerve and posterior branch of obturator nerve supply posterior aspect of knee capsule. According to our findings, five constant genicular nerves with accurate landmarks could be targeted for therapeutic purpose. CONCLUSION: The pattern of distribution of sensitive nerves supplying the knee joint capsule allows accurate and safe targeting of five constant genicular nerves for therapeutic purpose. This study provides robust anatomical foundations for genicular nerve blockade and radiofrequency ablation

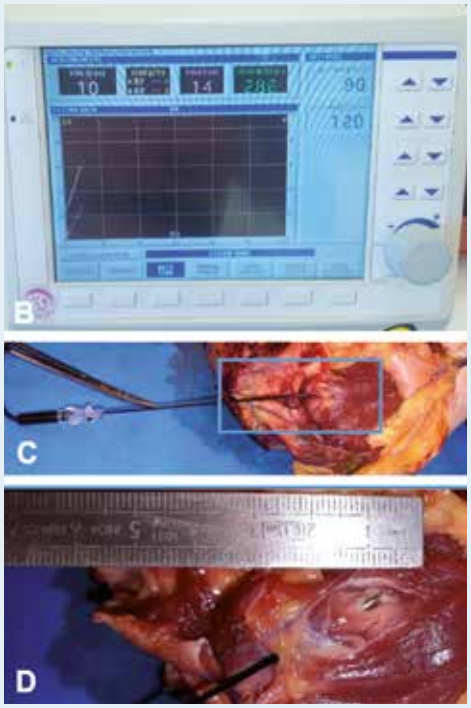

Figure 3. Radiofrequency (RF) lesioning on a cadaveric knee. A, electrodes placement (RFN and IPBSN). B, RF generator. C, RF lesioning of a muscle during the pilot trial. D, dissection around the active tip reveals a clearly visualized RF lesion. RFN, recurrent fibular nerve; IPBSN, infrapatellar branch of the saphenous nerve

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Exercise, aerosol and physiotherapy

The research projects of the group « Exercise, aerosol and physiotherapy » were based on the deposition of nebulized particles in the lung and in the nasal area. New tools for functional exercise capacity and for comorbidities related to lung diseases evaluation were also investigated. Studies were mainly performed in neuromuscular patients and in children to validate these new tools. The dysphagia was one of the main topics this last year. Exercise training programs and telemedicine were tested in new indications (cancer, congenital heart disease, sleep apnea, Ehlers-Danlos). Prehabilitation in cancer and exercise during radiotherapy were investigated. Physiological effects of airway clearance techniques were studied by the group including original tools of evaluations (electrical impedance tomography, lung clearance index). Moreover, the oxygen delivery was also included in the thematic of the group with studies about high flow and way of delivery.

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AWARDS AND HONORS 2019

- **On July 9th, Pr Benoît Lengelé was honoured by the French Ambassador, Mrs. Claude-France Arnould, the insignia of Knight of the Legion of Honour, for having practiced, together with Bernard Devauchelle and Sylvie Testelin, the first human face partial transplantation.**
- **On September 27, Pr Benoît Lengelé was awarded by Pr Mohammed Benlahsen, President of the University of Picardy Jules Verne (UPJV-Amiens) with the title of "Doctor Honoris Causa".**

The members of MORF focus on

- **tissue, cell and molecular interactions in several models or pathologies such as Grave's disease ophthalmopathy (see Metabolism, Obesity and Diabetes), osteoarthritis, osteogenesis imperfecta and parimplantitis**
- **composite tissue engineering allowing to improve allotransplantation and surgical tissue reconstruction (see Regenerative Medicine)**
- **anatomical investigations of spinal cord and fetal cardiovascular system to allow better clinical assessment.**

Osteoarthritis: effect of knockout of hyaluronidase Spam-1 on age-related bone and cartilage changes in mouse knee.

Sébastien Lafont, Daniel Manicourt, Catherine Behets

In order to investigate the role of Spam 1 hyaluronidase in age-related cartilage loss in the mouse knee, Spam1-/- and WT mice were euthanized at different ages from 10 to 52 weeks. Spam1-/- mice did not exhibit specific morphological characters up to 52 weeks of age. From 20 weeks, the proximal tibia of Spam1-/- mice had a significantly lower bone mineral density than WT mice. At 52 weeks, the modified Mankin score was significantly lower in Spam1-/- than WT mice. Spam1-/- chondrocytes expressed significantly less Hyal2 than WT ones at all ages and less Mmp13 at 52 weeks. Through all the experiment, the Hyal1 expression of Spam1-/- chondrocytes remained similar as that of WT chondrocytes. In conclusion, Spam1 knockout reduced significantly cartilage degradation in mouse knee whereas the chondrocyte expression of Hyal 1, Hyal 2 and Mmp13 was modified, suggesting a role of this hyaluronidase in cartilage metabolism.

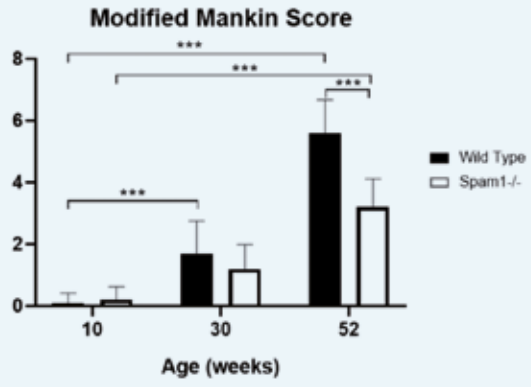

Figure 4. Histological analysis of. (A) Modified Mankin Score assessed in Safranin-O stained frontal sections in the right knee of WT and Spam1-/- mice aged 10, 30 and 52 weeks. Data are expressed as mean + SD. n = 10/age/group. ***: $p < 0.001$.

Osteogenesis imperfecta: therapeutic strategy through inhibition of osteoblastic Wnt pathway and Cathepsin K knockout in oim mouse

Mickaël Cardinal, Thomas Roels, Julie Fosséprez, Daniel Manicourt, Catherine Behets

In osteogenesis imperfecta (OI), vertebrae brittleness causes thorax deformations and leads to cardiopulmonary failure. Sclerostin-neutralizing antibodies have been shown to increase bone mass and strength in animal models of osteoporosis via osteoblast Wnt pathway stimulation. In a randomized controlled trial in oim/oim mice, an established model of human severe OI type III due to a mutation in Col1a2, 9 week treatment of sclerostin antibody (Scl-Ab) markedly reduced the fracture prevalence in the pelvis and caudal vertebrae, enhanced osteoblast activity (L4), increased cervico-sacral spine BMD, and improved the lumbosacral spine bone cross-sectional area. Scl-Ab did not impact vertebral height and body size but enhanced the cortical thickness and trabecular bone volume significantly in the Scl-Ab treated mice. These data suggest Scl-Ab may be beneficial for reducing vertebral fractures and spine deformities in patients with severe OI.
Another therapeutic strategy would consist in osteoclastic resorption inhibition, since bone resorption is increased in OI. Therefore, we used oim/oim and crossed them with CatK KO mice. We hypothesize that CatK KO

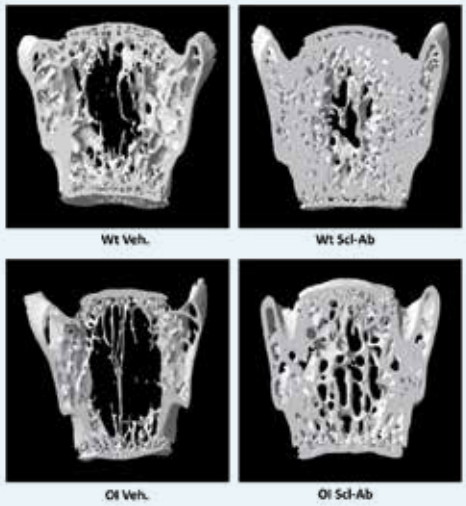

Figure 5. MicroCT analysis of L1 vertebral body of Wild-type (WT) and oim (OI) mice treated with either Vehicle (Veh) or Scl-Ab) from week 5 to 14.

in the osteogenesis imperfecta mice would reduce the number of fractures and increase the BMD in the axial skeleton. Female mice were distributed into 4 groups: wildtype - Wt, Osteogenesis imperfecta - Oim(-/-), CatK knockout - CatK(-/-) and double homozygous Oim(-/-) CatK(-/-) mice and were sacrificed at 13 weeks. CatK knockout in Oim mice reduces the fracture rate in pelvis and tail, increases cancellous bone mass throughout the axial skeleton of Oim(-/-) and Wt, improves the connectivity of trabecular bone and increases the number of trabeculae. Accordingly, CatK knockout in the Oim(-/-) improves different cancellous bone parameters contributing to a reduced fracture number. Therefore, CatK inhibition might be a promising therapy for human type III OI.

Besides bone fragility, patients with osteogenesis imperfecta (OI) type III have typical craniofacial abnormalities. However, in the osteogenesis imperfecta mouse (oim), few descriptions exist about craniofacial phenotype. Analysis of the heads of 4 mice genotypes (Wt, oim, CatK-/-, oim/CatK-/-) euthanized at 13 weeks showed that the craniofacial skeleton of oim mouse is frailer than the Wt one and presents dysmorphism, similar as the one observed in human with OI type III. Those abnormalities were not improved in the oim/CatK-/- group. These results suggest that oim mouse could serve as a complete model of the human OI type III, including the craniofacial skeleton. They also suggest that invalidation of Cathepsin-K has no impact on the craniofacial abnormalities of the oim model.

MicroRNAs and proteins profile in periodontitis and periimplantitis

Marco Macri, Catherine Behets, Jérôme Lasserre, Virginie Joris, Selena Toma

MicroRNAs (miRNAs) are small noncoding RNA molecules playing a major role in posttranscriptional gene regulation. They can induce dysregulation of molecular processes involved in inflammatory pathways and contribute to the development of chronic inflammatory diseases. Periodontitis and periimplantitis are characterized by a host immune and inflammatory response due to oral biofilm. The innate and adaptative immunity cooperate to limit the bacterial proliferation and launch the periodontal tissue healing. However, few data are available about miRNA expression related to periodontitis and periimplantitis. Therefore, we explore the expression of different miRNAs (146a, 155, 29b) and inflammatory proteins by comparing miRNA profiles of inflamed and healthy gingival and periimplant tissues. Preliminary data show a higher expression of miRNAs 146a, 155 and 29b, as well as TNF-α, NFKβ and Il-6, in periodontitis and periimplantitis gingival biopsies than in healthy gingiva. This overexpression of specific miRNAs and pro-inflammatory cytokines could provide new understanding of the pathogenesis of periodontal and periimplant diseases.

Morphometric study of human spinal cord segments

Anthony Nunès, Aegryan Lété, Catherine Behets, Aleksandar Jankovski

In absence of visible transverse segmentation on the surface of the spinal cord (SC), the functional segments are currently defined by the attachment of the spinal nerve roots. The length of those segments varies according to the extent of the attachment of the successive pairs of nerves in the different regions of the SC and cannot be assessed with imaging techniques. We here try to delineate and describe quantitatively each functional segment in order to constitute a diagnostic tool in clinics and research. Preliminary dissection data of 32 human cadavers (aged 85.5 ± 8.7 years, 18 women) show that the mean length of spinal segments vary from 4.7mm (S5) to 24.7mm (T6). This length is highly correlated to that of the vertebral canal in thoracic region, but lesser or not at all in the cervical and lombal regions. We will further focus on correlations between functional segments length, on one hand, and gender and length of the spine, on the other hand, in order to highlight differential lengthening of the SC segments.

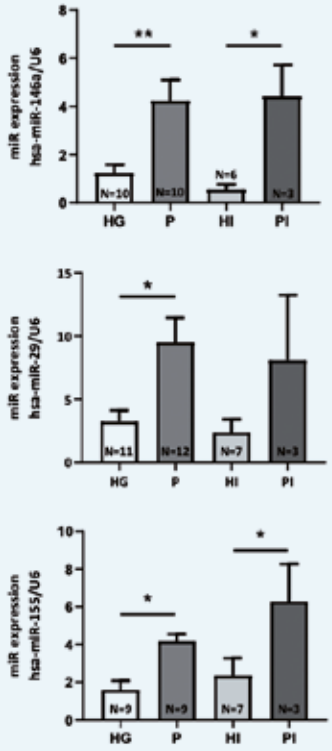

Figure 6. Expression of miR146a, miR155 and miR29b in human gingiva biopsies from patients presenting healthy gingiva (HG), periodontitis (P), healthy periimplant gingiva (HI) and periimplantitis (PI).

Stillborn child postmortem angiography and cinematic rendering technique

Jessica Vanhaebost, Xavier De Spiegeleire, Grégory Schmit, Catherine Behets, Emmanuel Coche

A Post-Mortem Computed Tomography Angiography (PMCTA) was performed in a stillborn girl in the department of Radiology. The cause of death was not determined during autopsy and no significant abnormality was observed during PMCTA. Arterial opacification was made by manual injection through the umbilical artery and after clamping the umbilical cord using 47 mL of a liposoluble contrast media (Angiofil® 6% mixed with low viscosity paraffin oil) to limit post mortem extravasation. Images were acquired immediately after injection using the following parameters: 128 x 0.6 mm, 80 kVp, 168 mAs. Total body coronal and oblique reconstructions were performed using a dedicated workstation and a cinematic rendering post-processing (Syngovia, Erlhangen, Germany) mode. This technique allows the visualization of small arteries down to 4 mm diameter. This new technique of postmortem angiography in stillborn could provide essential information for pathologist before autopsy and highlight very small vessels invisible at the autopsy to give answers to obstetrician and genetician about potential cardiovascular malformations not detected during pregnancy or during autopsy.

EQUIPMENTS

- **Serial 6-dof robot**
- **6-axis force sensor**
- **3D rapid-prototyping printer**
- **3D visualisation, simulation and planning platform**
- **3D measurement tool**
- **Dedicated softwares for image analysis and CAD/CAM**
- **3D haptic system**
- **Intraoperative surgical navigation system (sawing, milling)**
- **Intraoperative robotic imaging system**
- **Stiffness muscle apparatus**
- **Lab Gait: instrumented treadmill fitted with 3D force sensors, 8 infrared 3D cameras, 16 channels of Wifi**
- **EMG, ergospirometer**
- **Articial lung**
- **Rheometer**
- **Lung function equipmen**
- **Animal facility**
- **Conventional histology, histomorphometry, immunohistochemistry**
- **Molecular biology: PCR (genotyping), western blot**
- **Calcified tissue histology and microradiography**
- **Densitometry (peripheral Quantitative Computed Tomography)**
- **Anatomy lab facility**

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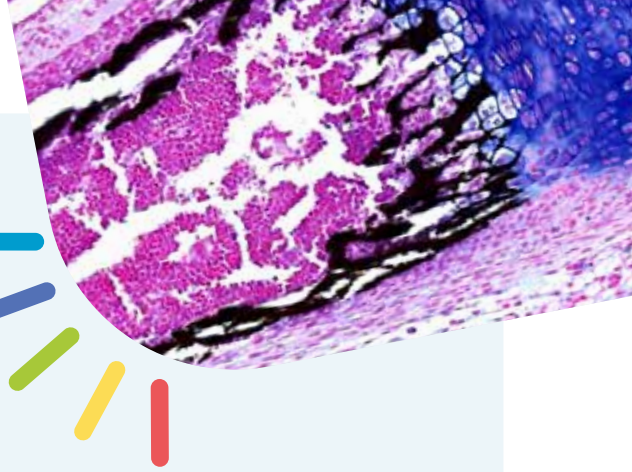

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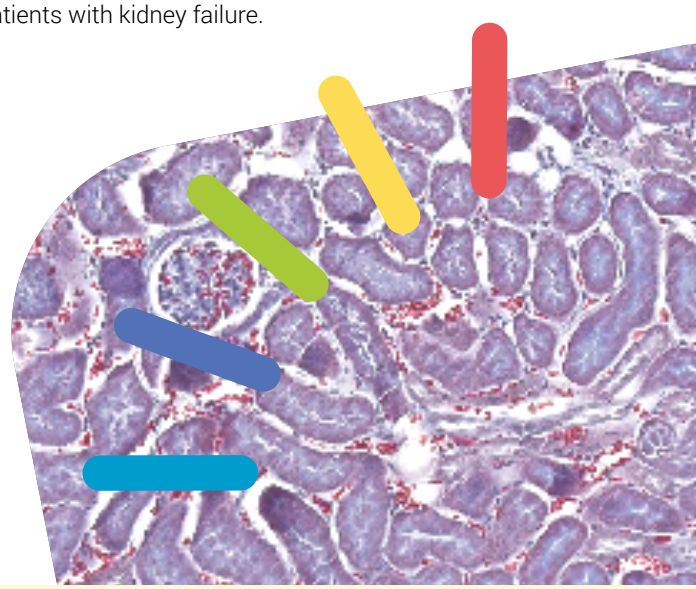
NEPHROLOGY

Chronic kidney disease (CKD) is a global public health burden, affecting as many as 10-15% of the population worldwide, and exceeding 20% in individuals above 60 years. Patients with CKD are at risk for kidney failure, requiring kidney replacement therapy (i.e. dialysis or transplantation) and suffering from severely reduced quality of life, CKD-related comorbidities and reduced life expectancy. Even in the early stages, CKD is associated with increased prevalence and severity of multiple disorders and adverse outcomes, and it is a major risk factor for accelerated cardiovascular disease and ageing.

Very few pharmacological interventions have been developed specifically for treating CKD, essentially due to (i) the lack of mechanistic understanding of chronic kidney damage; (ii) the unclear biochemical property needs required for novel therapeutic approaches; and (iii) the lack of renal biomarkers reflecting the severity of organ damage, complicating the design of effective clinical trials.

Our research is deciphering the genetic basis of kidney diseases to gain insights into physiological and disease mechanisms and potential therapeutic targets for CKD. We also use fundamental knowledge in the molecular basis of transport systems to improve treatment modalities for patients with kidney failure.



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Research Projects

Since the 1990s, the group is using a multi-level experimental approach to investigate mechanisms governing solute and water transport in various cell types including kidney tubular cells and endothelial cells. These studies are relevant for:

• Regulation of epithelial functions in rare and frequent kidney diseases;

• Mechanisms of water and solutes transport in peritoneal dialysis;

• Progression and treatment of autosomal dominant polycystic kidney disease, the most frequent form of inherited kidney disorder.

Epithelial cells lining tubular structures are of vital importance for all terrestrial organisms. In most mammals, the maintenance of water balance and plasma electrolytes levels critically depends on the appropriate handling of water and solutes by the kidneys. This essential function involves specific transport systems operating in the epithelial cells lining kidney tubules. The study of these processes in various segments of the kidney, their regulation and ontogeny, and the pathophysiology of genetic disorders yielded essential information about the functions of the kidney tubule in health and disease. Insights obtained through these investigations are relevant for common conditions such as blood pressure regulation, kidney stones, progression of renal failure, and cardiovascular complications of kidney diseases.

Transport mechanisms are also relevant for water and solute transport across the peritoneal membrane, sustaining peritoneal dialysis (PD) - a therapeutic modality for patients kidney failure. In that line, we developed innovative mouse and rat models of PD; established the influence of uremia and nitric oxide on the peritoneal membrane; documented the role of genetic factors to explain individual variability in transport parameters; substantiated the link between vascular proliferation or fibrosis and loss of ultrafiltration; demonstrated the role of water channels in PD; and unraveled the molecular mechanisms of the immune response during acute PD-related peritonitis and their impact on membrane integrity and transport. All these studies have immediate relevance for improving patient and technique survival on PD.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, accounting for up to 10% of all patients on renal replacement therapy. The disease leads to relentless development of cysts causing progressive kidney enlargement associated with hypertension and multiple complications. ADPKD is a systemic disorder with potentially serious complications such as massive hepatomegaly and intracranial aneurysm rupture. Until recently, there was not specific cure to delay the progression of ADPKD. Our group has participated in mechanistic and clinical studies paving the way for the development of novel therapies in ADPKD. In particular, we contributed to randomized controlled trials which evaluated the effect of tolvaptan, a vasopressin V2 receptor antagonist, on ADPKD disease progression. Based on these pivotal studies, tolvaptan has been approved as the first disease-modifying therapy in ADPKD.

Our investigations are based on a multi-disciplinary approach including studies on patients, human and mouse genetics, and analysis of mouse, fish and cellular models. Over the years, our studies benefited from fruitful international collaborations, leading us to initiate and participate in several European networks and collaborations, including with the National Institute of Health (USA). These collaborations allow us to develop our projects using genome, transcriptome and proteome analyses; genome-wide association studies; conditional KO and randomly mutagenized mice; in translation with studies of human tubular disorders collected at the European level. Our clinical center is a founding member of ERKNET, the European Reference Network for rare Kidney Diseases (EU-funded, H2020).

FINANCIAL SUPPORT

- **Actions de Recherche Concertées (ARC), Communauté Française de Belgique**
- **Commission européenne (EURenOmics, ERKNET, IMPROVE-PD, TrainCKDis)**
- **Fondations Roi Baudouin, Alphonse et Jean Forton**
- **Fondation Saint-Luc et Fonds de Recherche Clinique**
- **Fonds de la recherche scientifique - FNRS et FRSM**
- **Région wallonne**
- **Cystinosis Research Foundation (USA), NIH (Bio-PD)**

METHODOLOGY AND RESOURCES

- **Transgenic mouse models, conditional knockout, segment-specific invalidation**
- **Immortalized cell lines and primary cell culture systems**
- **Zebrafish models and reporter lines**
- **In situ hybridization, advanced quantitative RT-PCR**
- **Immunoblotting, immunoprecipitation, and immunohisto-/cyto-chemistry**
- **Transport studies in cells and native tissues (Ussing chamber)**
- **Deep phenotyping in mousemodels: kidney, cardiovascular, multi-systemic**
- **Biochemical profiling on dedicated platform optimalized for rodent samples**
- **Development and automation of ELISA**
- **Mouse models of peritoneal dialysis**
- **Biobanking: kidney failure samples (1000+); kidney biopsies (3000+); urine samples from isolated populations (6000); peritoneal biopsies (300+)**
- **DNA cohorts: ADPKD (300); rare kidney disorders (500); renal transplant (300); peritoneal dialysis (1000)**
- **EU-funded networks: EUROSPAN, EURenOmics, ERKNET, IMPROVE-PD)**

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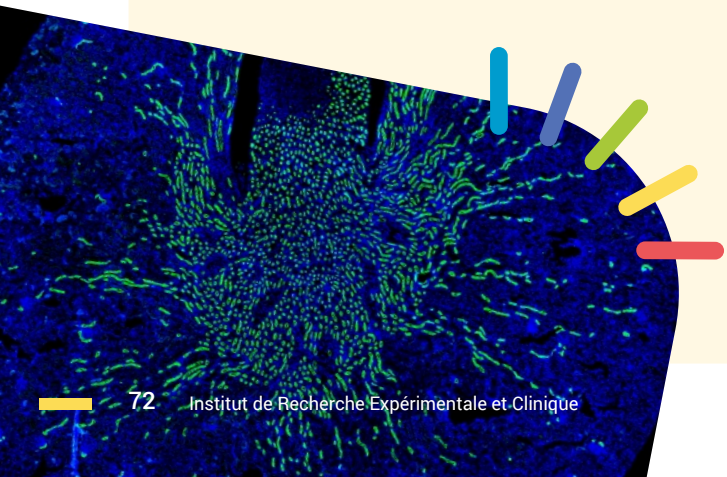

ONCOLOGY

The Oncology thematic brings together laboratories with basic and translational research activities. These laboratories have a strong link with the clinical research performed at "Institut Roi Albert II", the oncology center of Cliniques universitaires Saint-Luc. Regular interactions between clinicians and PI of these laboratories ensure a dynamic environment for scientific interactions and sharing resources. In particular, physicians and scientists from different IREC poles collaborate through various translational research programs to develop, validate and optimize new cancer treatments and biomarkers.

The year 2019 was certainly the year of Dr Cyril Corbet (Pole FATH) who was awarded with a mandate of "Chercheur Qualifié du FRS-FNRS" and obtained the Prix Galien for the work carried out in the last 7 years in the group of Prof. O. Feron. Their collaboration was also acknowledged end of december by a publication in *Nature Communications* about the role of tumor acidosis in metastatic dissemination and how to prevent it by using drugs targeting lipid metabolism. Among the 2019 achievements of the clinical research groups (Pole MIRO) are the participations to numerous clinical trials the results of which have been reported in leading scientific journals including **Lancet Oncol, Lancet, Ann Oncol, Clin Cancer Res, J Clin Oncol and New Engl J Med;** the diversity of evaluated targeted therapies speaks for itself: ramucirumab, atezolizumab, panitumumab, regorafenib, murlentamab, tisotumab, nivolumab, pembrolizumab, erdafitinib, trastuzumab emtansine, tucatinib, niraparib, etc.

Research Poles

POLE OF PHARMACOLOGY AND THERAPEUTICS (FATH)

Cyril Corbet, PhD

Olivier Feron, PhD

Pierre Sonveaux, PhD

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Octavia Cadassou, PhD
Natalia Trempolec, PhD
*Joao Santiago, PhD student (Télévie)**
Bastien Doix, PhD student (ITN Marie Curie)
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Website: https://uclouvain.be/fr/instituts-recherche/irec/fath/

POLE OF MOLECULAR IMAGING, RADIOTHERAPY AND ONCOLOGY (MIRO)

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Severine Rossomme, PhD
Pierre Scalliet, MD, PhD
Cédric van Marcke, MD, PhD
Stefaan Vynckier, PhD

Other groups from various IREC Poles are also involved in oncology research:

- **Pole of Pneumology, ENT and Dermatology (PNEU), S. Ocak**
- **Pole of Hepato-Gastroenterology (GAEN), I. Borbath, I. Leclercq, P. Starkel**
- **Pole of Pediatrics (PEDI), I. Scheers, E. Sokal**
- **Louvain Centre for Toxicology and Applied Pharmacology (LTAP), F. Huaux, D. Lison**

Website https://uclouvain.be/fr/instituts-recherche/irec/miro/

MAJOR FUNDINGS

Members of the IREC poles involved in cancer research are supported by ongoing grants from various foundations engaged in the fight against cancer (including Fonds Maisin, Fondation contre le cancer et Télévie) and from major regional, national and european agencies, including the following:

- **F.R.S.-FNRS-PDR-Télévie** (2018-2022) **O. Feron** and N.E. Sounni (ULg). Lipid droplets: origins and roles upon alterations of the tumor microenvironment.
- **WALLinov (2018-2022)**. **JP Machiels**. Predictive biomarkers for CDK4 inhibition in cancer.
- **F.R.S.-FNRS**: Grands Equipements. U.G002.19. Préat V (Spokesperson), **Sonveaux P**, Van Den Eynde B, Sokal E, Gallez B, Lucas S, des Rieux A, Vanbever R. In vivo optical imaging to track cells and to monitor biodistribution of therapies
- **Fondation Belge Contre le Cancer**: Fundamental Research Grant. FAF-F/2018/1282. **Sonveaux P**, Frédérick R. Lactate dehydrogenase B (LDHB) inhibition for anticancer treatment
- **EU Horizon2020**: Marie Skłodowska-Curie Innovative Training Networks (ITN-ETN) #860245, with **Sonveaux P** as one of the beneficiaries. International Network for training and innovations in therapeutic radiation (THERADNET).

FATH

Three groups within the Pole of Pharmacology and Therapeutics (FATH) are dedicated to the study of cancer metabolism, including the metabolic plasticity of cancer cells with respect to fluctuating microenvironmental conditions, tumor progression to metastasis, cancer resistance to treatments and cancer-host cells relationships. Most research programs include translational aspects, with the aim of identifying new anticancer approaches targeting tumor metabolism. Current research topics of the group of O Feron include the study of different aspects of the tumor metabolism impacting on, or influenced by, the tumor microenvironment, in particular hypoxia and acidosis. O. Feron has also implemented a technological platform to identify and validate new chemical entities targeting tumor metabolism and stimulating anticancer immunity, as well as innovative prognostic cancer biomarkers. The group of P. Sonveaux currently investigates the contribution of monocarboxylate transporters (MCTs) to tumor development, metabolic remodeling during metastasis and metabolic changes associated with acquired radio- and chemoresistance in cancer. They also collaborate with chemists to develop new drugs targeting the oxidative pathway of lactate in cancer. The group of C. Corbet explores how the issue of resistance to targeted therapies may be tackled by a better understanding of the interplay between TME and oncogenic pathways in part via a comprehensive dissection of associated metabolic preferences. The main oncology-related research programs in the FATH pole include the following studies:

- **Metabolism and signaling pathways driven by alternative tumor substrates (besides glucose and glycolysis): from the characterization to the development of innovative therapeutic targets**
- **Mitochondria at the crossroads of metastasis and resistance to anticancer therapy**
- **How acidosis and hypoxia independently and coincidentally influence tumor metabolic preferences**
- **How to recapitulate TME using 3D cultures including tumor spheroids and organoids**
- **Development of hypoxia-related prognostic biomarkers and lactate tracers for PET scan**

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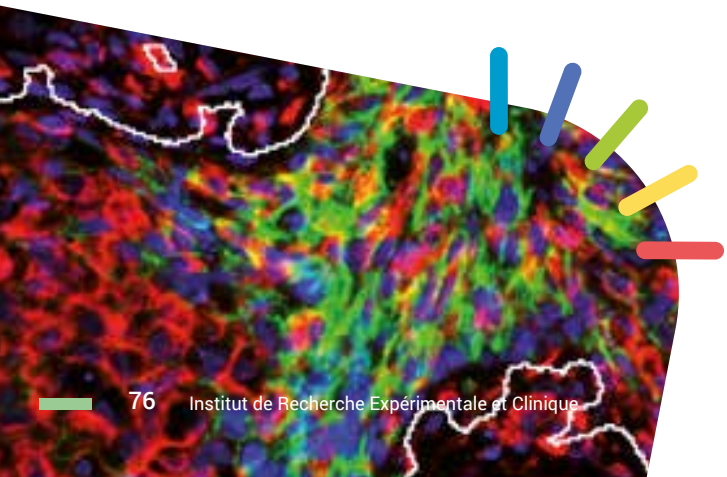
MIRO

The pole of Molecular Imaging, Radiotherapy and Oncology includes two independent laboratories, the lab of Molecular Imaging and Radiation Oncology led by Prof. John Lee, and the lab of Medical Oncology led by Prof. JP Machiels. The driving force of these two laboratories including both clinical and basic scientists is to build bridges between the clinical applications and the bench within their specific research areas.

MIRO (1/2) - Laboratory of Molecular Imaging and Radiation Oncology

Radiation Oncology -delivered as single modality or in combination with surgery and/or medical treatments- represents one of the most effective options to cure cancer at a local or loco-regional stage. It also has a prominent palliative role for the management of patients with metastatic disease. Although indisputable progresses have been made over the last few decades in the treatment of cancer, patients still die from uncontrolled loco-regional disease. Inaccurate definition of the target volumes, insufficient or sub-optimal radiation dose distribution, and intrinsic radiation resistance are, among others, factors that explain these treatment failures. In this framework, the Laboratory of Molecular Imaging and Radiation Oncology developed several lines of research aiming 1) at improving the radiation delivery, 2) at a better understanding of the role of tumour microenvironment in radiation response, 3) at integrating molecular imaging with various PET tracers in the radiation treatment process. This laboratory includes various scientists with as different background as physicians, biologists, physicists, radio-chemists and engineers. Here below is a non-exhaustive list of ongoing projects in the lab.

- **Mechanisms of cancer radiosensitization by human papilloma-virus (HPV)**
- **Robust planning and adaptive treatment in proton therapy**
- **Calorimetry in hadron beams**
- **Automatic segmentation of CT images using a registration-free atlas**
- **Preclinical in vivo imaging**



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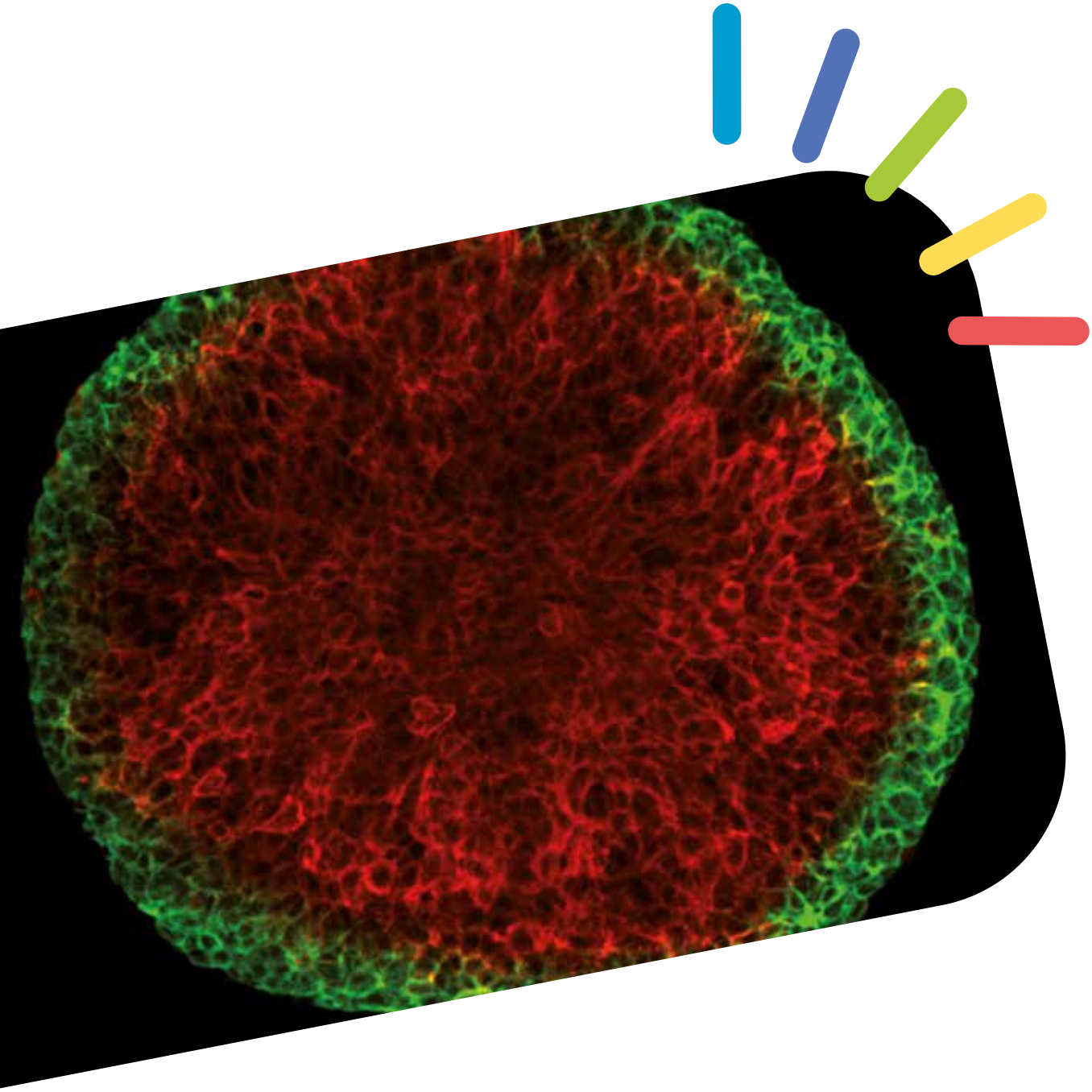
MIRO (2/2) - Laboratory of Medical Oncology

The development of targeted therapies has considerably modified clinical practice during the last ten years. Targeted therapies are new anticancer drugs that are more selective than chemotherapy for cancer cells because they aim to block the proteins involved in the genesis of the cancer process. They thus spare the normal cells while at the same time destroying part of the tumour, resulting in treatments that are potentially more effective and theoretically less toxic. However, many issues still need to be resolved since only a minority of patients benefits from this new approach. In this context, the lab of Medical Oncology is investigating new cancer treatment approaches (i.e. targeted therapies and immunotherapy), predictive and prognosis biomarkers (i.e. the role of tumor immune cell infiltration) as well as constitutional cancer predisposition parameters (breast cancer). Our pre-clinical models help us to better understand the best sequences of treatment as well as some mechanisms of treatment resistance that help us to design better clinical trials. Current research programs in the Lab of Medical Oncology include:

- **Optimization of molecular targeted therapies and immunotherapy, in particular for head and neck cancer**
- **Cancer Immunotherapy, in particular for melanoma**
- **Characterization of immune infiltration during the treatment of metastatic colorectal cancer, role of targeted therapies and implication for therapeutic immune-oncology development.**
- **New constitutional genetic alterations in patients with a family history of breast cancer**
- **Neoadjuvant combination of chemoradiotherapy and anti-PD-L1 antibody for patients with locally advanced rectal cancer**



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Institut Roi Albert II (Oncology Center)

The Institut Roi Albert II is the oncology center of the Cliniques universitaires Saint-Luc (http://www.institutroialbertdeux.be). This is the largest cancer center in the Brussels and Wallonia regions with more than 4000 new cancers diagnosed per year. All the cancers from the Adults and Children are treated in this center.

Besides the excellence in the daily cancer care, the Institut Roi Albert II has an internationally recognized expertise in clinical research. More than 300 patients are included in clinical trials per year. The center participates to all the development phases of new compounds including early drug development (phase 1 department, with expertise with "first in man" trials). The clinical investigators of the Institut Roi Albert II have developed many international collaborations. Among them, the European Organization for Research and Treatment of Cancer (EORTC) headquarter is implemented on the UCLouvain site and located just besides our offices (https://www.eortc.org).

AWARDS AND HONORS 2019

- **The 1st prize for best oral communication at the annual Belgian Association for Cancer Research (BACR) meeeting 2019. was attributed to Joao Santiago (O. Feron's team).**
- **The Prize Jeanne et Marie-François 2019 (Royal Academy of Medicine of Belgium) was awarded to Valéry Payen for his work on tumor metabolism in cancer metastasis (Pierre Sonveaux's team).**
- **The Prix Galien 2019 was awarded to Cyril Corbet for his work on the therapeutic targeting of tumor metabolism (O. Feron's team).**

REPRODUCTIVE MEDICINE

Our research activities on reproductive medicine focus on topics related to human reproduction, both male and female aspects:

- **Fertility preservation: ovarian and testicular tissue cryopreservation and transplantation in order to preserve and restore fertility in cancer patients. Development of artificial gonadal organs (see Regenerative Medicine section).**
- **Benign gynecological diseases affecting reproduction: endometriosis and uterine fibroids.**

A pluridisciplinary team (gynecologists, molecular biologists, clinical biologists and veterinary surgeons) investigate reproductive tissue physiology at the molecular and cellular level, both on patient biopsies and in experimental animal models.

The teams involved in these projects work in close cooperation with the gynecology, hematology and oncology departments of the Cliniques Universitaires Saint-Luc.

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OVARIAN TISSUE AND OVARIAN FOLLICLE CRYOPRESERVATION AND TRANSPLANTATION

Cryobanking

M.M. Dolmans, P. Jadoul

Chemotherapy and/or radiotherapy can induce premature menopause in young cancer patients especially if alkylating agents or bone marrow transplantation are needed. Certain benign conditions carry also the risk of premature menopause, such as recurrent ovarian cysts, and some autoimmune and hematologic disorders requiring chemotherapy.

Fertility preservation remains a challenge, particularly in case of breast cancer and hematologic diseases, which constitute the most frequent indications for fertility preservation (1,4).

The ovarian tissue bank at Cliniques Universitaires St Luc (one of the first and largest in the world) contains tissue from more than 700 patients. The pregnancy rate after autotransplantation is 40%, in line with the top 3 world best centers.

Each year, a workshop "Course on cryopreservation and transplantation of human ovarian tissue and preantral follicle isolation and in vitro culture" is organized in close collaboration between the research laboratory and the Cliniques Universitaires Saint Luc.

Development of an optimal cryopreservation procedure and transport condition for human ovarian tissue

C.A. Amorim, E.C. Leonel, J. Vilela, M.M. Dolmans

In the last years, we have been testing vitrification approaches in order to increase follicle survival after transplantation.

In a series of experiments conducted with non-human primate model (Papio Anubis), after vitrification, warming and long-term grafting, follicles were able to grow (5). However, their function may have been negatively affected by vitrification and/or transplantation, as expression of kit ligand and c-kit differed from fresh ungrafted tissue. Corpora lutea and/or ovulation stigma were observed in grafts (Fig. 1), indicating successful ovulation in all the baboons, with estrogen levels comparable to those in adult female baboons.

In parallel, we also decided to test another vitrification approach called stepped vitrification (SV). The goal of this strategy is avoiding ice crystal nucleation, while decreasing the toxic effects of high cryoprotectant concentrations. Human ovarian cortex was subjected to a SV protocol performed in an automatic freezer, which allowed sample transfer to ever higher concentrations of dimethyl sulfoxide (DMSO) as the temperature was reduced (6). DMSO perfusion rates were evaluated by X-ray computed tomography, ice crystal formation by freeze-substitution, and cell toxicity by transmission electron microscopy. Although cryoprotectant perfusion was considered normal and no ice crystals were formed in the tissue, ultrastructural analysis detected typical damage due to DMSO toxicity in both stromal and follicular cells. The findings indicated that the method failed to preserve follicles. However, adaptations can be made to avoid toxicity to follicles caused by elevated levels of cryoprotectants.

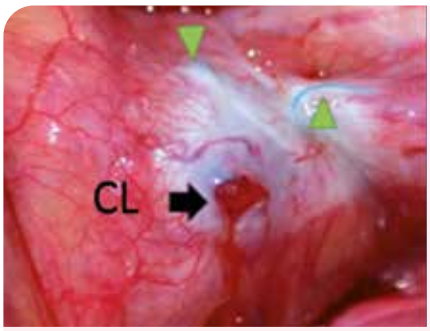


Figure 1. Corpus luteus (black arrow) found after 12 months of autografting of vitrified baboon ovarian tissue.

We are also working on the importance of the transport medium for ovarian tissue (7). Indeed, although low temperatures are known to decrease metabolic activity, we observed high lactate release from ovarian tissue transported for up to 24 hours at 4°C, shedding new light on the impact of ovarian tissue transportation media.

Immunodetection and quantification of enzymatic markers in theca cells

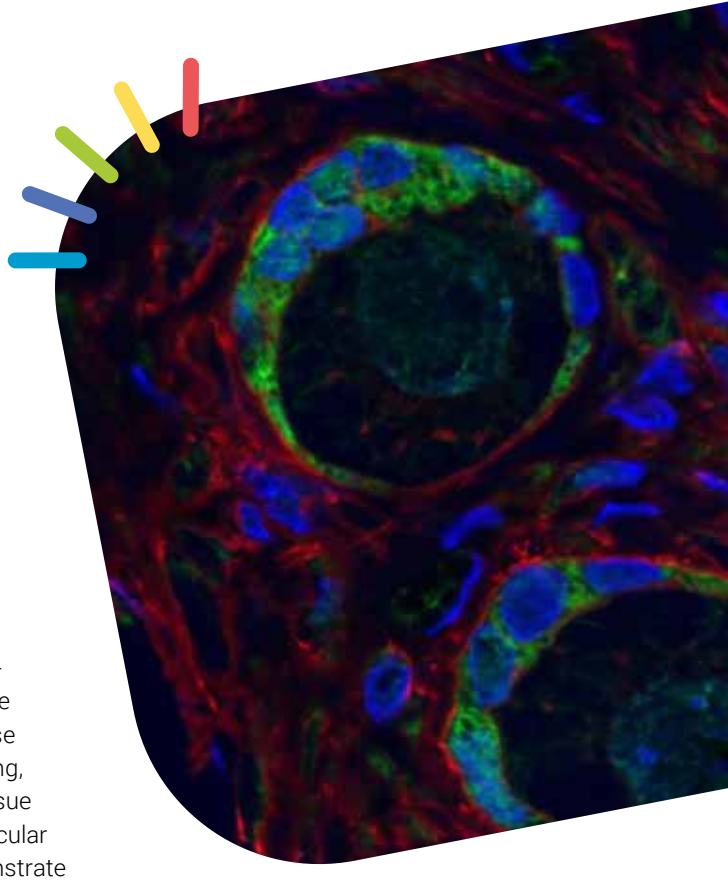
P. Asiabi, E.C. Leonel, M.M. Dolmans, C.A. Amorim

Follicle development requires complex bidirectional signaling between the oocyte, granulosa cells and ovarian stroma. At the primary stage, when follicles are activated, they start to secrete factors in order to recruit theca precursor cells from the stroma. The association between theca cells and granulosa cells is pivotal to steroid biosynthesis in the ovary. During the late secondary follicle stage, theca cells form a layer around granulosa cells, after which their steroidogenic function falls under the control of luteinizing hormone that activates the cAMP signaling pathway via a G protein-coupled receptor.

To better understand the localization and quantify expression of key steroidogenic proteins at both intracellular and tissue levels in the human ovary, ovaries from nine adult women (age range: 35-43 years) were collected and follicles from all the stages were studied (8).

Pathways of follicular activation after transplantation

R. Masciangelo, C. Hossay, M.M. Dolmans



Ischemia occurring during the first week after transplantation of frozen-thawed ovarian tissue leads to massive follicle loss through two mechanisms, which are follicular atresia and follicular activation (known as burnout effect). We focused our work on understanding the processes and pathways involved in follicular activation. We firstly confirmed the fact that after so little than 3 days of grafting, a significant decrease in the proportion of primordial follicles occurs together with a significant increase in the proportion of growing follicles, indeed demonstrating the process of follicular activation (9). Then, we highlighted the role of the PI3K and Hippo pathways in follicular activation, allowing to specifically target their effectors (10). In the case of patients having a low ovarian reserve, we judged wise to evaluate if promoting follicular growth prior to grafting, by cutting and incubating the frozen-thawed ovarian tissue with PTEN inhibitors and Akt stimulators, could boost follicular growth after grafting. However, our results did not demonstrate any beneficial effect of the procedure on promoting follicular growth after grafting (11).

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UTERINE FIBROIDS

G. Courtoy, MM Dolmans

Current treatments for fibroids are mainly surgical and expensive, so alternatives need to be found. It is, therefore, vital to develop and evaluate alternatives to surgical procedures, especially when fertility preservation is the goal. Selective progesterone receptor modulators (SPRMs) are synthetic compounds that have either an agonistic or antagonistic impact on target tissues determined by their binding to progesterone receptors.

When considering less invasive techniques (uterus-sparing options like myomectomy), the choice is guided by the size, number and location of fibroids, as well as the personal experience of the gynecologist and available equipment. There is now a growing body of evidence pointing to the crucial role of progesterone pathways in the pathophysiology of uterine fibroids. SPRMs should, therefore, be considered an alternative to surgical therapy, or at least an adjunct to surgery, as illustrated in the algorithms.

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DEEP NODULAR ENDOMETRIOSIS

S Mosele, CA Stratopoulou, MM Dolmans

Some symptoms of endometriosis, such as severe dysmenorrhea, overlap with those of uterine adenomyosis, a disease characterized by growth of endometrium into the myometrium. From a histologic point of view, deep endometriosis and uterine adenomyosis appear to be very similar.

To have an idea of the prevalence of their coexistence, we conducted a retrospective analysis in a series of 100 women with clinically confirmed deep posterior endometriotic nodules of ≥3 cm, who had all undergone MRI before surgery followed by excision according to the shaving technique. We applied Bazot and Darai's MRI classification of uterine adenomyosis, dividing the lesions into three subgroups: 1) internal adenomyosis (anomalies of the JZ); 2) external adenomyosis (posterior or anterior); and 3) intramural adenomyosis (cystic or solid).

In our series, external uterine adenomyosis was observed in 97% of subjects, strongly suggesting that uterine adenomyosis and deep endometriotic (adenomyotic) nodules are indeed linked. External posterior uterine adenomyosis was found in the posterior part of the uterus in 39 cases and the posterior part of the cervix in 40 cases, whereas in 20 cases the adenomyotic lesions were situated in the lowest part of the cervix involving the posterior vaginal fornix. In two women, external adenomyosis involved the posterior part of both the uterus and the cervix (Fig. 1).

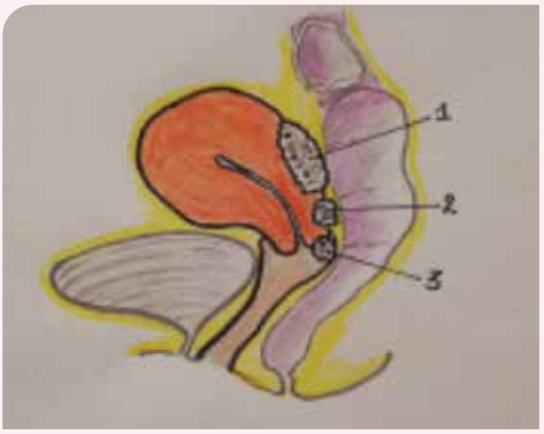

Figure 1 Diagram of the three localizations of external posterior uterine adenomyosis: 1) posterior part of the uterus; 2) posterior part of the cervix; 3) lowest part of the cervix involving the posterior vaginal fornix.

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FERTILITY PRESERVATION AND RESTORATION APPROACHES FOR PREPUBERTAL BOYS

Due to advances in cancer therapies, survival rates of pediatric patients are around 80%. Unfortunately, fertility in adult life is often impaired by their treatments. As gonadotoxic therapies are also used to cure non-malignant disorders a growing population is exposed to fertility-threatening therapies. In addition, some patient suffering of genetic diseases (e.g. Klinefelter syndrome) are also at risk of infertility in adulthood, mainly due to a dysfunctional testicular environment. Solutions to preserve fertility before puberty are thus awaited.

Our research focuses on two main axes:

a) Fertility restoration from cryopreserved immature testicular tissue (ITT) by autotransplantation and in vitro maturation

b) Creation of a bioengineered testicular organoid as an in vitro study model for the spermatogonial stem cell (SSC) niche pathophysiology

Fertility preservation and restoration from cryopreserved immature testicular tissue (ITT) containing SSCs

J. Poels, F. de Michele, M. Vermeulen, F. Del Vento, M. Kanbar, C. Wyns

We developed a slow-freezing protocol for prepubertal human testicular tissue that has yielded good structural integrity of cells and tissue. Consequently, indications for SSC banking were established and banking of ITT from prepubertal boys undergoing gonadotoxic treatments was started. As xenotransplantation of thawed ITT showed loss of a high proportion of SSCs, studies to optimize cryopreservation protocols were conducted. Studies comparing slow-freezing and vitrification of ITT showed that the grafting method and host environment were partially responsible of SSC loss. Fertility restoration with human frozen-thawed ITT has not been achieved so far and our research focuses thus on two different fertility restoration strategies from cryopreserved ITT:

1) Autotransplantation of the stored ITT for patients with no risk of contamination of the tissue by cancer cells. We demonstrated that encapsulation of mice ITT in hydrogels supplemented with VEGF nanoparticles improved vascular density, VEGFR2 activation and endothelial proliferation, and that spermatogonial survival following encapsulation of ITT in alginate doubled. Further improvement was achieved by supplementation of the hydrogel with anti-necrotic nanoparticles.

2) In vitro maturation of SSCs as a procedure that circumvents the risk of reintroducing cancer cells in a cured patient. We developed an organotypic culture system able to achieve Sertoli cell maturation, Leydig cell functionality and partial establishment of the blood-testis barrier. After optimizing culture media, we were the first team to demonstrate the successful differentiation of SSCs up to the haploid stage. Our current aim is to improve the efficiency of human ITT culture and complete the final maturation of the haploid cells.

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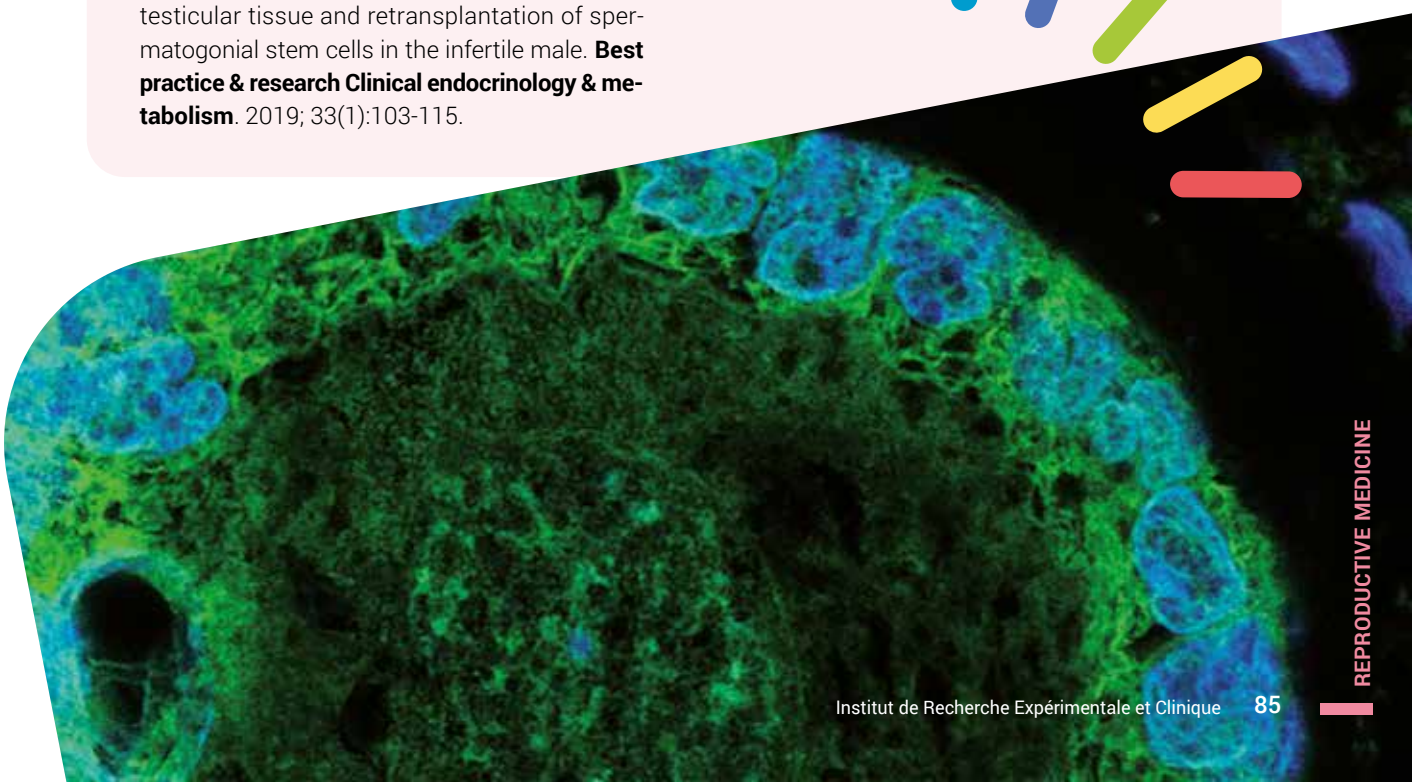

MICROBIOLOGY

Although the research theme "Microbiology, Infectious Diseases and Antimicrobial Agents" has to be developed, the pole of microbiology will contribute to its setting up, the research theme being intended to cover and promote collaborations in fundamental and translational research lines within the various research institutes and the Cliniques universitaires Saint-Luc.

The objectives of the various research lines are to better understand the causes and consequences of infectious diseases as well as factors related to the host and the infectious agent, to develop and apply innovative diagnostic approaches, to better understand the mechanisms involved in microbial resistance to drugs, to identify new therapeutic targets, to test new treatments in order to improve patient care.

The pole of microbiology includes the virology and the bacteriology groups and is devoted to clinical microbiology research. It acts as a Belgian National AIDS Reference Laboratory (ARL), and houses the National Reference Centers for *Clostridium difficile and Borrelia*, including expertise in the diagnosis of Yersinia, The group has also developed important activities in the fields of Mycobacteriology and rapid diagnosis of septicemia.

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BACTERIOLOGY

Diagnosis and epidemiology of C. difficile Infections (CDI)

Anne Simon, Michel Delmée, Eléonore Ngyuvula Mantu, Kate Soumillion, François Dufrasne

C. *difficile* is the main cause of hospital acquired diarrhea and has become one of the most frequent bacterial pathogen isolated in healthcare settings. Emergence of a hyper-virulent clone (called 'ribotype 027') in the first years of this century increased the morbidity and the mortality linked to the disease.

Our group has acquired a nationally and internationally renowned expertise in the diagnosis and the study of the epidemiology of C. *difficile* infections and is the National Reference Center (NRC) for this pathogen, a contract with ScienSano, the National Institute of Public Health was renewed in 2020 for 4 years in order to conduct national epidemiological surveys in collaboration with ScienSano and Belgian hospitals. Cultured isolates are collected and typed by ribotyping. Strains considered as possibly epidemiologically linked are sub-typed by MLVA (multilocus variable number tandem repeats analysis). A typing project by whole genome sequencing (WGS) in collaboration with the French National Reference Center was initiated in 2018.

Development of metagenomic analysis of microbiome for clinical use

Jean Ruelle, Eléonore Ngyuvula Mantu, Kate Soumillion, Benoît Kabamba

Project of Dr. Jean Ruelle: development of metagenomic analysis for clinical use in an accredited framework: the primary objective is to make available in the short term to clinicians, researchers and industry or third parties outside the University a metagenomic analysis service for the microbiome. Our ambition is to offer a quick response time within an ISO15189 accredited framework.

The longer-term secondary objective is to demonstrate its cost-effectiveness for health thanks to clinical collaborations, in order to ensure the sustainability of the analysis on the basis of stable funding.

Microbiological diagnosis of septicemia

Hector Rodriguez-Villalobos, Alexia Verroken

Bloodstream infections are associated with high rates of morbidity and mortality and the rapid initiation of an appropriate antimicrobial treatment is crucial.

The microbiology laboratory plays a major role in the diagnosis of bloodstream infections through the identification and susceptibility testing of the pathogen causing the disease.

The projects in 2019 focused on reducing time to AST results. The first study evaluated the microbiological and clinical performances of an innovative tool based on light scattering measurements and allowing susceptibility testing directly from positive blood cultures. The turn-around-time of this approach is approximately 5-7 hours compared to 18-24 hours with actual routine AST techniques. Microbiological performances compared to routine antimicrobial susceptibility testing for Gram negative and Gram-positive bacteria reached respectively 89.5% and 88.1%. Clinical evaluation of the tool showed a high percentage of opportunities allowing treatment tailoring of patients with bloodstream infections within a reduced timing compared to subculture antimicrobial testing.

The second study challenges MALDI-TOF mass spectrometry for the rapid detection of beta-lactamases produced by blood culture strains. Third generation cephalosporin and carbapenem hydrolysis by strains producing the ESBL- and carbapenemase is measured by the disappearance of antibiotic pics and the appearance of degradation components. MALDI-TOF MS testing is performed directly from a positive blood culture bottle growing an Enterobacteriaceae /Pseudomonas aeruginosa or Acinetobacter baumannii strain. At present 80 Enterobacteriaceae have been tested for the detection of resistance to third generation cephalosporins and a concordance of 82% has been observed. Additional testing is ongoing.

Tuberculosis and Mycobacteriology

Anandi Martin, Eléonore Ngyuvula Mantu, Kate Soumillion

Within three years, the Tuberculosis and mycobacteria research group has gained national and international visibility.

Concerning non-tuberculosis mycobacteria (NTM), our laboratory provides diagnostic capacities for Saint-Luc academic hospital and other clinical laboratories based in Belgium and abroad. Recent research projects include the development of diagnostic methods for the detection of resistance of NTM to new compounds such as bedaquiline. Mycobacterium abscessus is one of the NTM that are the most resistant to antibiotics.

The first project aims to establish a novel M. abscessus infection model in *Galleria mellonella larvae* (wax worms), the second project focuses on the study of the effect of efflux pump inhibitors on the susceptibility of M. abscessus to bedaquiline and other antimycobacterial drugs, the third project is to understand the molecular mechanism of action of bedaquiline and the development of resistance and the fourth project aims to study new antibiotic strategies to enhance current treatment options for M. abscessus infections in biofilms using a combination of different enzymes and antimicrobials drugs.

Borrelia burgdorferi

Benoît Kabamba-Mukadi, Najet Lamarti, Anne-Thérèse Pâques

In 2019, the Borrelia NRC contributed to the publication of an article evaluating the value of seroprevalence data as surveillance tool for Lyme borreliosis in the general population in Belgium. Although the use of residual samples for seroprevalence estimates has several advantages, it seems to be a limited tool for serological surveillance of Lyme borreliosis in Belgium, other than follow-up of trends if repeated over time. In 2019, the NRC did the evaluation of the kits Testline (Alphadia) and Euroline Borrelia RN-AT IgG and IgM (Euroimmun) compared to recombLine (Mikrogen).

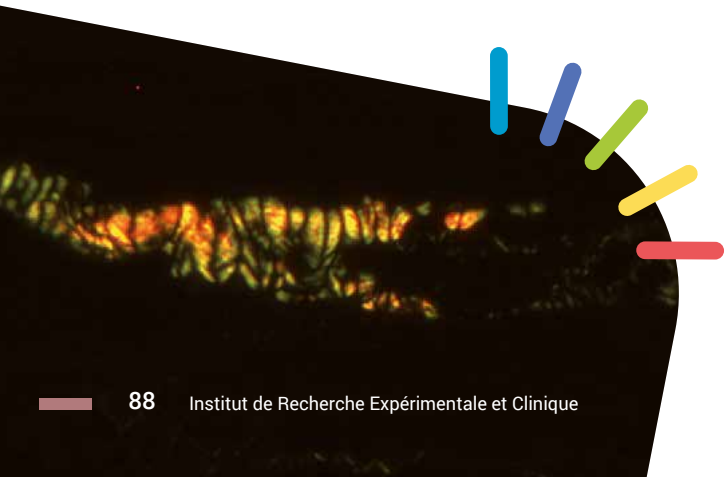
A PhD study conducted by Laurence Geebelen is ongoing with the overall objective of estimating the health and cost burden of Lyme borreliosis and other tick-borne infections in Belgium.

The Borrelia NRC is involved in an ongoing study in collaboration with CODA-CERVA and the Earth and Life Institute (ELI) of the UCLouvain aiming to detect pathogens in collected ticks in the "Bois de Lauzelle" in Louvain-la-Neuve (Belgium).

Yersinia

Anne Simon, Michel Delmée, Eléonore Ngyuvula Mantu, Kate Soumillion, François Dufrasne

Acting as an expert lab for *Yersinia* together with the KULeuven, an increase of incidence of *Yersinia pseudotuberculosis* in 2015 has been studied by MLVA typing. This led to the identification of a specific epidemic clone which was shown to be similar to strains isolated recently in Scandinavia. We initiated a retrospective study by sending a questionnaire to the 22 patients involved. Preliminary results (12 questionnaires sent back so far) tend to demonstrate an important severity of the disease (11/12 patients were admitted to hospital) and no evident inter-human transmission. All isolates are being processed by a panel of laboratory typing methods (PFGE, MLVA,). Pending on results and eventual additional need for discrimination, NGS may also be considered.



VIROLOGY

Antiretroviral drug resistance

Benoît Kabamba-Mukadi, Géraldine Dessilly, Anne-Thérèse Vandenbroucke, Eléonore Ngyuvula Mantu, Kate Soumillion, Najet Lamarti, Isabelle Lefèvre, François Dufrasne

The AIDS reference laboratory (ARL) is active in the surveillance of drug resistance transmission. In collaboration with the other Belgian ARLs and Sciensano, we have showed that local HIV-1 transmission in Belgium remains exclusively driven by native MSM (men who have sex with men) despite the overall heterogeneous composition of the infected population with regard to patient origin and transmission route. Transmission clusters of mixed patient origin may constitute opportunities for the crossover of non-B subtypes to the native MSM population and this is an evolution that needs to be monitored (Verhofstede C. et al., 2018).

The recent widespread use of integrase inhibitors (INSTI) to treat people who are infected with HIV led to a surveillance program of potential transmission of resistance. The significance and impact of several natural genetic polymorphisms on drug efficacy is currently investigated within national and international collaborations. With this in mind, INSTI resistance mutations are investigated by the semi-automated NGS platform.

Indeed, the lab is the first in Belgium, to have validated and used in clinical routine the NGS for the identification of HIV1 resistance mutations (Dessilly et al.2018).

An ongoing study was also initiated to investigate the utility of NGS on HIV-1 proviral DNA for the detection of resistance mutations in patients for therapeutic simplification.

Towards an HIV cure

Benoît Kabamba-Mukadi, Géraldine Dessilly, Anne-Thérèse Vandenbroucke, François Dufrasne

Study on the HIV-1 provirus (Dr Géraldine Dessilly), project having obtained funding from the Louvain Foundation: the objectives of this project consist in carrying out an evaluation of the effectiveness of the NGS platform for sequencing proviral DNA; a comparison of resistance mutations within intracellular proviral DNA versus plasma RNA; an analysis of genetic variations in viruses. This study should allow a better understanding of the mutations of resistance preserved or not between RNA and proviral DNA as well as their clinical impact on the potential activity of ARVs. The ultimate goal is to optimize ARV therapy in patients with an undetectable or low viral load, in order to change their therapy, in particular by simplifying it or because of the side effects.

Although antiretroviral drugs considerably changed the disease prognosis, the HIV infection cannot be currently cured. In this field, we particularly focus on the detection of residual viremia on therapy and its clinical significance by the validation of ultrasensitive methods as "droplet digital PCR or ddPCR" for genome quantification.

HIV-2 and restriction factors

Benoît Kabamba-Mukadi, Géraldine Dessilly, Anne-Thérèse Vandenbroucke, Najet Lamarti, Anne-Thérèse Pâques, François Dufrasne

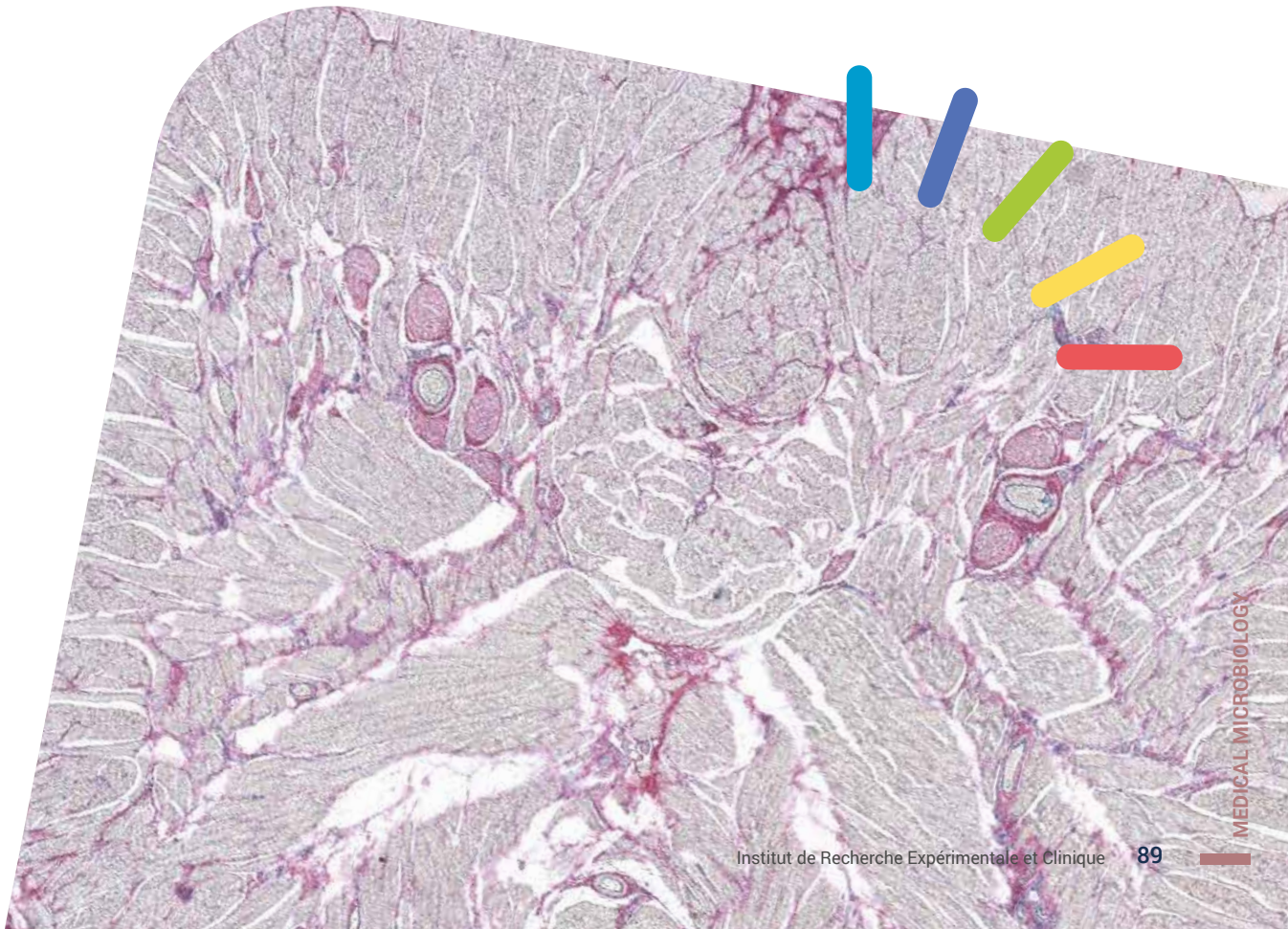
Over recent years the ARL of UCLouvain has become the reference for HIV-2 in Belgium and Luxemburg, for both fundamental research and clinical follow-up. We focus on the host-virus interaction characterizing the replication of HIV-2, which is thought to be less pathogenic and better controlled by the immune system than HIV-1. Deciphering the mechanisms by which the innate and adaptive immune responses can more efficiently inhibit the HIV-2 than the HIV-1 may open the way to new therapeutic approaches towards in functional cure of AIDS.

In 2019, Mr François Dufrasne, assistant at the faculty of medicine and dentistry, defended his thesis on June 11, 2019 entitled "Multilayered and versatile functions of the HIV-2 envelope glycoprotein in the viral replication cycle", this project was carried out within the AIDS reference laboratory with Prof. emeritus Patrick Goubau as promoter. He studied the antagonism capacity of the HIV-2 envelope glycoprotein (Env) to overcome a potent host restriction factor, named BST-2/Tetherin, that play a crucial role in the antiviral response by activating the NF-κB signaling pathway. In his study, it was confirmed that human BST-2 and HIV-1 Env proteins can trigger potent activation of NF-κB. He demonstrated for the first time that the HIV-2 Env induces NF-κB activation in HEK293T cells.

Dr François Dufrasne was hired for a post-doctoral project on HIV-2. He has launched new projects on HIV-2, including the study of cellular restriction factors and activation pathways to understand the differences in pathogenesis between HIV-1 and HIV-2. Cellular restriction factors, inducible by interferons, represent a first barrier during an infection and are able to fight the pathogen following an initial contact with it. Recently, it has been shown that Mx GTPases can restrict the spread of various viruses. Since very few studies describe the ability of myxovirus restriction protein (Mx) to restrict HIV-2 infection, but the inhibition of HIV-1 replication by MxB has already been characterized, overall objective of this project is to define if HIV-2 is also susceptible to restriction by a protein of the GTPase family.

EQUIPMENTS

- **Nucleic acid sequencing facilities**
- **Safety laboratory (BL3)**
- **Digital PCR technology**
- **Next-Generation Sequencing (NGS) platform**



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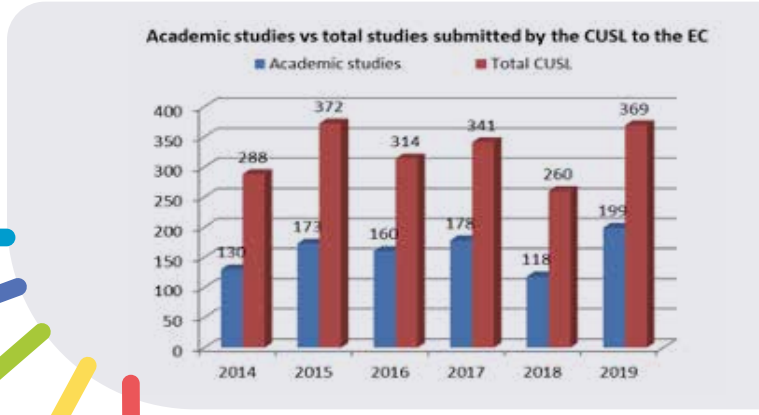
Clinical research at the Cliniques Universitaires Saint-Luc (CUSL) :

DEVELOPMENT OF CLINICAL RESEARCH AT THE CUSL

Ethics Committee (EC) submissions at the CUSL: in 2019, academic studies (master theses not included) represented 54% of the total submissions.



RESEARCH MANDATES

NEW « FRC » STARTING GRANTS SINCE 2017

	2017	2018	2019	2020	Total
Starting grant	4	4	5	**3**	**16**

«FRC» MANDATES FOR CLINICAL RESEARCHERS AND RESEARCHERS (NEW APPOINTMENTS AND RENEWALS) SINCE 2011

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
TOTAL : Clinical researchers (CUSL)	7	9	13	3	8	5	14	18	13	**26**	**116**
Of which renewals :		1	7	0	4	2	5	5	6	**11**	**41**
TOTAL : Researchers (UCL)	12	9	9	3	12	11	8	10	7	**2**	**83**
Of which renewals :		1	7	1	2	2	3	6	3	**2**	**27**

« SAINT-LUC FOUNDATION » MANDATES FOR CLINICAL RESEARCHERS (SINCE 2011)

	2011	2012	2013	2014	2015	2016	2017	2018	2019	Total
TOTAL	6	8	8	9	10	12	10	8	6	**77**

FNRS MANDATES SINCE 2012 (NEW APPOINTMENTS AND RENEWAL)

	2012	2013	2014	2015	2016	2017	2018	2019	Total
Clinicians (Clinical service)	6	11	11	9	13	13	13	13	**89**
Researchers (Poles)	5	4	3	3	4	4	2	7	**32**

The Clinical Trial Center

MISSION AND COMPOSITION

The mission of the CTC is to professionalize the organization and coordination of biomedical research at the CUSL.

During 2019, the CTC FTE went from 11,8 to 11,3 + 0,7 for the academic support to research performed by an UCLouvain researcher.

The Board of Directors is composed of the Medical Director of the CTC (Prof JL Vanoverschelde), the Administrative Director (Mrs D Van Ophem) and the Deputy Chief Administrative Officer (Dr M Van Hassel). In 2019, the Strategic Council of Clinical Research met once to discuss the CTC annual report and also CUSL and UCLouvain biobanks.

TASKS AND ACTIVITY REPORT OF EACH CTC COMPONENT

COMMERCIAL AND ACADEMIC CONTRACTS:

The contracts and finances team manages all the contractual and financial aspects of clinical research.

Type of research contracts	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Commercial (new + amendments+ CD+CTR)	239	224	232	267	266	260	316	319	291	309	282	343
Academic (external and internal agreements)	21	10	17	34	48	92	49	64	74	76	148	160

Additionally, 531 contracts divided into 29 consultancies, 223 sponsoring/grants, 9 subsidies have been managed by the CTC and the legal department.

EUROPEAN PROJECTS SUPPORT (TYPE H2020)

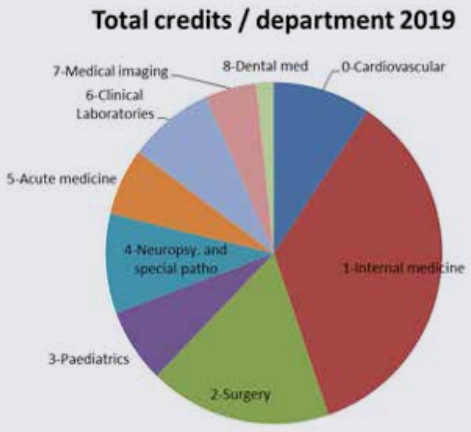
The European projects support officer coordinates the administrative management of research projects financed by European funds.

Ten European projects are ongoing on December 31, 2019

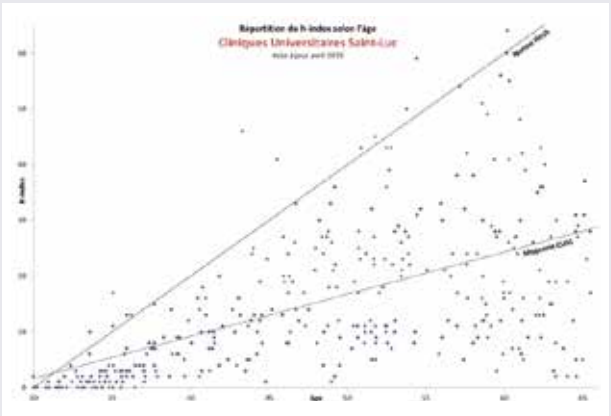
- Types of projects: 6 H2020/RIA (Research Innovation Action), 4 IMI (Innovative Medicine Initiative)
- Types of contracts : 2 where the CUSL are a linked third party and 8 where the CUSL are direct contractors.

REPORTING AND ACADEMIC INDICATORS FOR THE CUSL MEDICAL DEPARTMENTS

Credits/Departments



GROUPED H-INDEX (04/2019 career managerial physicians) BY AGE



CENTRAL DESKS

A: COMMERCIAL CENTRAL DESK

- The « commercial central desk » is the single institutional entry point for the submission of commercial studies files to the Ethics Committee (CEHF).
- In 2019, 170 commercial studies were submitted to the CEHF.

B : ACADEMIC CENTRAL DESKS

The academic central desks and support officers are responsible for giving regulatory and administrative support to the Ethics Committee submission and for the implementation of academic research at the CUSL Academic Desk or at the UCLouvain.

B1: CUSL Academic Desk: ethics committee submissions in 2019

Prospective non-interventional	Prospective interventional without IMP (investigational medicinal product)	Prospective interventional with IMP	Retrospective	Human Residual Bodily Material	FAHMP submissions	CUSL Sponsor	UCL Sponsor	TOTAL
19	67	27	67	17	8	95	36	197

This represents a 71% increase over 2018.
Additionally, 11 masters' theses were submitted to the EC.

B2: UCLouvain Academic Desk

The academic UCLouvain central desk is supporting UCLouvain researchers performing clinical research at the UCL or at the CUSL. In 2019, her working time increased from 0,5 et 0,7FTE.

The UCLouvain central desk provided support to 36 studies and 5 master theses involving UCLouvain researchers performed at the CUSL and 26 studies performed only at the UCLouvain.

QUALITY AND ACCREDITATION

The CUSL were granted from the full AAHRPP (Association for the Accreditation of Human Research Protection Programs) re-accreditation in September 2018 for a period of 5 years. In 2019, the "Quality Management System" was improved with emphasis on a better internal and external communication. The website has been completely redesigned (https://www.saintluc.be/en/research/index.php). Investigators (13 medical services) and study coordinators (5 training sessions) have benefited from internal training.

OPERATIONAL SUPPORT FOR THE STUDY COORDINATORS

The CTC is coordinating the financial aspect of the hiring and the training of the study coordinators.

Eleven new study coordinators were hired in 2019: 5 with a permanent contract and 6 with a fixed term contract.

Study coordinators at the CUSL on 31 December 2019: 84 employees: 74 FTE allocated to 24 medical services.

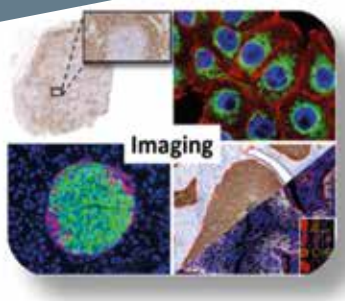
LEGAL SUPPORT

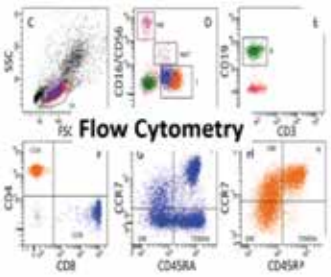
Since August 2018, a half-time legal officer from the legal department of the CUSL is dedicated to the CTC.

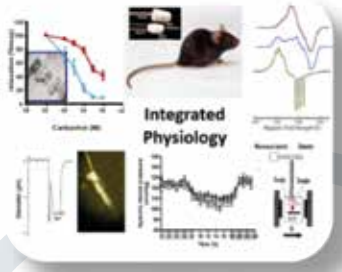
Together with other members of the legal department, she is involved in the legal review and advices for research contracts, consultancy agreements, master agreements, etc

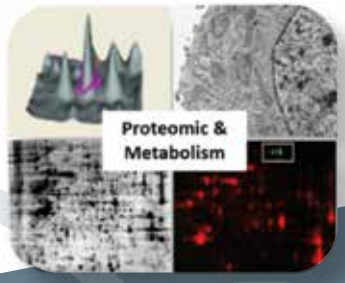
The legal officers provided support for 665 agreements of various types related to clinical research or consultancy and 5 medical legal advice.

IREC TECHNOLOGICAL PLATFORMS









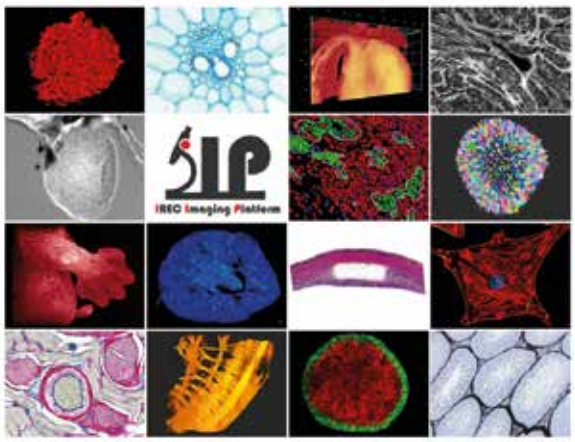
THE OBJECTIVES TARGETED BY THE TECHNOLOGICAL PLATFORMS ARE:

- the optimal use and maintenance of centralized high-end equipment;
- costs optimization ;
- the acquisition of new equipments according to common needs and technical advances;
- knowledge transfer to students and researchers;
- continuous training of the logisticians and dissemination of methodological innovation;
- collaboration creation or reinforcement ;
- improvement of our competitiveness.

IMAGING PLATFORM 2IP

2IP 2019 AT A GLANCE

182	users
49	research groups
2844	bookings
11 254	sections
5703	stainings
4640	immunostainings
1535	hours slide scanning
997	hours fluorescence imaging
7146	hours image analysis
support	management & user committees account manager



PROPOSED SERVICES

2IP is composed of two research logisticians (Caroline Bouzin and Guillaume Courtoy) and two technicians (Aurélie Daumerie and Michele de Beukelaer) and offers access to:

Sample preparation services (Histo-lab):

- Paraffin & cryo-sectioning
- Histological stainings
- Immunostainings (chromogenic-fluorescence-TSA multiplex)

Image acquisition:

- Brightfield whole slide imaging
- 2D fluorescence microscopy (widefield - confocal NEW - structured illumination)
- 3D fluorescence microscopy (lightsheet NEW)
- Polarized light imaging

Image analysis:

- 2D images : ImageJ/Fiji support - ZEN (Zeiss)
- 2D whole slide images (BF and fluorescent): Author (Visiopharm)
- 3D images: Arivis (Zeiss)

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https://uclouvain.be/en/research-institutes/irec/2ip

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Altered generation of ciliated cells in chronic obstructive pulmonary disease. Gohy S, Carlier FM, Fregimilicka C, Detry B, Lecocq M, Ladjemi MZ, Verleden S, Hoton D, Weynand B, Bouzin C, Pilette C. **Sci Rep.** 2019 Nov 29;9(1):17963.

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Invasive Ductular Reaction Operates Hepatobiliary Junctions upon Hepatocellular Injury in Rodents and Humans. Clerbaux LA, Manco R, Van Hul N, Bouzin C, Sciarra A, Sempoux C, Theise ND, Leclercq IA. **Am J Pathol.** 2019 Aug;189(8):1569-1581.

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Increased IgA Expression in Lung Lymphoid Follicles in Severe Chronic Obstructive Pulmonary Disease. Ladjemi MZ, Martin C, Lecocq M, Detry B, Nana FA, Moulin C, Weynand B, Fregimilicka C, Bouzin C, Thurion P, Carlier F, Serré J, Gayan-Ramirez G, Delos M, Ocak S, Burgel PR, Pilette C. **Am J Respir Crit Care Med.** 2019 Mar 1;199(5):592-602.

CTMA

PROPOSED SERVICES

As technological platform of the IREC institute, CTMA offers technological support and expertise to IREC-researchers members. CTMA is composed of a multidisciplinary team including doctors, PhD in biology, biostatistics and engineers. Two research logisticians (J. Ambroise and B Bearzatto) are dedicated to the services to IREC community.

CTMA provides to the IREC researchers an access and a support to use numerous molecular technologies including quantitative PCR, Sanger Sequencing, Pyrosequencing, Next-Generation-Sequencing (NGS) (Illumina-Miseq, Oxford Nanopore-MinION).

This support integrate the experimental design (technological choice, experimental workflow, sample size), the pre-analytical (DNA and RNA quantification and Quality control) and analytical steps, as well as the bioinformatic and biostatistic analysis of the data.

Since 2014, CTMA has particularly developed its **Illumina** platform and associated expertise through different NGS applications:

- Whole-genome sequencing
- Amplicon panel sequencing
- Metagenomics (Shotgun / Targetted)
- CRISPR Validation
- mRNA sequencing
- Targeted RNA sequencing

Since 2016, CTMA participated to the MinION Access Program from Oxford Nanopore. Since that time CTMA acquired an expertise in the preparation, use, and analysis of the MinION long reads sequencer

- Resequencing of Bacterial, viral and protist whole genome.
- RNAsequencing
- 16S Metagenomic analysis

CTMA has also developed specific activities and acquired solid expertise in developing immune assays and customized lateral flow assay. These rapid screening tests are user-friendly and can be used as a diagnostic device to confirm the presence or absence of target analytes, such as pathogens or biomarkers in humans or in animals, or contaminants in water supplies, foodstuffs… etc. To make the picture clearer, think of the common known type of lateral flow rapid test strip which is the pregnancy test.

Our platform is endowed with sciFLEXArrayer S3, ultra-low volume dispensing system, which within seconds, liquid volumes between 50 picoliters of various types of samples (biological, organic, nanoparticle) can be spotted on nitrocellulose membranes or other supports for diagnostics, genomics, proteomics purpose. CTMA may offer technological support to researchers starting from the assay design to the final validation according to the need. The following aspects and steps can be realized:

A- Elaboration Antibody-based lateral flow

- Antigen selection and production of antibodies through outsourcing
- Spotting of captures antibodies with sciFLEXArrayer S3 on nitrocellulose membrane.
- Conjugate pad preparation and device assembly
- Functional validation through thorough evaluation of specify and sensitivity

B- Development of nucleic acid lateral flow

- Amplicon preparation using isothermal amplification
- Probes spotting on the membranes with sciFLEXArrayer S3 robot
- Preparation of conjugate pad adapted for amplicon detection
- Functional validation

CTMA 2019 AT A GLANCE

12	Research groups
242	NGS Libraries Preparation/analysis
	ILLUMINA: MiSeq/HiSeq/NovaSeq
85	- TRANSCRIPTOMIC (RNA-SEQ)
150	- GENOMIC (De NOVO / Resequencing)
96	- METAGENOMIC (Targeted)
703	- CRISPR Validation
	OXFORD NANOPORE: MinION
12	- GENOMIC (De NOVO / Resequencing)
30	- METAGENOMIC (Targeted / Shotgun)
250	GB of NGS DATA sequenced/analyzed

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CYTOMETRY

PROPOSED SERVICES

The platform was created at the beginning of the 2017 but only in middle June it moved in the current locals. In November 2017, we presented the request for the recognition of the platform to UCL. The platform is composed by a logistician (Davide Brusa), supervised by the IREC coordinator (Jean-Luc Balligand).

The Flow Cytometry Platform offers the following services:

- Experiment design
- Sample preparation and cells manipulation with researchers
- Panel design
- Acquisition of samples
- Cell Sorting experiments
- Data interpretation

FLOW CYTOMETRY AND CELL SORTING PLATFORM 2019 AT A GLANCE

62	Users
28	Research groups
22	Trained people
647	Bookings
915	Flow cytometry hours
333	Cell Sorting hours

The platform is equipped with the following instrumentations:

- FACSCalibur, analyzer, 2 lasers, 4 fluorescences;
- FACSCantoII, analyzer, 3 lasers, 8 fluorescences;
- FACSAriaIII, cell sorter, 4 lasers, 16 fluorescences;
- Analysis workstation, equipped with FACSDiva, FlowJo, FACSkin and R softwares.

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UCLouvain - IREC Flow Cytometry Platform

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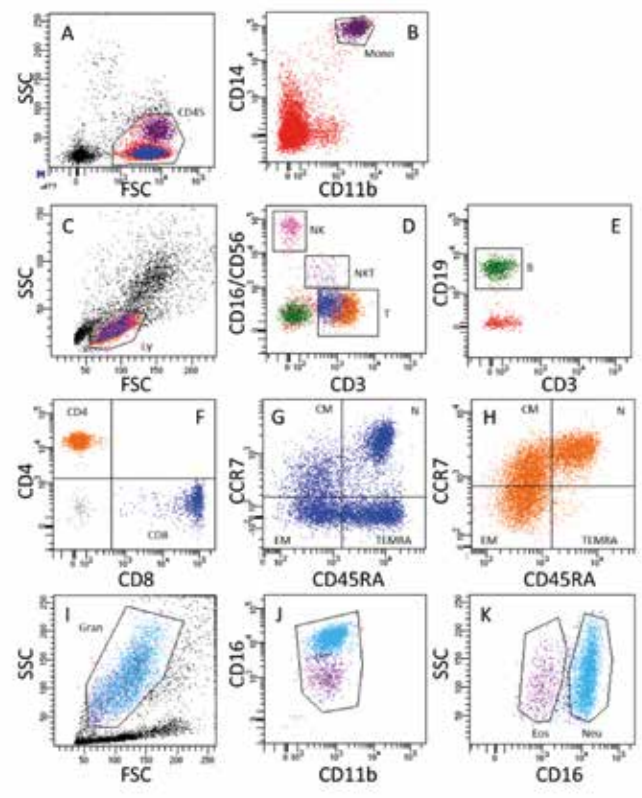
https://uclouvain.be/en/research-institutes/irec/cytometrie-de-flux.html



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ANIMAL FACILITY

PROPOSED SERVICES

The main goals of this platform are to procure improved living conditions for animals in a state-of-the-art facility, as well as give access to high-end equipment for researchers, in an effort to mutualize equipment, skills and knowledge within the institute. The platform is currently composed of a logistician (Solveig Mouterde) and two technicians (Rachid El Kaddouri and Mihaly Palmai-Pallag).

The Animal Facility Platform offers the following services:

- Housing of rodents used in experimentation according to the legal requirements
- Daily care of the animals (daily check-up, cage changes etc.)
- Follow-up of the welfare and sanitary status of the animals
- Access to laboratories situated in the same confinement zones as the animals
- Training as well as protective equipment for the users entering the facility
- Building, equipment and procedure-based barriers ensuring the preservation of the animals' sanitary status
- Advice and help regarding in-vivo experiment design and animal experimentation techniques

The platform is serviced with the following equipment:

- Individually ventilated cages (IVC)
- Cage-changing stations with laminar air-flow
- Bedding disposal stations with laminar air-flow
- Cage-washers
- Autoclaves
- H2O2 disinfection rooms
- Air showers for the personnel and users' entrance
- Air pressure differentials between rooms (sanitary barriers)
- Laboratories incl. chemical hoods

The laboratories are being progressively equipped through a joint effort from the research teams using the facility, and following a philosophy of mutualisation, in order to give access to the following services:

- Conventional area: surgery, laser Doppler, intravital imagery, tumor induction, ultrasonography, telemetry, metabolic cages
- Linné-like area: surgery, laser Doppler, intravital microscopy, tumor induction, viral infection (L2 biosafety lab), metabolic cages
- SPF-like area: surgery, cell therapy, tumor induction, inhalation cage

THE IREC ANIMAL FACILITY AT A GLANCE

3 Rodent confinement zones: Conventional, Linné-like and SPF-like areas

1 Zone opened in 2019: Conventional area. The other zones are due to open in 2020

480 Mice cages available in the Conventional area

140 Rat cages available in the Conventional area

6 Research teams (PIs) using the Conventional area since its opening mid-April 2019

35 Users trained to get access to the Conventional area since its opening

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Université catholique de Louvain

IREC Animal Facility
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1200 Bruxelles

INTEGRATED PHYSIOLOGY

PROPOSED SERVICES

This platform is installed on the 2d floor of the Harvey Tower (55). Other equipements have been installed within the animal experimentation platform.

- **Vascular reactivity (55 +2):** Conductance and resistance artery reactivity, Calcium and contractility measurements, Tissue isolation. The platform proposes a full access to equipments, training of new users, help in setting experiment protocols and result analyses.
  Teaching and scientific support: C Dessy (FATH)
- **Telemetry (52 +5, transferred in the animal facility platform.):** Surgery, Haemodynamic profiling (HR/P), Variability evaluation, ECG.
  Technical support : H Esfahany (FATH)
  Scientific support : JL Balligand/C Dessy (FATH)
- **Electronic paramagnetic resonance (55+2):** Quantitative evaluation of nitric oxide (NO, HbNO); ROS (with DMPO, CAT-1, CP-H or CMH); thiol-containing molecules in biological samples (cultured cells, Blood and tissues); and metal-containing proteins (methemoglobin, ceruloplasmin etc).
  Technical and scientific support : I Lobysheva/ Joel Cosse (FATH)
- **Echography (55+3):** The echography platform is equipped with a Vevo 2100 (FujiFilm/VisualSonics) echography machine allowing for 2D / 3D non-invasive ultrasound imaging of the heart and big vessels in small rodents. Offering capabilities for B-mode, M-mode and Doppler modalities (measurements and analysis of data). The equipment and the expertise is available for expansion of activities in cancer studies and other domains of interest within the IREC.
  Technical support: EP Daskalopoulos (CARD)
  Scientific support: C Beauloye / EP Daskalopoulos (CARD)
- **Islet Perifusion (55+2):** The platform is equipped with 6 chambers of perifusion for dynamic measurements of hormone secretion from pancreatic islets, cellular suspensions or organoids.
  Technical and scientific support: JC Jonas (EDIN)
- **Patch-clamp (55+2):** A dark room is equipped for patch-clamp / live-cell imaging dual measurements.
  Technical and scientific support: P Gilon (EDIN)

Contact

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Ongoing Collaborations

UCL : IREC (LTAP, CARD, GAEN, FATH); LDRI (MNUT)

KUL : Pneumology

UHasselt : BIOMED-Faculty of Life Science (Group COS)

UNAMUR: URPhyM

PROTEOMICS & METABOLOMICS

PROPOSED SERVICES

Coordinated by Olivier Feron, this platform is installed in dedicated rooms at the second floor of Building 55 (Tour Harvey). The platform is currently equipped with instruments bought by Profs O. Feron and P. Sonveaux (with the help of other co-promoters when grants were obtained from the FRS-FNRS) and directly managed by them together with Dr. Cyril Corbet and Céline Guilbaud. The platform provides an access and a support (through collaborations or specific training of external investigators when possible) to use technologies listed here below:

"Proteomics" equipment :

- two-dimensional (2D)-gel running platform (IpgPhor III, Ettan DALT6, TE77 transfer units, SE600 electro-phoresis unit, SG100 gradient maker) and associated materials for 2D-DIGE studies (Laser Scanner Typhoon FLA9500 incl. Decyder analysis software) and spot picking (Ettan) (GE Healthcare)
- Akta Microscale liquid chromatography (GE Healthcare)
- Bioplex - multiplex immunoassay system (Biorad)

"Metabol.om.ics" equipment :

- Hypoxia worstation (Don Whitley H35) [cell culture at 0.1-21% O2]
- Seahorse XF96 Bioenergetic analyzer (Agilent)
  - real-time measurements of oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) for adherent and non-adherent cells
  - assessment of the specific activity of electron transport chain complexes (ETC) in isolated mitochondria and in permeabilized cells
  - fatty acid oxidation measurements
- Iscus-flex CMA400 (Microdialysis) for metabolites monitoring [eg, lactate, pyruvate, urea, glutamate]
- Radiolabeled nutrient/metabolite flux [eg, glucose, lactate, pyruvate, palmitate]
- Conventional laminar flow hood and 5% CO2 incubator to handle cell exposure to a home-made library of metabolism-targeting drugs in order to probe bioenergetics/biosynthetic preferences

The platform also aims to act as an interface with external academic and non-academic resources (through privileged interactions at KULeuven and GIGA-ULg), in particular for 13C metabolomics studies and MS peptide identification.

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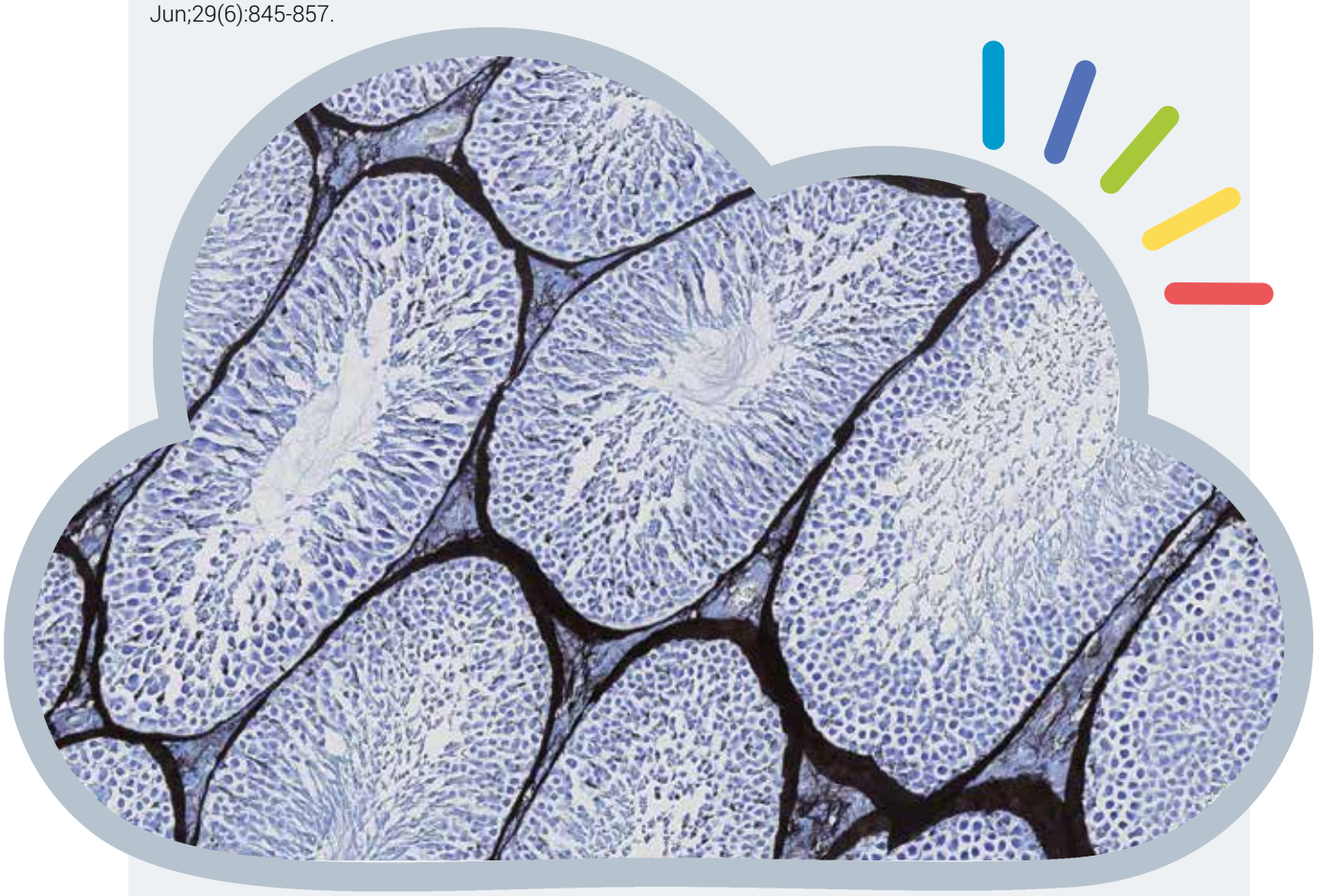

CTMA

The Centre de Technologies Moléculaires Appliquées (CTMA - Centre for Applied Molecular Technologies) is a mixed academic-clinical-military biotechnological platform where each of the three pillars mutualizes resources for the other two components:

- Experimental and Clinical Research Institute (IREC/UCLouvain) which is the civilian UCL academic pillar;
- CBRN-Defence Laboratories Department for the BE-Defence (DLD/BE-MOD) which is the military CBRN research and CBRN operational pillar working for DLD; the CTMA activities as DLD Biothreat control unit" define the full acronym CTMA/DLD-Bio..
- St Luc academic hospital (Cliniques Universitaires St Luc, CUSL) for which clinical development and testing in molecular genetics and associated clinical (human) and environmental research are provided.

On the top if this, CTMA actively develops its own proprietary research, following the Russian Dolls strategy, which integrate research applied sciences activities at Regional , Federal, European and International level .

CTMA/DLD-Bio is also actively developing service activity for industry by producing fungal biomass for the preparation of vaccines in its CTMA-MYCO premises.

According to its integrated activities, CTMA fulfils synergistically its academic, clinical and military missions while also hosting and supporting at the same time UCLouvain researchers' scientific work with and outside UCLouvain.

CTMA/DLD-Bio hosts at the same location researchers from the Belgian Defense (MOD) and UCLouvain/IREC/CTMA as well as the clinical staff working for the academic hospital Cliniques universitaires Saint-Luc (CUSL):

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Post-Doc:

Jerôme Ambroise, Ir, PhD

Bertrand Bearzatto, PhD

Mostafa Bentahir, PhD

Léonid Irenge, MD, PhD

Michel Heuterspreute, PhD

Omar Nyabi, PhD

Olga Vybornova, PhD

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Dumont Catherine, ***MOD***
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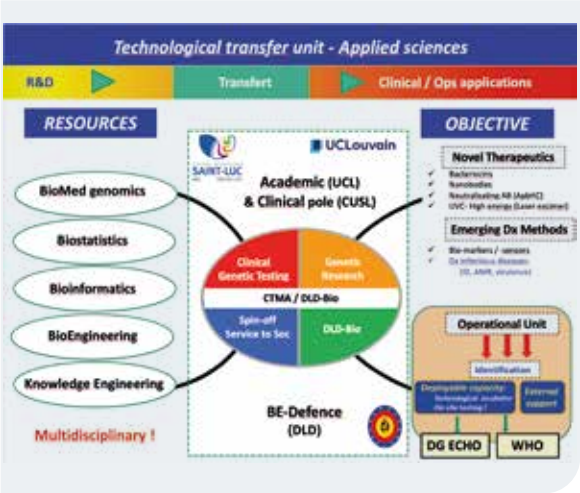
Carlier Antoine, ***MOD***
Chibani Nawfal, ***IREC***
Cruz Mitjans Dennys, ***IREC***
Cruz Mitjans Olga, ***IREC***
Delcorps Cathy, ***MOD***
Delhez Huguette, ***CUSL***
Fastre Gilles, ***MOD***
Lakcher Oumaima, ***MOD***
Smits Benjamin, ***IREC***
Van Cauwenberghe Stéphane, ***MOD***
Vieren Lander, ***MOD***

CTMA/DLD-Bio is notably active in microbial research (bacteria, viruses, fungi, helminths…) by developing novel therapeutics and emerging detection methods. Whereas novel therapeutics developments encompass bacteriocins, camelids immunoglobulins, neutralization AB and UVC- High energy (laser excimer), new rapid diagnostic tools focus on isothermal amplification, multiplex immuno-chromatographic lateral flow assay and 3d generation sequencing for a better detection and protection against known and unknown biological agents.

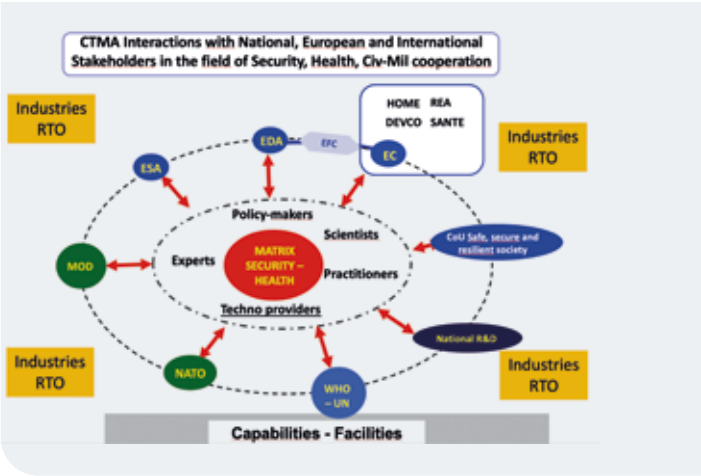
All these tools are designed to meet the constraints of use in the EU-certified deployable box-based laboratory B-LiFE (Biological Light Fieldable Laboratory for Emergencies) developed by CTMA/DLD-Bio for national and international missions justified by major CBRN or public health crisis. B-LiFE is part of the European box-based laboratory network coordinated by the Robert Koch Institute, and supported by WHO and the European Commission.

The R&D activities imply multidisciplinary resources (Bio-medical genomics, -statistics, -informatics and Bio-engineering and knowledge engineering).



The R&D activities are interconnected and benefit from funding by the Belgian Defense, the Brussels (Innoviris, WBI) and Walloon (BioWin and WALinnov) regions, Federal (Defence, BELSPO, Food Chain Safety) and international institutions (EC, EDA and ESA).

By its R&D activities CTMA/DLD-Bio is acting as an interface between the community of users for a secure, safe and resilient society and the academic, military and industrial research world.



CTMA/DLD-Bio interacts with National, European and International Stakeholders in the field of Security and Health within a frame of Civilian-Military cooperation (CIMIC).

Research Projects

Through its involvement in several past EC FP7, HORIZON 2020, ESA and Defence projects, CTMA/DLD-Bio has developed and is continuously improving a rapidly deployable Bio-laboratory capacity thanks to the ESA funded B-LiFE project and used it as an operational capacity in case of health crisis or as testbed (technological incubator) for developing and/or testing emerging technologies for use under field conditions.

B-LiFE: Biological Light Fieldable Laboratory for Emergencies - Demonstration Project - Extension 2 (CCN#2) - Funding: ESA IAP Artes 20 (2018-2020)

Jean-Luc GALA, Jean-Paul MARCEL, Alexander VYBORNOV

The successful management of sanitary crises relies on the ability to perform rapid detection and identification of pathogens. National and international agencies dealing with the response to bio-security crises need rapidly deployable capacities carrying out analyses close to the crisis area, and equipped with autonomous transmission and geo-location capabilities. The B-LiFE system contributes to fill this gap.

The B-LiFE system, developed during the Demonstration project (2014-2017), integrates space technologies, i.e. satellite telecommunications to communicate with the distant reach back home base laboratory, stakeholders and end users, GNSS (Global Navigation Satellite System) for geo-location and Earth Observation for site selection and monitoring. B-LiFE is also equipped with management tools (LIMS, decision support software…).

Users have requested to extend the B-LiFE capacities with new telecommunication and crisis management assets. Therefore the CCN#2 extension of the demonstration project will enable to develop a new Field Communication and Control System, integrating space assets with increased capacities and new tools for crisis and logistics management.

The B-LiFE system is regularly deployed in international exercises. The last operational deployment was the support of an Ebola Treatment Unit in Guinea (N'ZEREKORE) during the last Ebola outbreak in West-Africa (2014-2015).

Following the Ebola mission B-LiFE has been registered in the European Medical Corps (EMC) belonging to the European Emergency response Capacity (EERC) within the frame of the European Union Civil Protection Mechanism (EUCPM). Through this mechanism, teams and equipment from the EU Member States are rapidly deployed to provide worldwide medical assistance and public health expertise in response to national and international emergencies. It is now collaborating with national public health, DG DEVCO and WHO.

Federal Police Special Intervention Unit and Scientific Police investigating the clandestine Laboratory

Terrestrial Telecommunication Terminal

Bio-analysis performed on clandestine Laboratory Samples

Intervention of the Medical Team on the Injured Federal Police Special Intervention Unit Member

Decontamination Team at Work with observers Looking to the Scene (with white overcoat)

Within the frame of the B-LiFE consortium the exercise Stayin' Connected took place in November 2019 on the ground of the Civil Protection in Brasschaat. A terrorist incident with biological agents was simulated in a fictitious foreign context. The exercise was organised by the Civil Protection, part of the B-LiFE consortium, to train the specialized capacities for CBRNe incidents (chemical, biological, radiological, radiological, nuclear and explosives) in special circumstances, as well as to test the mutual information and communication possibilities.

The scenario of the exercise was a biological terrorist threat during a fictitious winter festival called Connect, that saturated the communication network in the area. Specialized services had to intervene to investigate a suspicious location and to take appropriate actions. This particular scenario required extensive technical testing of a specialized communication and imaging technology, and the deployment of a logistical Base of Operations.

The B-LiFE consortium validated during this exercise the integrated satellite communications with terrestrial communication networks TETRA (TErrestrial Trunked Radio), LTE (Long Term Evolution) to communicate with the distant reach back home base laboratory, stakeholders and end users, GNSS (Global Navigation Satellite System) for geo-location and Earth Observation for site selection and monitoring and mission management tools.

The exercise implied the active participation of 75 people from the B-LiFE Consortium and specialized services of the Federal Police, Defence and Civil Protection, as well as the CBRNe Centre of Expertise of the National Crisis Centre. The specific combination of specialized teams was a first for Belgium.

About 50 observers and VIPs attended the exercise to further assess the operational and policy challenges in the field of CBRNe and telecommunications. Besides Belgian experts from the United Kingdom, Germany, the Grand Duchy of Luxembourg, the European Union and NATO attended the exercise.

EU faces growing security and health threats, e.g. an intentional use of CBRN agents, large external crises, and pandemics due to the convergence of risk factors driving disease emergence, amplification and dissemination of pathogens with pandemic potential. Protecting the health and security of EU citizens against these threats requires a coherent response by all stakeholders. For several years, CTMA/DLD-Bio has actively contributed by addressing those challenges as coordinator, end user or as operator of the B-LiFE laboratory on EC projects)

Horizon 2020 eNOTICE: European Network Of CBRN Tralning Centers - Funding: EU H2020 (2017-2022) - CTMA is Project coordinator

Olga Vybornova, Aleksandr Vybornov

The eNOTICE project seeks to better European preparedness, resilience and incident response to CBRN attacks and emerging threats through close multi- (stakeholders) and single-discipline (practitioners) interactions. Whilst using efficiently investments made across Europe in demonstration, testing, and training facilities for practitioners, this novel concept will issue meaningful users-guided recommendations to the EU R&D program, enhance CBRN product performance and competitiveness in order to reach long term sustainability.

eNOTICE is building a dynamic, functional and sustainable pan-European network of CBRN training centres (CBRN TC), testing and demonstration sites strengthening capacity building in training and users-driven innovation and research, based on well-identified needs.

The CBRN TC network organizes joint activities, training and debriefing, using real-life or simulated situations (e.g. field exercises, table top, serious gaming and simulations), with external partners, in order to foster the identification of 'genuine users' needs with users-driven technological solutions.

In 2019 eNOTICE organized 3 joint activities - a radiological training course in Joint CBRN Defence Centre of Excellence, Vyškov, Czech Republic, a table top exercise in Birmingham, UK and a large-scale field exercise in Dortmund, Germany, the latter one along with a Policy meeting with civilian and military policy representatives and a Workshop for training centers - members of eNOTICE network. 46 CBRN training centres are currently in the network.

Horizon 2020 ENCIRCLE: EuropeaN CBRN Innovation for the maRket CLustEr - Funding: EU H2020 (2017-2021) - CTMA is Project coordinator

Olga Vybornova, Omar NYABI

To improve its resilience to new CBRN attacks and threats, the EU needs a specialized, efficient and sustainable industry. Competitiveness requests a less fragmented EU market.

ENCIRCLE uses an innovative approach to reach address these issues in a short to long term perspective so that SMEs and large industries can propose and invest in the best end users-guided innovations.

The main expected impact is to enhance the EU CBRN industry competitiveness and enlarge its market while improving the impact and efficiency of EU research and innovation on CBRN preparedness, response, resilience and recovery.

A list of 241 needs and gaps has been reviewed from which 11 topics were identified and sent for consulting with EC and they will certainly be covered by the next coming calls.

CTMA/DLD-Bio is continuously developing new diagnostic tools for sample analysis usable under field conditions in the B-LiFE laboratory.

Horizon 2020 RKI Germany EuroBioTox: Validation of Biological Toxins Measurements after an Incident - Development of Tools and Procedures for Quality Control. - Funding: EU H2020 (2018-2023) - CTMA is End User by participating to the Proficiency Tests

Mostafa Bentahir

Recent incidents in Europe and worldwide have threatened civil society by the attempted use of different biological toxins and have thereby shown that increased vigilance and adequate preparation is of growing importance in a world facing more and more risks of man-made disasters.

There is a lack of robustness in European preparedness for biotoxin incidents. Using current best practice, the EuroBioTox core members will develop and validate improved analytical tools, reagents and standard operating procedures based on realistic incident scenarios. Certified Reference Materials for the threat biotoxins will be developed and, by establishing a European repository, will be made available to the EuroBioTox network including more than 50 European organisations, expert laboratories, industrial partners and end-users. Training courses at basic and advanced levels will be developed and attended by the EuroBioTox network partners, followed by a series of proficiency tests which, through these "outer circle" associates, will disseminate best practice methods across Europe. The outcomes are a pan-European network of competence, certified reference materials, standard operating procedures and a common way of handling biotoxin incidents.

CTMA has already performed 3 proficiency tests in 2018 on paralytic shellfish poisoning (PSP) toxin saxitoxin (STX) by competitive ELISA and staphylococcus aureus enterotoxin B (SEB) PT by ELISA and in 2019 on ricin/abrin by ELISA and Lateral Flow Immuno Assay (LFA) in the B-LiFE mobile laboratory. Ricin is a plant poison that regularly makes headlines. Chemical and biological knowledge is needed to detect it as it occupies a blurred area at the interface of classical biological and chemical weapon agents. This is why the proficiency tests on the samples sent to us were carried out jointly by the B-LiFE mobile laboratory and our colleagues at the DLD chemical analysis laboratory in Peutie. (DLD-CA).

CTMA at work in the B-LiFE Tent during the ricin proficiency test

DLD-CA chemical analysis in the Peutie Laboratory

HFM 17-3: Development of innovative methods for ultra-fast amplification and specific detection of high pathogenic bio-agents (CBRN) on Operation Theater - Funding: Belgian Defense Research Program (2017-2022)

Mostafa Bentahir

A panel of assays based on high-speed isothermal genomic amplification will be used to rapidly identify highly pathogenic biological agents in a field setting. RPA and LAMP isothermal amplification methods were compared to quantitative PCR using RNA and DNA viral biological agents as targets. Both methods were found sensitive and specific. RPA and LAMP specific assays were developed for the Bacillus anthracis bacterium and the middle east coronavirus (Mers-Cov). These assays are currently thoroughly validated for their specificity and sensitivity prior to their lyophilization. Following stability testing, these assays will be tested and validated for use under field conditions in the B-LiFE laboratory.

HFM 17-4: Development of on-site Next Generation Sequencing (NGS) and shotgun metagenomic analysis for unambiguous characterization of unknown and emerging agents in environmental and biological samples - Funding: Belgian Defense Research Program (2017-2021)

Catherine Dumont, Oumaima Lakcher

This study aims to circumvent the limitations of current identification assays, i.e. the need for multiple targeted diagnostic tests to cover clinical syndromes and all related differential diagnoses and the limiting use of tiny parts of target genomes. To do so, a shotgun metagenomic sequencing approach is used for the identification of "unknown viral and bacterial agents" using the benchtop MiSeq-Illumina Next Generation Sequencing (NGS) platform and a pre-analytical enrichment step. The identification workflow will be optimized and adapted to the pocket sized MinION® (Oxford Nanopore) NGS in order to enable us to carry out NGS analysis in the B-LiFE fieldable bio-laboratory in case of public health issues.

So far, several bacterial DNA enrichment methods have been assessed by qPCR and are now under NGS evaluation. These methods allow either to get rid of the background human DNA or to enrich specifically the targeted bacterial DNA. A similar process is also under investigation for viral enrichment. For this purpose, the study will work with two well-described simulants: the MS2 and the AcNPV.

TOXINE-ID: Specific multiplex and immuno-lateral flow detection of a well-defined panel of toxins inside a representative food sample - Funding: WALInnov (2017-2021)

Jamal Badir, Mostafa Bentahir, Omar Nyabi, Benjamin Smits

Accidental or intentional food poisonings are a source of growing concern for public health authorities and stakeholders in the food chain (producers, consumers). A portable detection system, multiplex immunochromogenic device also called lateral-flow based assays (LFA), is developed to provide a rapid, reliable and qualitative multiplex detection and identification (answer yes/no) of food toxins (i.e, toxin A, B, and E from clostridium botulinum; saphylococcus aureus enterotoxins A and B; shellfish toxins (okadaic acid and domoic acid); myco-toxins (aflatoxin, ochratoxin) and ricin.

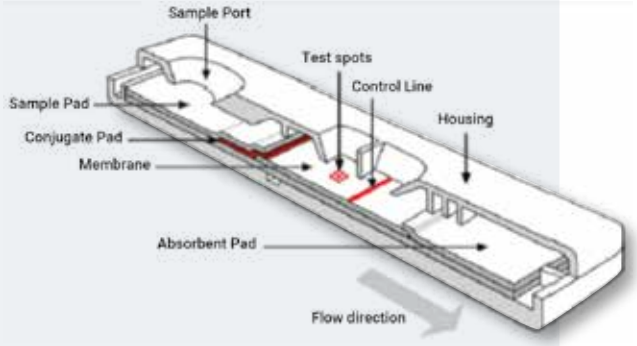
DEMASQUE: Differential Multiparametric and multiplex diagnosis of aroboviruses (Yellow Fever, Zika and Dengue) using combined RPA and lateral flow device. - Funding WALInnov (2019 - 2022)

Jamal Badir, Mostafa Bentahir, Omar Nyabi, Benjamin Smits

Arboviruses (Arthropod-Borne Diseases) are heterogeneous group of vector-borne diseases, some of which are associated with rapidly expanding fatal epidemics, posing a serious threat to public health. The global prevalence of these diseases has increased dramatically, threatening more than 3 billion people worldwide.

The objective is to develop an innovative Point Of Care Tests (POCT) device, fast, convenient and easy to use diagnostic assay that shorten turnaround time of intervention, integrating on the same support and in a single procedure the analysis of gene targets (viral RNA) together with the detection of protein targets (viral proteins and immunoglobulin type M (IgM) of the patient).

The assay should be robust and must achieved rapid differential diagnosis of acute human infections by flavivirus pathogens. In addition, this assay will incorporate the advantages of the lateral flow immunoassay (LFA) and the isothermal nucleic acid amplification (RPA) for the differential diagnosis of 3 arboviruses: ZIKV, DENV and YFV.



The LFIA consists of several elements assembled using an adhesive backing card. Target antigens are captured by the specific antibodies present in the conjugate pad and flow by capillarity through the membrane. This complex antibody-antigen is detected at the level of the test spots.

CTMA/DLD-Bio is continuously developing new methods for monitoring the quality of inactivation and decontamination procedures such as those used under operational field conditions when deploying the B-LiFE laboratory.

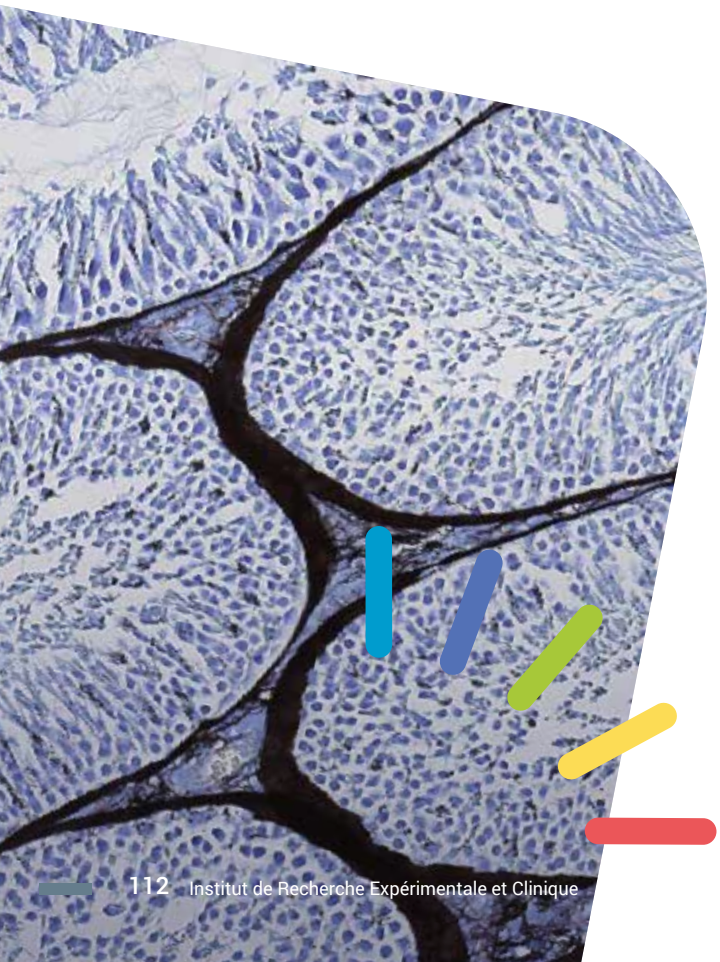
MSP 16-4: Development of procedures for biological agent inactivation to enhance biosafety conditions during the procedure of identification under field conditions - Funding: Belgian Defense Research Program (2016-2020)

Cathy Delcorps, Stéphane Van Cauwenberghe

Different methods of inactivation, (chemical methods with or without additional exposure to UV) are tested on different models of biological agents to assess the agent's viability and reach the best compromise in terms of specificity and sensitivity of their real-time identification.

The project selected three bacterial (B. thuringiensis spores, B. subtilis spores, P. agglomerans) and two viral (AcNPV, MS2) surrogates for simulating biological warfare agents. Optimal culture conditions and multiplexed real-time PCR assays were successfully developed. Seven commercial kits of nucleic acids extraction, selected through specific criteria's for mobile deployment, were tested on these simulants with interesting results, as most of them proved inefficacy against bacterial spores.

Gathered data allowed comparison of the commercial kits over their extraction yield, nucleic acids quality and inactivation efficiency. The study led to an efficient homebrew chemical method capable of inactivating all these surrogates, without interfering with PCR identification. The combination with UV exposure proved very effective at specific wavelengths.



HFM 18-10: Assessment of water quality prior and after decontamination under field conditions - Funding: Belgian Defense Research Program (2018-2022) - Cooperation with Laboratory for Hydrology, Bromatology and Air (LHBA) of the Veterinary Service of the Military Hospital (MHKA)

Leonid Irenge, Antoine Carlier

Presence of life-threatening pathogens in water is a major shortcoming, especially in developing countries. During military field deployments, water stocks are chlorinated in order to prevent contamination of the personnel with life-threatening agents potentially present in water. Whereas chlorination is efficient against viruses and several bacteria, it is inefficient against spore-forming bacteria and against cysts of several pathogenic protozoans. These latter are responsible for neglected diseases for which diagnosis is difficult, due to the lack of sensitive tests and the waning knowledge in the scientific community.

Rapid methods are developed to screen water sources or stocks reservoirs, both prior to and after chlorination, in order to identify the presence of well-defined pathogens (i.e., protozoans, helminthes eggs and bacteria). The goal is to provide military field commanders with a timely set of data, allowing them to select appropriate water sources and monitor them regularly and appropriately.

During 2019 following developments have been achieved:

Development and validation of a rapid molecular assay for detection of Vibrio cholerae, a pandemic diarrheal disease. It consists in a quadruplex real-time PCR assay for detection of Vibrio cholerae. This assay allows the detection of V. cholerae and discrimination between V. cholerae causing the current pandemic and other V. cholerae strains. It also discriminate V. cholerae with other closely-related agents which are present in water, like Aeromonas, Escherichia coli, Klebsiella and Salmonella. Of course, it does not detect parasites and fungi.

Development and validation of a molecular assay for detection of most prevalent parasites associated with diarrheic diseases, namely Entamoeba histolytica, Giardia intestinalis and Cryptosporidium

Development and validation of a molecular assay for detection of Cyclospora, Toxoplasma gondii and Schistosoma (detection of the genus Schistosoma including the following species: Schistosoma mansoni, Schistosoma haematobium, Schistosoma intercalatum, Schistosoma japonicum and Schistosoma mekongi).

These assays have been successfully used for detection of Cryptosopridium in water samples from various water sources used by Belgian servicement in the field.

HFM 19-11 : Development of custom pilot biosurveillance panels for the identification of biothreat agents and the detection of antimicrobial resistance and virulence markers by targeted Next Generation Sequencing technologies. - Funding: Belgian Defense Research Program (2019-2023)

Cathy Delcorps, Béatrice Sulka

Biothreat agents can induce symptoms of an infection which are often similar to numerous less harmful pathogens. Consequently, the simultaneous detection and identification of multiple biological agents will guide the appropriate response in case of an emerging public health crisis, especially in case of a bioattack incident to support clinical decision making (detection of relevant infections as well as antimicrobial resistance and virulence markers) and medical intelligence studies (identification of vectors and vector borne diseases).

A targeted NGS workflow with customised bio-surveillance panels will be developed and validated first on a lab-based sequencing platform and further implemented in a field deployable NGS device. These molecular tools will enable the simultaneous identification of wide-range of biothreat agents at least at species-level, the mapping of the evolution and the origin of these pathogens, as well as the detection of antimicrobial resistance and virulence markers.

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I**renge LM, Ambroise J**, Mitangala PN, **Bearzatto B**, Kabangwa RKS, **Durant JF, Gala JL**. (2019). Genomic analysis of pathogenic isolates of Vibrio cholerae from eastern Democratic Republic of the Congo (2014-2017). PLoS Neglected Tropical Diseases, in press 2020.

Ambroise J, Irenge L M, Durant J F, Bearzatto B, Bwire G, Stine O C, & **Gala JL**. (2019). Backward compatibility of whole genome sequencing data with MLVA typing using a new MLVAtype shiny application for Vibrio cholerae. PloS one, 14(12).

Irenge LM, Ambroise J, Bearzatto B, Durant JF, Chirimwami RB, **Gala JL**. (2019). Whole-genome sequences of multidrug-resistant Escherichia coli in South-Kivu Province, Democratic Republic of Congo: characterization of phylogenomic changes, virulence and resistance genes. BMC Infectious Diseases, 2019, 19(1), 137.

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PHD THESES

Date: 18/01/2019 Name: **DELIRE Bénédicte**
Lab: GAEN
Thesis: Macrophages infiltration and extracellular matrix remodeling in liver fibrosis and hepatocellular carcinoma
Promotor: STARKEL Peter Copromotor: LECLERCQ Isabelle

Date: 23/01/2019 Name: **POIRÉ Xavier**
Lab: Cellular Therapy Lab - CUSL
Thesis: Improving allogeneic stem cell transplantation in the setting of acute myeloid leukemia: Refining risk stratification
Promotor: LATINNE Dominique Copromotor: EECKHOUDT Stéphane

Date: 04/02/2019 Name: **MONTIEL Virginie**
Lab: FATH
Thesis: Aquaporin 1 and Left Ventricular remodeling
Promotor: BALLIGAND Jean-Luc Copromotor: LATERRE Pierre-François

Date: 07/02/2019 Name: **SCHNEIDER Karolin**
Lab: MIRO
Thesis: Increased response to ionizing radiation in human papillomavirus-associated head and neck squamous cell carcinoma: contributing to unravel the physiopathology
Promotor: GREGOIRE Vincent

Date: 12/02/2019 Name: **BEGHIN Jean-Christophe**
Lab: MBLG
Thesis: Immunovirological long-term outcome of HIV-infected children living in a resource-limited setting of South Africa. Implication of an early treatment initiation
Promotor: GOUBAU Patrick Copromotor: BRICHARD Bénédicte

Date: 27/02/2019 Name: **CICCARELLI Olga**
Lab: GAEN
Thesis: Clinical and experimental contributions to the study of phenotypic changes in chemotherapy-treated hepatocellular carcinoma
Promotor: STARKEL Peter Copromotor: REDING Raymond

Date: 05/04/2019 Name: **DEI ZOTTI Flavia**
Lab: FATH
Thesis: Quantification and regulation of erythrocyte HbNO as an index of vascular NO using EPR spectroscopy
Promotor: BALLIGAND Jean-Luc Copromotor: LOBYSHEVA Irina

Date: 23/05/2019 Name: **SOW Amadou**
Lab: NEFR
Thesis: The water channel aquaporin-1 : multi-faceted role in the peritoneal membrane
Promotor: DEVUYST Olivier

Date: 11/06/2019 Name: **DUFRASNE François**
Lab: MBLG
Thesis: Multilayered and versatile functions of the HIV-2 envelope glycoprotein in the viral replication cycle
Promotor: GOUBAU Patrick Copromotor: MICHIELS Thomas

Date: 14/06/2019 Name: **DUFEYS Cécile**
Lab: CARD
Thesis: Exploring the role of fibroblastic AMPKα1 in ventricular remodelling after myocardial infarction: Implication of connexin 43 and miR-125b
Promotor: HORMAN Sandrine Copromotor: BEAULOYE Christophe

Date: 20/06/2019 Name: **DE MONTJOYE Laurence**
Lab: PNEU
Thesis: Immunological aspects of chronic spontaneous urticaria
Promotor: BAECK Marie & DUMOUTIER Laure

Date: 26/06/2019 Name: **MUBENGA-MUKENGESHAI Léon-Emmanuel**
Lab: Urology - CUSL
Thesis: Association hypertrophie béninge de la prostate et diabète sucré de type 2 au Sud-Kivu
Promotor: TOMBAL Bertrand Copromotor: HERMANS Michel

Date: 16/09/2019 Name: **GUY-VITERBO Vanessa**
Lab: LTAP
Thesis: Towards individualization regimen of tacrolimus in pediatric liver transplantation
Promotor: WALLEMACQ Pierre Copromotor: REDING Raymond

Date: 24/10/2019 Name: **CARDINAL Mickaël**
Lab: MORF
Thesis: Anticorps antisclérostine et ostéogenèse imparfaite, évaluation chez la souris oim/oim
Promotor: BEHETS WYDEMANS Catherine Copromotor: MANICOURT Daniel

Date: 30/10/2019 Name: **DOIX Bastien**
Lab: FATH
Thesis: Anticancer photodynamic therapy from direct cytotoxic effects to immunogenic cell death induction
Promotor: FERON Olivier Copromotor: GREGOIRE Vincent

Date: 15/11/2019 Name: **VAN MARCKE DE LUMMEN Cédric**
Lab: MIRO
Thesis: Deciphering the genetic background in unexplained high-risk breast cancer families : integration of somatic data to unravel heredity
Promotor: DUHOUX François Copromotor: VIKKULA Miikka

Date: 18/11/2019 Name: **ANDRE Emilie**
Lab: FATH
Thesis: Modulation of adult cardiac progenitors differentiation through specific interventions on epigenetics, paracrine signaling & metabolism
Promotor: BALLIGAND Jean-Luc

Date: 21/11/2019 Name: **VAN CALOEN Gabrielle**
Lab: MIRO
Thesis: Pre-clinical activity of cyclin dependent kinase 4 and 6 inhibitors in squamous cell carcinoma of the head and neck
Promotor: MACHIELS Jean-Pascal Copromotor: SCHMITZ Sandra

Date: 13/12/2019 Name: **VALET Maxime**
Lab: NMSK
Thesis: Multiple sclerosis-related fatigue and functional impairments. A rehabilitative approach
Promotor: LEJEUNE Thierry & STOQUART Gaëtan

Date: 17/12/2019 Name: **MEURISSE Guillaume**
Lab: NSMK
Thesis: La phase de transition d'un pied à l'autre durant la marche chez la personne âgée. Un pas vers la compréhension du risque de première chute
Promotor: SCHEPENS Bénédicte & BASTIEN Guillaume

Date: 20/12/2019 Name: **KAUTBALLY Shakeel**
Lab: CARD
Thesis: Investigating the platelet metabolic AMPK-ACC signaling in Coronary Artery Disease
Promotor: BEAULOYE Christophe Copromotor: HORMAN Sandrine

IREC SEMINARS 2019

DATE	SPEAKER	TITLE/THEME
14/02/2019	**Prof. Benoît Lengelé** (MORF, IREC, UCLouvain et Cliniques universitaires Saint-Luc)	Vascularized composite tissue engineering: the new frontier in regenerative surgery
25/02/ 2019	**Prof. Joerg Heeren** (Universitätsklinikum Hamburg-Eppendorf)	Brown fat and lipid metabolism
01/03/2019	**Dr. Pauline Montigny** (RUMA, IREC, UCLouvain) **Dr. Micaela Orsi** (LTAP, IREC, UCLouvain)	CD8+ T cells in the pathophysiology of lupus nephritis Origin, phenotype and function of mesotheliomagenic macrophages
01/04/2019	**Dr. Thomas Kirchgesner** (IMAG, IREC, UCLouvain)	MRI: Comparison of Dixon (IDEAL) with fat saturation sequences in rheumatoid hands
29/04/2019	**Prof. Nathalie Delzenne** (LDRI MNUT, UCLouvain)	The role for the gut microbiota in cardio-vascular dysfunction : hope for new therapeutic approaches?
02/05/2019	**Prof. Michel Hermans** (EDIN, IREC, UCLouvain) & **Prof. Patrice Cani**, (MNUT, LDRI, UCLouvain)	Targeting the gut to modulate metabolism: myth or reality? • The gut as endocrine organ (M. Hermans) • Impact of the gut microbiota (P. Cani)
27/05/2019	**Dr. Alexis Broisat** & **Dr. Pascale Perret** (INSERM - French Institute of Health and Medical Research)	Development of an imaging agent targeting VCAM-1 for the non-invasive detection of inflammation
23/09/2019	**Prof. Denise Hilfiker** (Hannover Medical School - Germany)	Pathophysiology and Management of Peripartum Cardiomyopathy
23/09/2019	**Dr. Julie Hussin** (IVADO - Université de Montréal)	Multi-omics data analysis in cardiovascular research

30/09/2019	**Prof. Olivier Devuyst** (NEFR, IREC, UCLouvain)	From rare to common: The genetic architecture of kidney disorders
07/10/2019	**Dr. Valery Payen** (PEDI, IREC - ADDB, LDRI, UCLouvain)	Single cell RNA sequencing reveals human liver heterogeneity
21/10/2019	**Julie Vanacker** (Clinical Trial Center, Cliniques universitaires Saint-Luc)	Organisation de la recherche clinique au sein des CUSL et support à la recherche académique UCLouvain
28/10/2019	**Dr. David Dombrowicz** (Institut Pasteur de Lille)	Metabolic and Innate Immune Cues Merge into a Specific Inflammatory Response via the UPR
14/11/2019	**Dr. Jérémy Fauconnier** (Université de Montpellier - Laboratoire de Physiologie et Médecine Expérimentale du Coeur et du Muscle)	Mitochondria at the heart of the diabetic cardiomyopathy
21/11/2019	**Prof. Sandrine Horman** (CARD, IREC, UCLouvain)	Metabolic signaling in the control of platelet functions
21/11/2019	**Dr. Shakeel Kautbally** (CARD, IREC, UCLouvain)	Implication for the coronary artery disease
25/11/2019	**Dr. Celine Bugli** & **Dr. Lieven Desmet** (Louvain School of Statistics, Biostatistics and Actuarial Sciences, UCLouvain)	A gentle introduction to Mixed Models in biomedical and clinical research
26/11/2019	**Prof. Jeremy Goldman** (Michigan Technological University, Biomedical Engineering, USA)	In vivo effects of metallic zinc in the arterial environment
16/12/2019	**Prof. Christiani A. Amorim** (GYNE, IREC, UCLouvain)	Artificial ovary

PHD DAY

PROGRAM

9h-9h30 *Registration and poster installation*

9h30-10h30 First session

Welcome

Marine Angé (CARD) - Ampk protects against lps-induced endothelial hyperpermeability via activation of p38 mapk/hsp27 pathway and control of junction

Violaine Sironval (LTAP) - HIF-1α is a key event of the lung toxicity induced by LiCoO2 particles

Tanguy Demaret (PEDI) - PEX1 p.G844D +/+ NMRI mouse: a robust pre-clinical model for mild Zellweger spectrum disorder

LTTO

10h30-11h15 *Posters & Sponsors*

11h15-12h15 Second session

CorSci

Laura Ferté (CARD) - Contribution of SGLT1 in cardiac glucose transport

Bilal Singh (EDIN) - Etude du contrôle de la sécrétion de glucagon par le glucose et les modulateurs des canaux KATP

Catherine Lambert (CUSL) - ross-cultural adaptation of a quality of life measure (CHO-KLAT) for boys with haemophilia in Ivory Coast.

BD Biosciences

Moderators AM: Cyril Corbet (FATH), Janice Vilela (GYNE), Anaïs Schaschkow (CHEX), Parinaz Asiabi (GYNE)

12h15 -13h45 *Lunch - Posters & Sponsors*

13h45-14h45 Third session

Geneviève Van Ooteghem (MIRO) - Breathing modulation with MANIV for patients treated with radiotherapy for thoracic or upper abdominal tumours: moving forward

Arnaud Devresse (NEFR) - No clinical benefit of rapid vs gradual tapering of immunosuppression to treat sustained BK virus viremia after kidney transplantation: a single-center experience.

Rossella Masciangelo (GYNE) - The role of Akt and mTOR pathways in follicle activation after grafting of human ovarian tissue

Julien Lebleu (CARS) - The challenge of ecological assessment

14h45-15h30 *Posters (top 4 announced) & Sponsors*

15h30-16h30 Fourth session

Pauline Montigny (RUMA) - Pathogenesis of lupus néphrites in a mouse modelof Systemic Lupus Erythematosus

Emna Ouni (GYNE) - Understanding the mechanical properties of human ovarian tissue through study of its elastic fibers

Matias Ramirez (CHEX) - Virtually assisted evaluation of Biocompatibility

Tom Darius (CHEX) - Brief O2 uploading at the onset of continuous hypothermic machine perfusion results in comparable early graft function compared

Moderators PM: Caroline Bouzin (2IP), Khan Bao (EDIN), Joao Santiago (FATH), Cristina Pavan (LTAP)

16h30 *Public vote & Awards*

POSTERS

DONTAINE Justine (CARD) A new possible way to reverse cardiac hypertrophy development: the inhibition of O-GlcNAcylation

GEORGES Coralie (CARD) Interaction of psychological profile, blood pressure level and drug adherence in hypertensive patients seen in an academic hospital

OCTAVE Marie (CARD) Oxidized low-density liproproteins activate platelet AMPK-ACC signalling through a CD36-dependent pathway

PETTINARI Matteo (CARD) New insight in functional tricuspid regurgitation : right ventricle evaluation by cardiac magnetic resonance before and after mitral valve surgery

ORIOLI Laura (EDIN) Impact of changes in muscle secretome on type 2 diabetes remission induced by bariatric surgery

RUIZ Lucie (EDIN) Role and regulation of δ-cell somatostatin secretion

NKAMBA MUKADI Dalau (EPID) Three out of four women are not screened for hypertensive disorders in pregnancy in kinshasa, dr congo

VAN GOETHEM Nina (EPID) Status and potential of pathogen genomics for public health practice: a scoping review

MELLY Ludovic (CELL/GENE) Myocardial infarction stabilization by cell-based expression of controlled Vascular Endothelial Growth Factor levels

NACHIT Maxime (GAEN) A longitudinal study of skeletal muscle alterations in NAFLD

LHEUREUX Alexis (NMSK) Autocorrelated Rhythmic Auditory Stimulations as the best way to use a metronome for Parkinson's Disease patients: a prospective

PIRAUX Elise (NMSK) Effects of preoperative combined aerobic and resistance exercise training in cancer patients undergoing tumour resection surgery

POILVACHE Hervé (NMSK) Study of the effect of pulsed washing on antibiotic susceptibility of Staphylococcus aureus biofilms.

CAYROL Timothée (NMSK) No evidence of widespread mechanical pressure hyperalgesia after experimentally induced central sensitization

WAUTIER Delphine (NMSK) Radiolucent Lines around Knee Arthroplasty Components: A narrative review

BLACKMAN Marine (FATH) Characterization of the metabolic control of brain metastasis in breast cancer

DIERGE Emeline (FATH) Therapeutic exploitation of tumor addiction to fatty acids under acidosis

VANDER LINDEN Catherine Metabolic plasticity and adaptive resistance to metabolic inhibitors in (FATH) tumor cells

COHILIS Marie (MIRO) A fully automated method for Monte Carlo commissioning in proton therapy

D'ABADIE Philippe (CUSL/MIRO) Dosimetric parameters using 90Y-PET-CT predict tumor and patient outcome after radioembolization of hepatocellular carcinoma

VAANDERING Aude (MIRO) Implementing a quality indicator project on a national basis: a feasibility study

LAFONT Sébastien (MORF) Role of the hyaluronidase Spam-1 in the pathogenesis of osteoarthritis

ALEVRA SARIKA Niki (PEDI) Production and characterization of human liver extracellular matrix hydrogels for in vitro culture of human liver cells.

GERARD Ludovic (PNEU) Hypoxic regulation of lung mucosal immunity

PLANTÉ-BORDENEUVE Thomas The role of the IgA/pIgR axis in idiopathic pulmonary fibrosis: lifting the (PNEU) tip of the veil

SANTOS RIBEIRO Diana (PNEU) GCN2 signalling is dysregulated in pulmonary fibrosis

GOLETTI Sylvie (RUMA) MMP7 and CXCL12: Two Promising Biomarkers in Lupus Nephritis

TRIAILLE Clément (RUMA) Comparison of transcriptomic profiles between paired joint biopsies from Rheumatoid Arthritis patients.

BALUNGWE BIRINDWA Patrick Evaluation de la fonction olfactive de patients présentant une dysfonction (CUSL-ORL) olfactive au Sud-Kivu (R.D.Congo)

VAN NIEUWENHOVE Sandy Follow up of patients with low and intermediate-risk PCa by imaging: Is MRI (CUSL) predictable of withdrawn from active surveillance?

Moderators posters: Bastien Doix (FATH), Debora Grasso (FATH), Olivia Lacroix (EPID), Micaela Orsi (LTAP), Gabrielle Van Caloen (MIRO), Amandine Colin (PNEU), Thomas Kirchgesner (CUSL), Guillaume Courtoy (2IP)

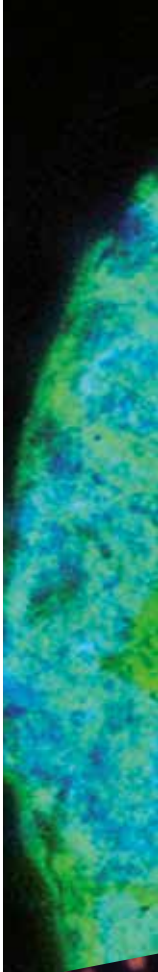
IREC LUNCH


4TH LUNCH
IREC
JOIN US ON THURSDAY, SEPTEMBER 12TH
AT 12:00 PM, -1 VESALE TOWER BY THE POND
Enjoy delicious french fries by
La Maison Antoine, cold drinks & desserts !
Fries

24H VÉLO LOUVAIN-LA-NEUVE

NOTES

Design: www.acg-bxl.be



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