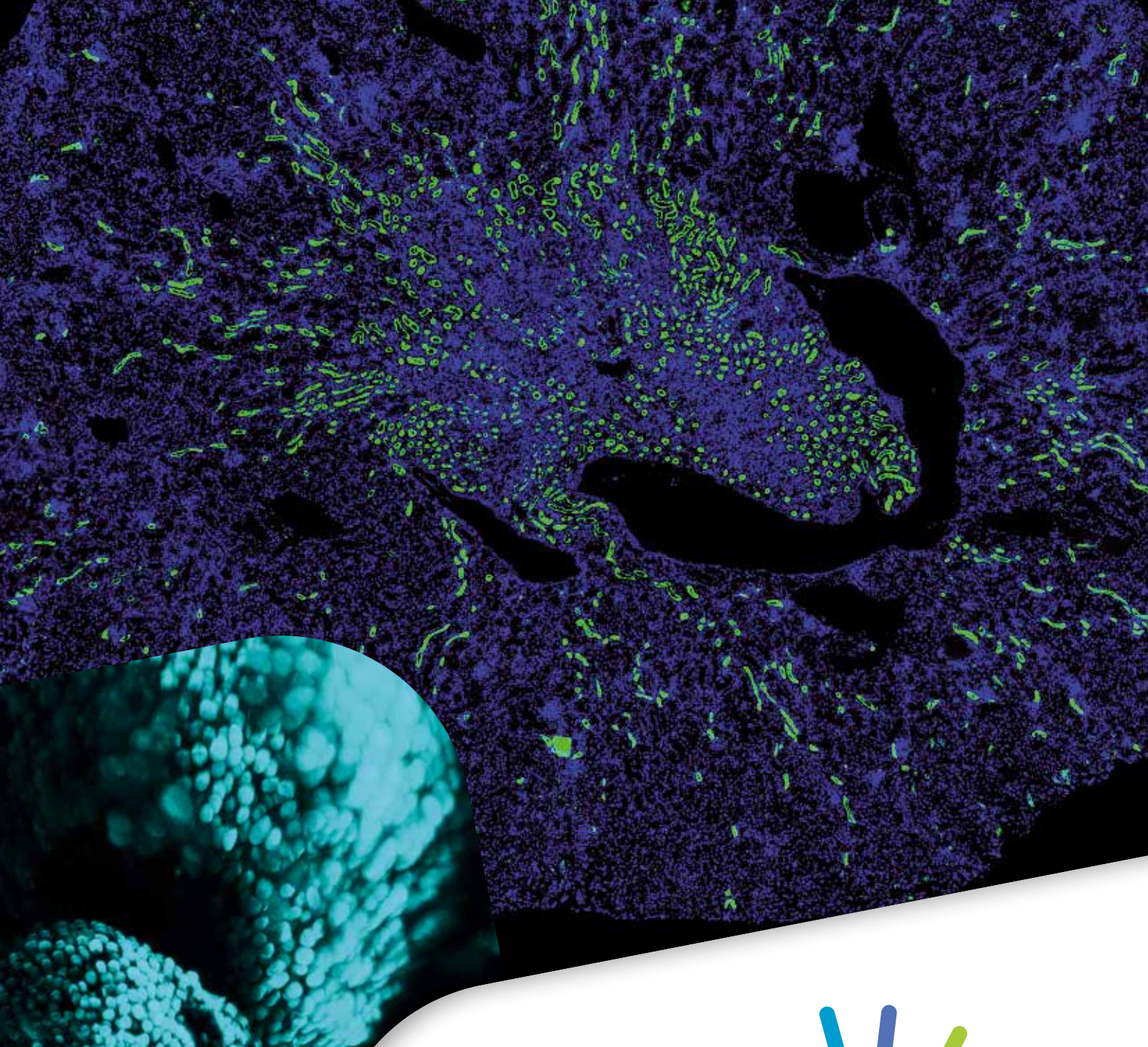
2020

ACTIVITY REPORT

IREC



« 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 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.

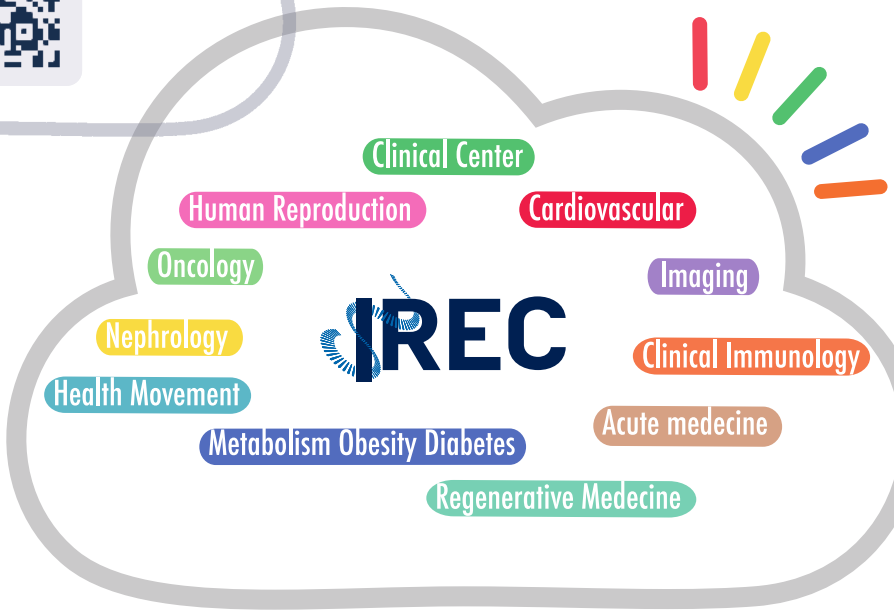
In this and other buildings of IREC, our technological platforms were further developed with the acquisition of state-of-the-art research tools accessible to our members, as well as external collaborators, thereby fostering intense exchanges of experimental protocols across disciplines and raising the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

The activities of the year 2020 were, of course, heavily impacted by the COVID-19 pandemic, as everywhere. Through concerted disciplined and patient adaptation, all members of the Institute, particularly our Clinician-scientists, managed to maintain adequate continuity in their research projects, as well as first-line care of patients at the height of the pandemic peak. Nevertheless, as in past years, we enjoyed the virtual lectures of prominent national and international scientists at our monthly Seminars. Through this year 2020, we have enjoyed the company and collaboration of many international young scientists, a number of whom (virtually) defended their PhD thesis, others competitively obtained research Fellowships and more senior ones were promoted to permanent-including academic- positions. A number of members of our technical and administrative staff were also promoted in their career tracks. These achievements are 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

SCAN TO WATCH IREC VIDEO:



UCLouvain

ADMINISTRATIVE STRUCTURE

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

President : *Professor Jean-Luc Balligand*

ADMINISTRATIVE COORDINATOR:

Veronica Curto

SCIENTIFIC COORDINATOR:

Nancy Van Overstraeten

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http://uclouvain.be/en/research-institutes/irec

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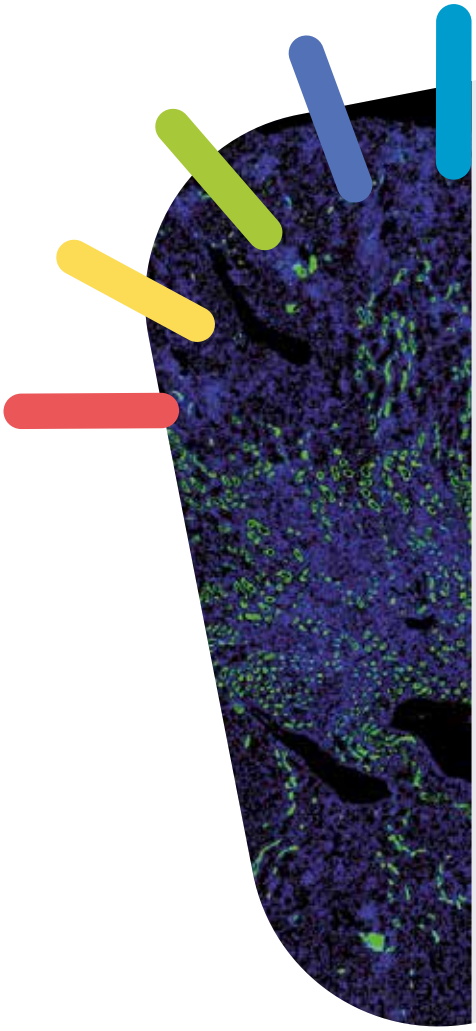
SCIENTIFIC ADVISORY BOARD

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 IS 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 IT INCLUDES :



Prof. B. Vanhaesebroek,
Professor at 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. Ferré,
Professor at Centre de Recherche des Cordeliers,
Paris, France

Prof. M. Goldman,
Professor emeritus at Faculty of Medicine,
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.

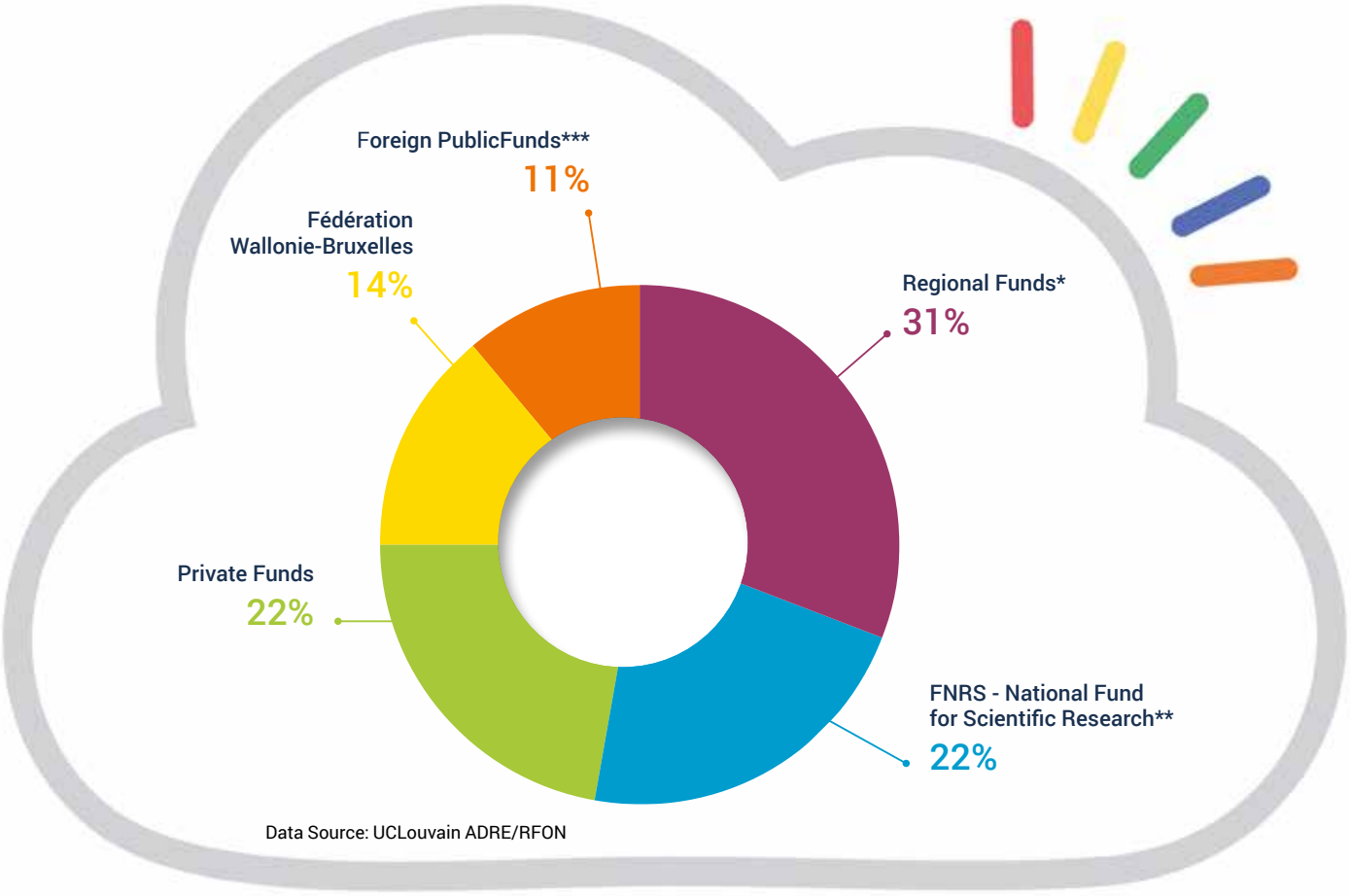
The SAB will regularly visit the Institute to monitor the progress and update the evaluation.

The next visit will take place in September 2021.

NEW RESEARCH AGREEMENTS AND CONTRACTS CONCLUDED IN 2020

Funding Sources	N. of agreements	Funding Amount
Regional Funds*	7	€ 4.041.420
FNRS - National Fund for Scientific Research**	95	€ 2.939.553
Private Funds	25	€ 2.925.007
Fédération Wallonie-Bruxelles	23	€ 1.909.416
Foreign Public Funds***	2	€ 1.449.950
TOTAL	**152**	**€ 13.265.346**

SIGNED FUNDING AGREEMENTS PER FUNDING SOURCE (%) 2020



Data Source: UCLouvain ADRE/RFON

** DGO6 included*

*** Welbio included*

**** European Funds*

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

Gébrine El Khoury, 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

Cédric Hermans, MD, PhD

Sophie Piérard, MD, PhD

Members:

Marine Angé, MD, PhD student
Julie Bodart, PhD student
Laurent Bultot, Postdoctoral Fellow
Julien Cumps, PhD student
Evangelos Daskalopoulos, Postdoctoral Fellow
David De Azevedo Coutinho Pereira, MD, PhD student
Mélanie Dechamps, MD, PhD student
Julien De Poortere, PhD student
Justine Dontaine, PhD student
Cécile Dufeys, Postdoctoral Fellow
Laura Ferté, PhD student
Natacha Fourny, Postdoctoral fellow
Anais Gauthey, MD, PhD student
Coralie Georges, PhD student
Audrey Ginion, Research Scientist
Laura Guilbert, PhD Student
Vincent Hanet, MD, PhD student
Pauline Krug, MD, PhD Student
Sibille Lejeune, MD, PhD student
Sebastien Marchandise, MD, PhD student
Nassiba Menghoum, MD, PhD student
Alice Marino, Postdoctoral fellow
Marie Octave, PhD student
Laurence Pirotton, PhD student
Nour Rahnama, MD PhD student
Edith Renguet, PhD student
Valentine Robaux, PhD student
Delphine Thibou, Technician
Emmanuel Vandenhooft, Technician
Carole Verhaegen, PhD student

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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:

Ramona Bella, Postdoctoral Fellow
Charlotte Bisilliat-Donnet, Postdoctoral Fellow
Hasnae Boughaleb, PhD student
Joël Cosse, Technician
Delphine De Mulder, Technician
Laurent Dumas, Postdoctoral Fellow
Hrag Esfahani, Research Scientist
Charlotte Farah, Postdoctoral Fellow
Virginie Joris, PhD student
Irina Lobysheva, Postdoctoral Fellow
Dorothé Marchand, PhD student
Thomas Metzinger, PhD student
Lauriane Michel, PhD student
Virginie Montiel, MD, PhD
Lucie Pothen, MD, PhD student
Delphine Thibou, Technician
Nancy Van Overstraeten, Postdoctoral Fellow
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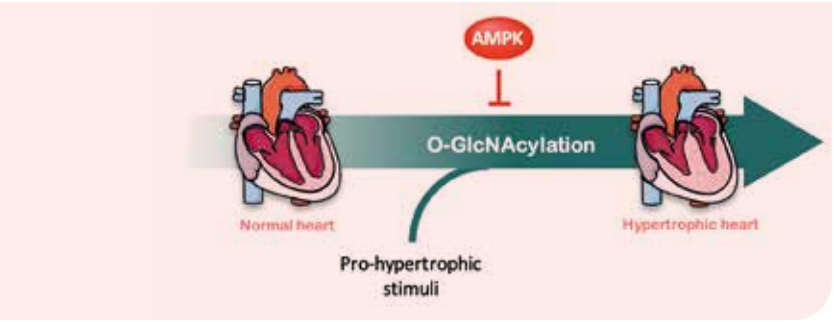
CARDIAC REMODELLING AND HEART FAILURE

CARDIAC HYPERTROPHY

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

J. Dontaine, L. Guilbert, N. Fourny, L. Bultot, S. Horman, C. Beauloye, L. Bertrand

We recently showed 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. More recently, we established an unbiased mass spectrometry approach to identify O-GlcNAcylated proteins in heart with the goal to find new therapeutic targets. Several candidates are currently investigated.



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.

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 (4). Deletion or inhibition of this channel also attenuates the hypertrophic remodelling in vitro/vivo. In search of underlying mechanism(s), we demonstrated that, in addition to facilitating rapid water movements, AQP1 conveys the transmembrane passage of H2O2 in specific subcellular compartments (e.g. caveolae). AQP1 is thus a bona fide "peroxiporin", and its expression in cardiac myocytes controls H2O2-dependent pro-hypertrophic signaling, in response to hemodynamic (TAC) or neurohormonal (angiotensin II, catecholamine) stress. AQP1-dependent regulation of oxidant signaling also modulates cardiac fibrosis, by controlling the paracrine effect of TGFbeta and CTGF. We demonstrated that an extract of the plant Bacopa monnieri, containing e.g. Bacopaside II, inhibits AQP1 permeability and also blocks hypertrophic remodeling in mice in vivo. The same extract taken orally in human volunteers blocks the uptake of H2O2 in erythrocytes (that express high amounts of AQP1). We identified a polymorphism of the human AQP1 gene that significantly modifies the expression of the protein in endothelial cells and cardiac myocytes. We are currently examining genotype/phenotype correlations between this SNP and cardiac hypertrophy in different cohorts of patients with different forms of hypertrophic cardiomyopathies.

Endothelial function and cardiac hypertrophy

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

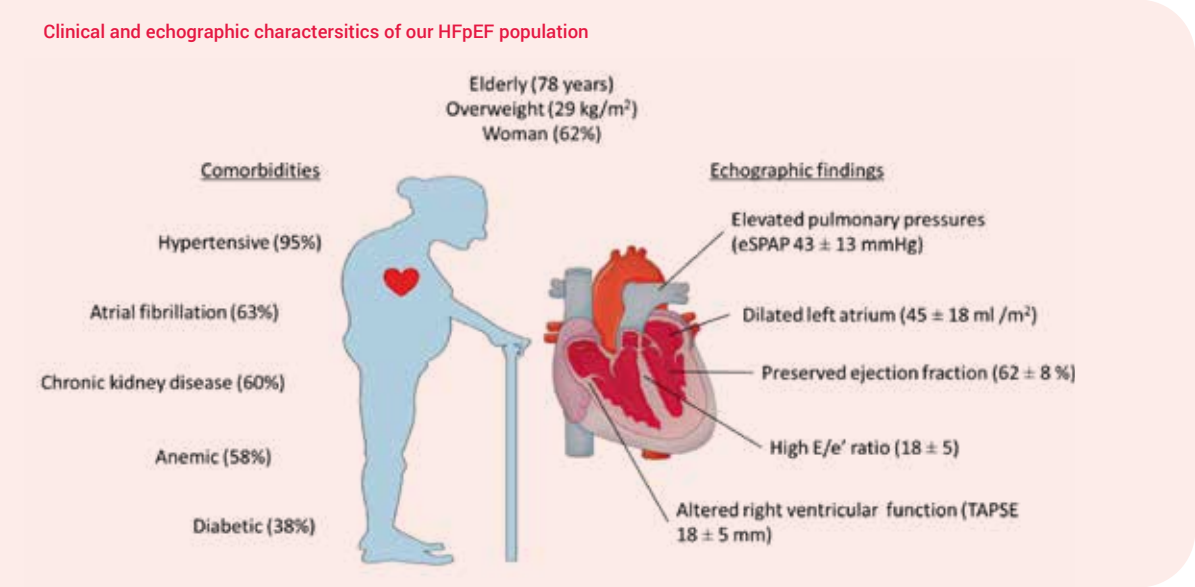
We are undertaking an unbiased comparative RNAseq analysis of endothelial cells in a mouse model of cardiac remodelling, before and after stress removal, to identify putative genes involved in the maintenance of endothelial dysfunction despite regression of hypertrophy.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

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

S. Lejeune, A. Ginion, L. Bertrand, S. Horman, B. Gerber, C. Beauloye and 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 are developing several mouse models recapitulating heart failure with preserved ejection fraction, with at least some echocardiographic aspects of the human phenotype. 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

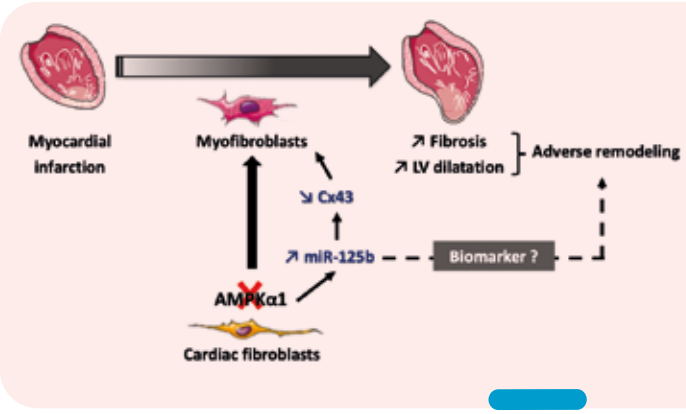
N. Hermida, H. Esfahani, J.-L. Balligand

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 myofibroblast differentiation and cardiac fibrosis. Conversely, activation of cardiac beta3-adrenergic receptors exerts anti-oxidant effects and protects against myocardial fibrosis and hypertrophy.

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.



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

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

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 myo-differentiation 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.

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. The role of several acetylated proteins in these processes is currently investigated. 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

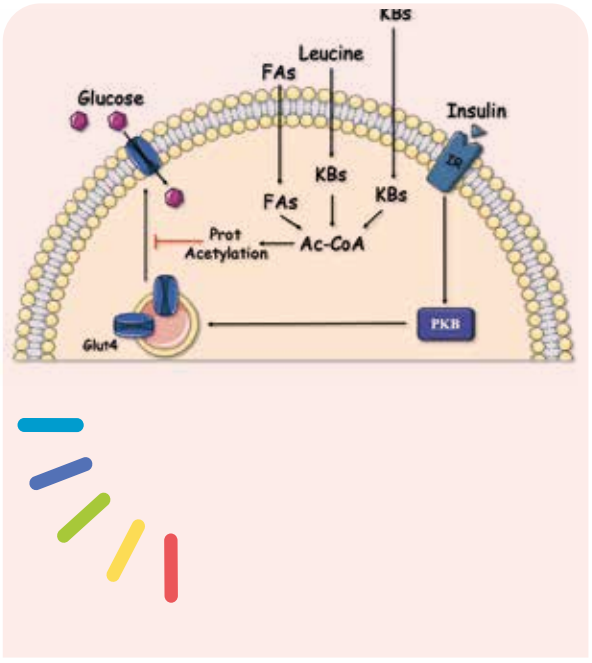
We found that expression of the beta3-AR in cardiac myocytes promotes glucose uptake under stress in these cells in vitro and in vivo (FDG-PET) and reverses insulin resistance, together with attenuation of the hypertrophic response. We are expanding this line of research with other metabolic substrates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

Role of sodium glucose co-transporters in the heart

L. Ferté, A. Marino, J. Cumps, L. Bultot, A. Ginion, S. Horman, L. Bertrand, C. Beauloye

Our laboratory showed that the sodium-glucose cotransporters SGLT1 and SMIT1 are expressed in mouse, rat and human cardiomyocytes. However, the role of these two transporters in the heart remain elusive and the aim of this project is to clarify their contribution in both cardiac glucose transport and pathophysiology of heart failure.

In our recent publication, we performed a deep characterization to investigate the contribution of SGLT1 in cardiac glucose transport. Using the pharmacological inhibitor phlorizin and genetic approach for inactivation of SGLT1, we demonstrated that in the murine heart SGLT1 is not responsible for glucose uptake. Moreover, for the first time we demonstrated that murine and human hearts present a truncated SGLT1 form, lacking important residues for glucose transport, explaining the absence of impact of SGLT1 in cardiac glucose transport. We previously showed that, in cardiomyocytes, SMIT1 responds to hyperglycemia inducing ROS production via



NOX2 activation, thus, in the light of our recent discovery, we can conclude that the sole SGLT isoform that actively transports glucose in the heart is SMIT1. Therefore, we have investigated whether SMIT1 plays a role in the pathophysiology of diabetic cardiomyopathy, in a model of type 1 diabetes induced by streptozotocin (STZ) in mice. We did not find significant differences in cardiac fibrosis (picro-sirius red staining) or hypertrophy (WGA staining) in Smit1-/- and WT mice kept hyperglycemic for 3 months. However, RNAseq analysis highlights a profound different gene expression in Smit1-/- and WT mouse hearts already at baseline, especially concerning fibrotic and hypertrophic genes. Given that cardiac fibrosis and hypertrophy are hallmarks of heart failure, ongoing studies are questioning whether myo-inositol and SMIT1 could impact cardiac properties and function in mouse models of pressure overload.

Protein O-GlcNAcylation, an important player in the development of diabetic cardiomyopathy

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

Diabetic hearts are characterized by elevated O-GlcNAcylation level. We are currently investigating the role of this O-GlcNAcylation in the development of the diastolic and systolic dysfunction occurring in diabetic cardiomyopathy. O-GlcNAcylomic studies allowed us to recently identify putative O-GlcNAcylated candidates. We plan to investigate their role in the next future.

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

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

Our work focuses on prognostic value of new non-invasive techniques for evaluation of the left and right ventricle performance. We performed work on cross modality comparison and validation of myocardial strain measurements by different techniques.

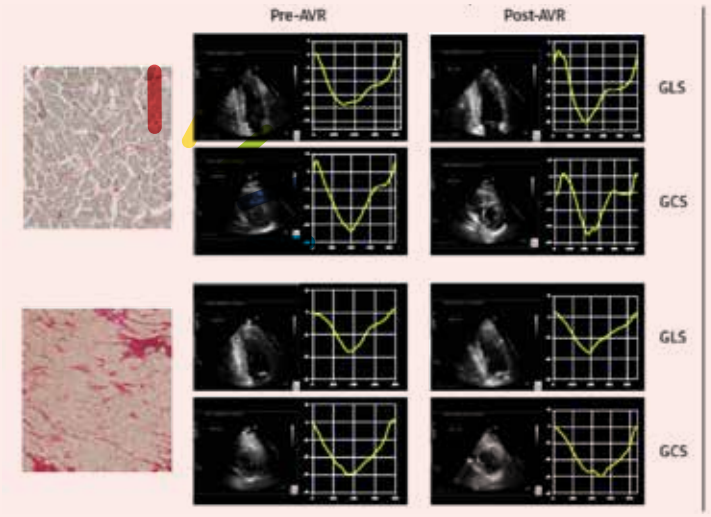
We also develop and validate new echocardiographic methods for quantification of regurgitant flow.

Finally, we performed studies validating pulmonary transit time as measurement for pulmonary congestion in heart failure by cT and MR and evaluated the prognostic value of this parameter on outcome of patients with heart failure with reduced ejection fraction.

VALVULAR HEART DISEASE

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

CARDIOONCOLOGY

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

Ongoing research focuses on determining the consequences of acute and chronic radiation exposure during radiotherapy for breast cancer on the heart on development of coronary artery disease, valvular heart disease and myocardial fibrosis. We will also start work on characterization of myocardial damage in patients treated by immune checkpoint inhibitors.

CARDIAC RHYTHM DISORDERS

A. Gauthey, S. Marchandise, B. Gerber

We performed work on the role of modulation of vagal tone on atrial fibrillation development. Other work was performed on optimizing left ventricular pacing by His bundle pacing and on studying impact of paced left ventricular dyssynchrony 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

CONGENITAL HEART DISEASE

N. Rahnama, S. Piérard

Ongoing research focuses on determining the consequences of congenital heart disease on fecundity, fetal development, and pregnancy complications as well as on ischemic placental lesions in women.

COAGULATION DISEASE

C. Hermans, C. Lambert

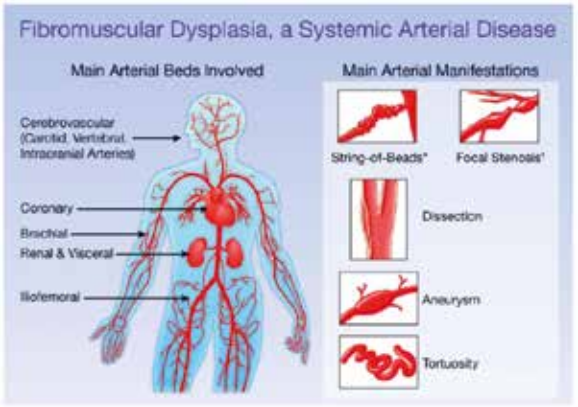
Research consists of evaluating genetics, arterial disease and new treatments for hemophila, in particular pharamacocinetics of coagulation factor VIII. Other works focusses on risk factors for thrombophilia, and in particular cutaneous and thrombotic lesions due to Covid-19 infection.

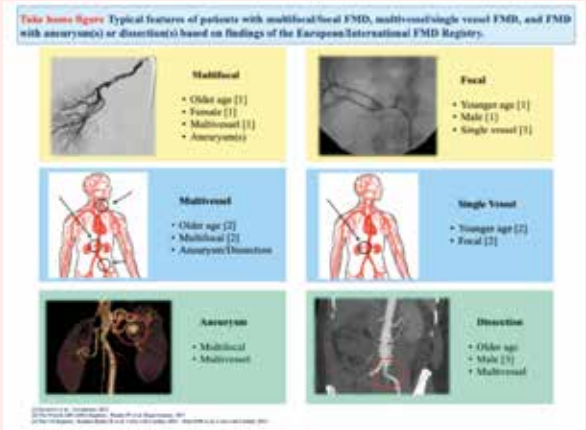
FIBROMUSCULAR DYSPLASIA AND RESISTANT HYPERTENSION

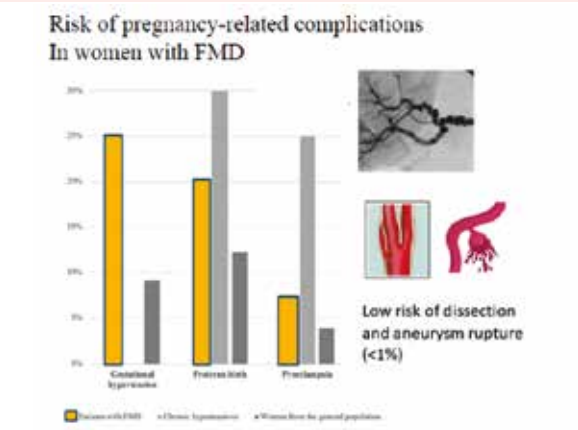
B. M. Pappaccogli, S. Ciurica, C. Georges, A. Persu

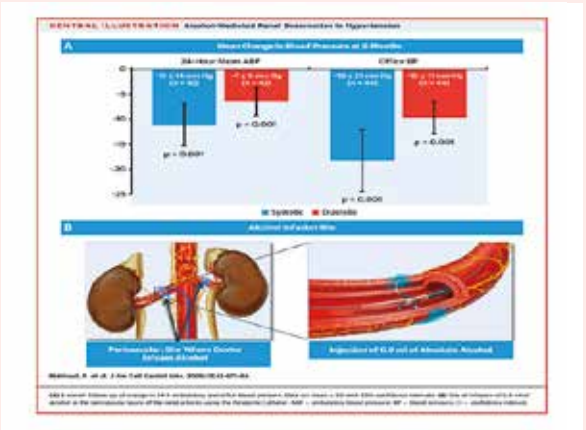
Fibromuscular Dysplasia (FMD): research consisted in identifying clinical phenotypes (Figure 1) and predictors of arterial complications (Figure 2) of FMD, based on in-depth analysis of 1000 patients from Europe and beyond, in looking for pregnancy-related complications in a large multicentre series of patients with FMD compared to normotensive and hypertensive women (Figure 3) and in assessing the role of rare variants in Loeys-Dietz Syndrome Genes in patients with FMD and Spontaneous Coronary Artery Dissection.

*Resistant hypertensio*n: research consisted in looking for the advantages of serum versus urine drug dosages to evaluate adherence to antihypertensive treatment and in investigating safety and efficacy of alcohol-mediated renal denervation in patients with resistant hypertension (see figure here below).









ENDOTHELIAL FUNCTION

MiR-199a and the NOS/NO pathway

V. Joris, D. Marchand, 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. Interestingly, both micro-RNA appeared to be differentially regulated in the heart and vessels from mice presenting a pathologic hypertrophy (following TAC surgery) versus mice allowed to freely exercise for 22 weeks and presenting a more physiologic cardiac hypertrophy. This suggest that the miR family is at miR targets that we have identified in both model of hypertrophy, regulate expression of proteins involved in cardiac metabolism and endothelial function. Our results suggest that alterations in endothelial cells and cardiac myocyte phenotypes accounting for cardiac and vascular adaptations are partly driven by changes in miR-199a abundance and place the miR-199a family at the cross-road between cardiovascular health and disease.

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. Our current work proposes to further document the mechanisms underlying the improvement in endothelial function.

Clinical assessment of endothelial (dys) function

J.-L. Balligand, H. Boughaleb, Ch. Bisilliat-Donnet, 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 (7, 8). 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.

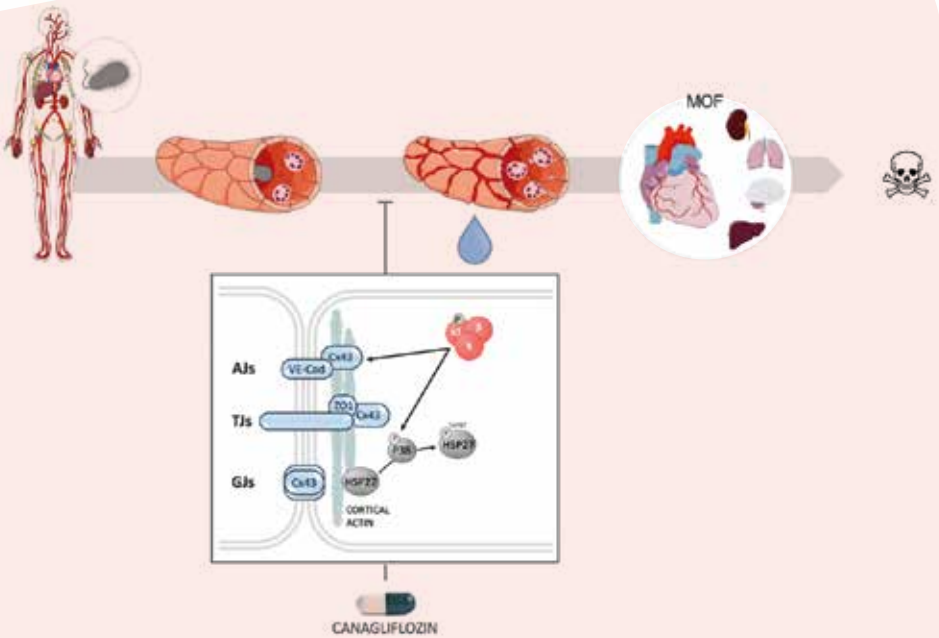
This biomarker is being validated in prospective clinical studies in patients with hypercholesterolemia and patients at risk for surgical operations, where it is correlated with classical cardiovascular risk factors to evaluate its interest to refine risk stratification.

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 in sepsis/AMPK signalling/SGLT2 inhibitors

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



travascular 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 disruption of interendothelial junctions 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, 2020).

In the continuity of this work, we have demonstrated the protective effects of Canagliflozin, a SGLT2 inhibitor, on sepsis induced vascular hyperpermeability, and highlighted AMPK as a key player involved in this protection (Angé et al, 2021). This might open the field to consider Canagliflozin as a new therapeutic support of sepsis induced capillary leak syndrome.

Vascular dysfunction and haemostatic disorders during sepsis/AMPK signalling

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

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.

Haemostatic disorders in Covid-19

M. Dechamps, J. De Poortere, Octave M, Ginion A, Robaux V, Pirotton L, Bodart J, V. Montiel, L. Bertrand, S. Horman and C. Beauloye

Host immune response to SARS-Cov2 infection induces a dysregulated inflammatory response associated with venous and arterial thrombosis called Covid-19 associated coagulopathy (CAC). During septic shock, inflammatory reaction activates the endothelium, which generates a procoagulant state with microvascular thrombi inducing disseminated intravascular coagulation (DIC). Although CAC and DIC both alter coagulation and fibrinolytic responses, their clinical outcomes are different. We have conducted a prospective clinical study in order to compare coagulopathy in septic shock and critical Covid-19 patients.

Endotheliopathy in Covid-19

V. Montiel and the CARD, FATH and MEDA teams

SARS-Cov2 infects a number of target cells in addition to pneumocytes. The virus may affect micro- and macro-vascular endothelial cells directly or indirectly. Contrary to septic shock, Covid-19 patients present with high plasma oxidant stress and NO-dependent endothelial dysfunction (low erythrocyte nitrosylated hemoglobin measured by EPR spectrometry) that is not related to overactivation of the RAAS or circulating leucocytes. Rather, TEM analysis of the lung microvasculature shows hyperactive, still intact endothelial cells, suggesting "hijacking" of the cell machinery towards virus replication known to be associated with high oxidative stress. The resulting endothelial dysfunction likely participates to the coagulopathy and thromboembolic complications of the disease.

PLATELETS AND THROMBOSIS

Metabolic signalling and protein acetylation

M. Octave, L. Pirotton, V. Robaux, 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, and on platelet biogenesis. We are currently testing this hypothesis, using pharmacological and genetic approaches to invalidate ACC activity.

Platelet GARP: a new player in cardiac fibrosis

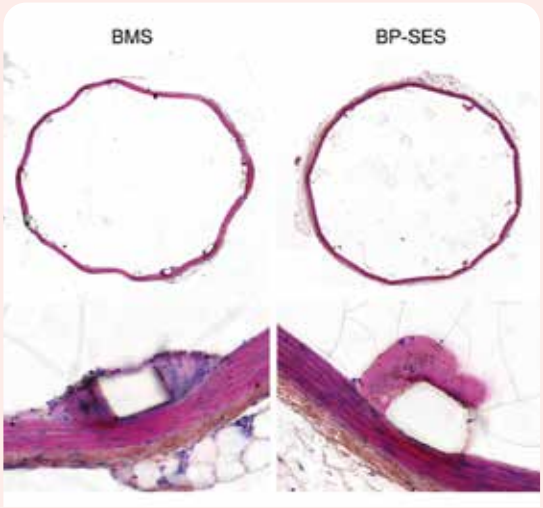
J. Bodart, C. Dufeys, L. Bertrand, C. Beauloye, S. Horman

Transforming growth factor (TGF)β is known to be a central player in the control of cardiac fibroblast properties and fibrosis. However, cellular and molecular mechanisms that trigger its activation remain poorly understood. Platelets are considered as a major source of TGFβ and recent evidence suggest that they are involved in TGFβ activation via Glycoprotein A Repetitions Predominant (GARP) present on their surface. We are conducting a study serching to evaluate the role of platelet GARP in TGFβ activation using platelet specific GARP knockout mice.

Early thrombogenicity of coronary stents: comparison of bioresorbable polymer sirolimus-eluting and bare metal stents

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

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. We therefore conducted a study aiming 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 data might be helpful to support the safety of a shortened 1-month DAPT duration following BP-SES implantation in the human coronary artery (Verhaegen et al, 2020).



Thrombus deposit at Day 1 following implantation. Left: Histological BMS section at Day 1 (at the top: magnification 1.7 ×; at the bottom: magnification 20 ×). Right: Histological BP-SES section at Day 1 (at the top: magnification 1.7 ×; at the bottom: magnification 20 ×).

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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 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

Whole-body magnetic resonance imaging for prostate cancer assessment: Current status and future directions.

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Collaboration with : Anwar R Padhani (Mount Vernon Hospital, London, UK), Vincent Vandecaveye (KUL), Joris Wuts (VUB)

Over the past decade, updated definitions for the different stages of prostate cancer and risk for distant disease, along with the advent of new therapies, have remarkably changed the management of patients. The two expectations from imaging are accurate staging and appropriate assessment of disease response to therapies. Modern, next-generation imaging (NGI) modalities, including whole-body magnetic resonance imaging (WB-MRI) and nuclear medicine (most often prostate-specific membrane antigen [PSMA] positron emission tomography [PET]/computed tomography [CT]) bring added value to these imaging tasks. WB-MRI has proven its superiority over bone scintigraphy (BS) and CT for the detection of distant metastasis, also providing reliable evaluations of disease response to treatment. Comparison of the effectiveness of WB-MRI and molecular nuclear imaging techniques with regard to indications and the definition of their respective/complementary roles in clinical practice is ongoing. This paper illustrates the evolution of WB-MRI imaging protocols, defines the current state-of-the art, and highlights the latest developments and future challenges. The paper presents and discusses WB-MRI indications in the care pathway of men with prostate cancer in specific key situations: response assessment of metastatic disease, "all in one" cancer staging, and oligometastatic disease.

OSTEOARTICULAR

Comparison between 3-point dixon- and chess-based omeract-recommended mri protocols in hands of patients with suspicion of early rheumatoid arthritis

Thomas Kirchgesner, Nicolas Michoux, Bruno Vande Berg

Collaboration with : Maria Stoenoiu (RUMA), Patrick Durez (RUMA)

PURPOSE: To compare fat suppression effectiveness, image quality and disease activity scores between MRI protocols based on the Dixon method and the Chemical Shift Selective (CHESS) technique in hands of patients with suspicion of early rheumatoid arthritis (RA).

METHOD: Both hands of 28 patients (19 women; mean age 45.2 years old) with suspicion of early RA were prospectively imaged with Dixon- and CHESS-based OMERACT recommended protocols at 1.5T including fat-suppressed T2-weighted and contrast-enhanced T1-weighted imaging. Two radiologists (R1/R2) separately assessed effectiveness of fat suppression and determined RAMRIS scores woth the Dixon- and CHESS-based protocols. R1 repeated the RAMRIS scoring and measured contrast-to-noise ratios (CNRs) on Dixon and CHESS images. Statistics included 2-way ANOVA test for the comparison of CNRs and Bland-Altman methodology for inter-technique and intra-observer agreement ($p<0.05$).

RESULTS: Fat suppression failure occurred in up to 1 patient with the Dixon- and 25 patients with the CHESS-based protocols. CNRs were significantly higher on T1-weighted and lower on T2-weighted Dixon images than on the corresponding CHESS images ($p\leq0.042$). Median bias of the difference between Dixon- and CHESS-based RAMRIS scores was not significantly different from 0 (-0.8 to +1.0 and -1.1 to +1.4 for R1/R2). Median bias of the difference between RAMRIS scores at first and second readings was significantly different from 0 with the CHESS-based protocols (-0.8 to +1.7) but not with the Dixon-based protocols (+0.0 to +1.0).

CONCLUSION: Dixon sequences yield more effective fat suppression and more reproducible RAMRIS scoring than CHESS sequences in hands with suspicion of early RA.

Topology of microfractures in osteonecrotic femoral heads at µCT and histology

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Collaboration with : Christine Galant(MORF), Emilie Wacheul (MORF), V Ganji ULB and Greet Kerckhofs (MORF)

METHOD : Sixteen resected human femoral heads with collapsed osteonecrosis (ON, n = 11) or osteoarthritis (OA, n = 5) were imaged at µCT with 12 µ nominal resolution. Forty-seven histological sections and µCT reformats with (n = 30) or without (8 from ON and 9 from OA femoral heads) osteonecrotic lesions were obtained and divided in 2 × 2 mm segments by a superposed grid. A radiologist and a pathologist separately assessed the presence of bone and cartilage microfractures in each segment on µCT and histological images, respectively. We determined the frequency and distribution of segments with bone microfractures according to a zonal distribution. Matrix analysis was performed by using Matlab to calculate the connectivity index and long/short axis ratios of clustered segments with microfractures. .

RESULTS : Segments with bone microfractures but not with cartilage microfractures were found more frequently in ON than in OA femoral heads. In the 38 matched µCT and histological images from ON femoral heads, 86%/82% of segments with cortical microfracture, 91%/96% of segments with trabecular microfractures involved ON lesions at µCT/histology. At histology, 83% of segments with cartilage microfractures involved ON lesions. In the 30 paired µCT and histological images containing necrotic lesions, the frequency of segments with trabecular microfractures in the superficial layers (55% at µCT/51% at histology) was statistically significantly higher than in the deep layer (25% P < 0.0001/35%; P = 0.0006). Clustered segments with cortical/trabecular microfractures, exclusively found in osteonecrotic lesions, had a connectivity index >2.0/20.0 and mean long/short axis ratio > 2.35/2.2, respectively.

CONCLUSION: Segments with bone microfractures predominate in necrotic lesions. Segments with trabecular microfractures form elongated clusters near the femoral head surface.

Diagnostic performance of sacroiliac joint MRI and added value of spine MRI to detect active spondyloarthritis

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Collaboration with : Marc Plier (RUMA), Adrien Nzeusseu Toukap (RUMA), Maria Stoenoiu (RUMA), Patrick Durez (RUMA), Bernard Lauwerys (RUMA)

PURPOSE: To investigate the diagnostic performance of sacroiliac joint (SIJ) magnetic resonance imaging (MRI) and the incremental value of spine MRI to "predict" clinical disease activity in patients with axial spondyloarthritis (axSpA).

MATERIALS AND METHODS : This cross-sectional study included adult patients with known axSpA according to the SpondyloArthritis International Society (ASAS) classification criteria, radiological arm. MRI disease activity was scored semi-quantitatively for SIJ and total spine MRI in each patient. Two cut-off levels (≥ 1.3 and ≥ 2.1) for ankylosing spondylitis disease activity score with C-reactive protein (ASDAS-CRP) were considered for clinical disease activity categorization. MRI scores were first evaluated individually. Then, SIJ score was combined with the score from a spine segment (lumbar, cervical, thoracic or total spine) to build a bi-parametric model using a classification tree. Receiver operating characteristic (ROC) curves were constructed to evaluate the classification performance according to disease activity category of these models.

RESULTS: Forty-four patients (30 men, 14 women; mean age, 37 years±10 [SD] [range: 17-64 years]) with a mean disease duration of 5 years±8 (SD) (range: 0-35 years) were included. Thirty-six patients (36/44; 82%) had ASDAS-CRP≥1.3 and 27 patients (27/44; 61%) had ASDAS-CRP≥2.1. The most frequently involved spinal segment was mid-thoracic (T7-T8). The SIJ MRI score was an informative model to identify active axSpA (AUC≥0.7, regardless of the cut-off level on ASDAS-CRP). Performance of bi-parametric models based on "SIJ+thoracic spine" (for detecting patients with ASDAS-CRP≥1.3) or "SIJ+total spine" (for detecting patients with ASDAS-CRP≥2.1) outperformed that of the individual SIJ score (P<0.05).

CONCLUSION: The combination of MRI of the SIJ and spine allows to accurately discriminate between active and inactive axSpA, outperforming SIJ MRI alone.

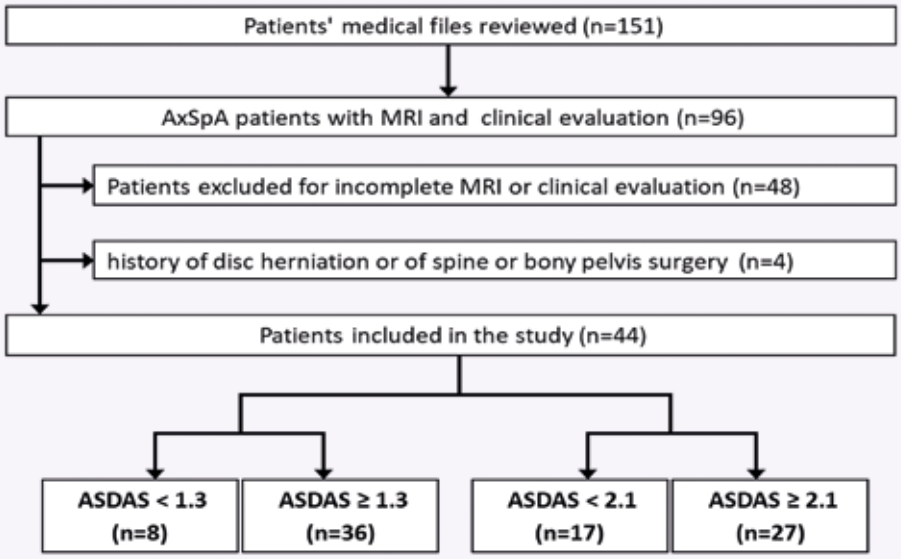

Figure 1: Flow diagram showing patients screened, included and excluded from the study.

DEEP LEARNING

Automatic Measurement of Kidneys and Liver Volumes from MRI of Patients with Polycystic Kidney Disease using Deep Learning

Nicolas Michoux, Vassiliki Pasoglou, Sabine Bodrero, Jorge Abarca-Quinones, Laurence Annet (IMAG – Radiology CUSL)

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PURPOSE: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited nephropathy, and the fifth cause of kidney failure (1). ADPKD is characterized by the progressive development of numerous cysts leading to kidney enlargement and impairment of kidney function. Total kidney volume (TKV) is an early predictor of chronic kidney disease (CKD) progression, unlike decline in glomerular filtration rate (GFR), which generally occurs late in ADPKD. TKV has accordingly been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a qualified biomarker for disease progression (2). Measurements of TKV and change in TKV are respectively used for patient selection and evaluation of efficacy of pharmacological treatments in ADPKD trials. TKV is most often measured using Magnetic Resonance Imaging (MRI). The gold standard technique for assessing TKV is manual tracing of kidneys contour, a task that is time consuming (up to 50 minutes per analysis) and thus is only performed for research purposes and interventional studies. Developing a faster as well as both, a non reader-dependent and non MRI vendor-dependent approach for segmenting the complex appearance (in terms of shape, contrast and texture) of polycystic kidneys would ease the quantitative follow-up of APKD patients in clinical routine.

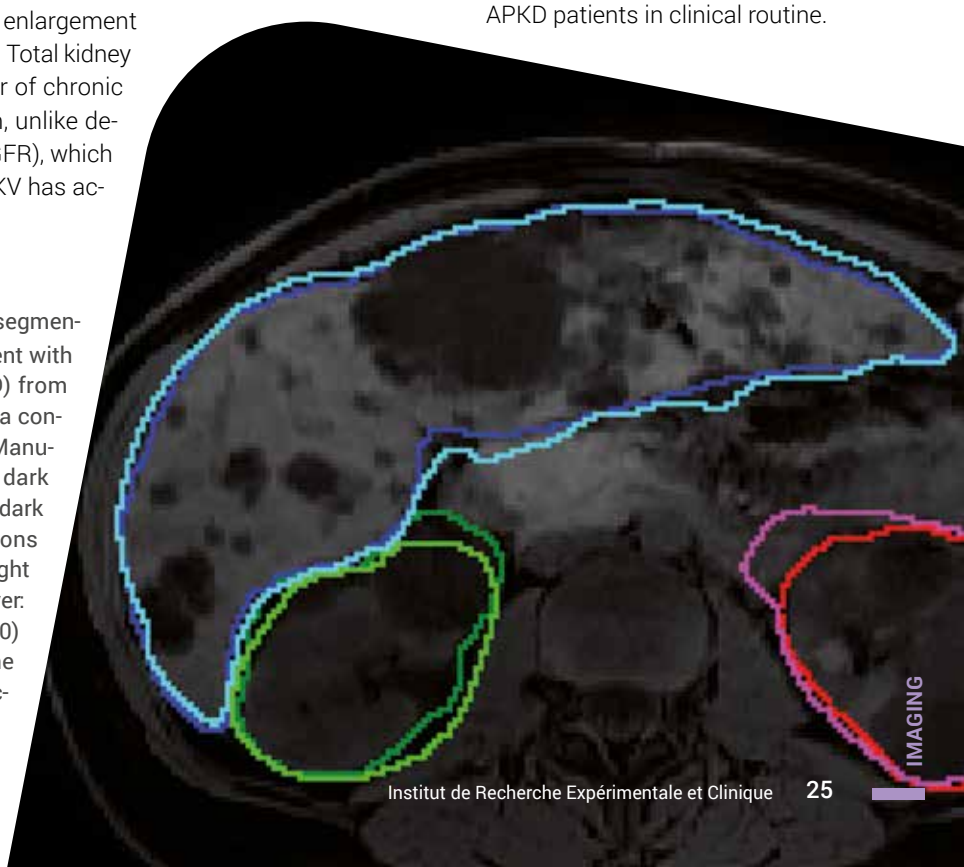

Figure 1: Manual versus predicted segmentation of kidneys and liver in a patient with polycystic kidney disease (ADPKD) from T1-weighted (DIXON) MRI in using a convolutional Neural Network (cNN). Manual segmentations are displayed in dark colors (liver: dark blue, right kidney: dark green, left liver: red), while predictions are displayed in light colors (liver: light blue, right kidney: light green, left liver: pink). The small training set (N = 100) of this preliminary study explains the differences observed between prediction and ground truth.

METHODS: A retrospective study based on N = 350 consecutive abdominal MRI examinations of patients with ADPKD followed in Saint-Luc Hospital (Brussels, Belgium) was performed. MR images were obtained for each patient including coronal T2-wieghted imaging, axial T1-weighted (DIXON) imaging. Segmentation was achieved using Vitrea® (Toshiba) software. The ground truth was based on the 2D contours from both kidneys and liver, manually drawn on the T1 (out-of-phase) images. Then, a Deep Learning approach based on a convolutional neural network (cNN) that predicts the probability of each voxel to belong to the left kidney, right kidney, liver or background was used. The architecture was based on U-Net (3) with a 6-layer depth, and included (i) a contracting path, which detects patterns in the input image and (ii) an expanding path, which recovers the original resolution of the image for the prediction. Dice statistics was used to assess the cNN performance in terms of predicted segmentations compared to the ground truth.

RESULTS: Preliminary results were based on N = 26 patients (training set), N = 10 patients (validation set) and N = 10 patients (test set), showing a cNN with a dice coefficient (mean ± std [min/max]) of 0.74 ± 0.15 [0.41/0.89] on the left kidney, 0.77 ± 0.10 [0.57/0.91] on the right kidney, 0.75 ± 0.10 [0.55/0.88] on both kidneys, and 0.87 ± 0.05 [0.76/0.92] on the liver.

CONCLUSION: This project continues in order to complete the analysis of the 350 patients. The building of a prospective testing set based on clinical MRI examinations scheduled on 3 different MRI vendors and 2 different magnetic fields (1.5T and 3.0T) is also in progress. The goal is to obtain a highly-accurate and fast delineation of polycystic kidneys (and liver) resulting in a routine measurement of TKV for following ADPKD progression.

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Automatic Measurement of Kidneys and Liver Volumes from MRI of Patients with Polycystic Kidney Disease using Deep Learning

EQUIPMENTS

New MRI research magnet : ***Availability of the new advanced MRI research magnet, dedicated to translational and clinical research, within the IMAG pole, to 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)

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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 IFNα displays direct effects on B cell activation and differentiation. In SLE B cells, IFNα 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-IFNα 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 IFNα 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.

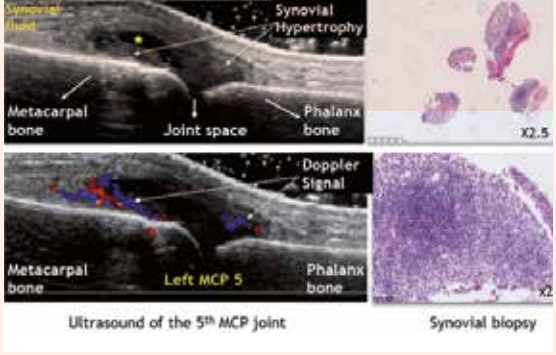

Figure 1: Ultrasound-guided synovial biopsies deliver material for a better stratification of RA patients based on the identification of specific molecular profiles in the tissue.

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LOUVAIN CENTRE FOR TOXICOLOGY AND APPLIED PHARMACOLOGY (LTAP)

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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.

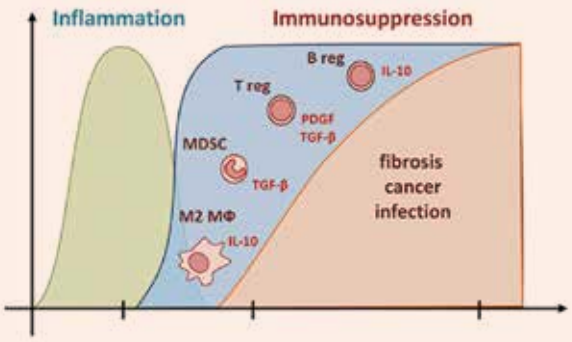

Figure 1: ***Pathological functions of persistent immunosuppressive cells and mediators during long-term responses to particles.*** Unresolved Immunosuppression (in blue) represents an alternative event during the responses to particles. According to this new pathological pathway, fibrogenesis, and carcinogenesis 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.

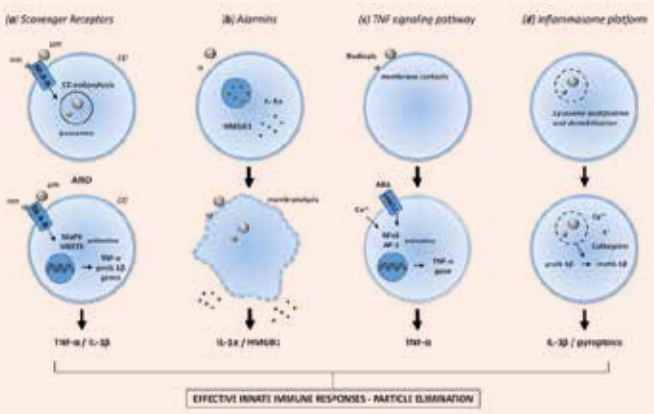

Figure 2: ***Early sensing and alerting processes are combined and mutually linked in response to inhaled particles.*** (a1) Micrometric (µm) and nanometric (nm) particles are internalized by phagocytes through the scavenger receptors (SR) A and B and clathrin-dependent (CD) endocytosis. (a2) Particle 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; biology of lung cancer and non-pharmacological treatment of these disease such as exercise and physiotherapy.

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. Spe-

cific 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. The place of exercise and rehabilitation in patients with lung cancer was largely investigated. Physiological effects of airway clearance techniques were also studied by the group including original tools of evaluations (electrical impedance tomography, lung clearance index). Their effect on the physical properties of sputum was quantified by the use of rheology. Moreover, the oxygen delivery was recently included in the thematic of the group with studies about high flow and way of delivery. In the particular context of the COVID-19 pandemic, the field of interest of the group was mainly focused on the consequences of the virus on oxygen need and functional exercise capacity.

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.

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.

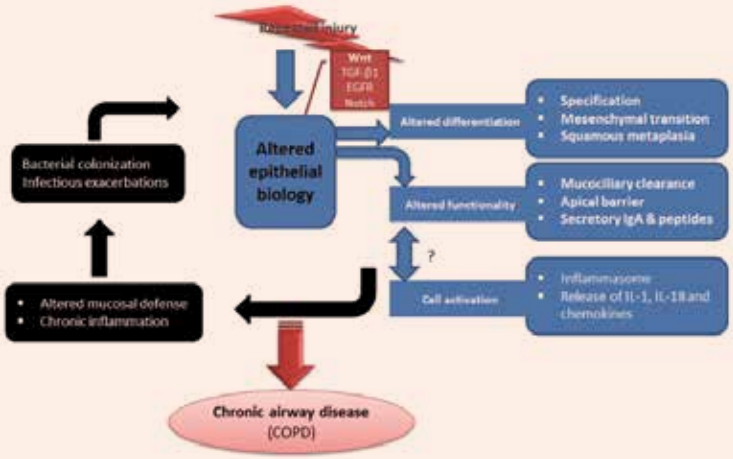

Figure 1. Hypothesis of airway epithelial cell dysregulation in COPD. The epithelium, repeatedly activated by cigarette smoke may become persistently dysregulated through aberrant signalling, with altered differentiation and functionality. This leads to impaired frontline defense against pathogens, further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

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.

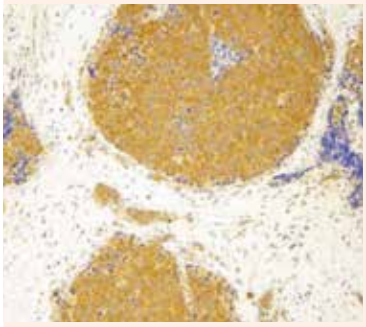

Figure 2. ***Total FAK expression in a small-cell lung cancer tissue.*** Two tissue microarrays consisting of SCLC tissues coming from 85 patients were incubated with an antibody against total FAK (A-17). In this figure is displayed a representative image of SCLC tumor with moderate total FAK expression.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

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.

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 PNEU) according to a translational research.

The research is primarily focused on the six following topics: (1) sepsis and septic shock; (2) thrombosis management; (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).

This 2020 year was particularly demanding for clinicians working in acute medicine due to the Covid 19 infection. This report will focus attention on research paper devoted to severe coronavirus disease, concerning various themes like the challenge of ventilator-associated pneumonia, the place of antibiotics, the role of Interleukin 7 immunotherapy, and the management of thrombosis including pulmonary embolism.

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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). PF. Laterre and X.Wittebolle coordinated a phase 2 clinical trial on the safety and efficacy of Nangibotide, which is a specific TREM-1 inhibitor that tempered deleterious host-pathogens interactions, restored vascular function, and improved survival, in animal septic shock models. The positive results in 49 randomized patients encourage further evaluation of Nangibotide and further exploration of plasma sTREM-1 concentrations as a predictive efficacy biomarker in septic shock.

F.Verschuren included 36 of 460 patients of a multicenter study aiming to evaluate the prognostic performance of endothelial biomarkers to early predict clinical deterioration of patients with suspected bacterial infection and sepsis admitted to the emergency department. One biomarker seems of interest to predict deterioration of patients with suspected bacterial acute infection upon ED admission and could help front-line physicians in the triage process.

PF Laterre coordinates the current European SEPCELL trial, A phase Ib/IIa, randomised, double-blind, multicentre trial to assess the safety and efficacy of expanded Cx611 allogeneic adipose-derived stem cells for the treatment of patients with community-acquired bacterial pneumonia admitted to the intensive care unit.

Management of thrombosis in the COVID 19 area

The year 2020 was marked by a pandemic caused by the new SARS-CoV-2 which shook the world of clinical practice and research. The first observations of patients with COVID-19 reported a laboratory hypercoagulable state which clinically translated into a high thrombotic risk, which could explain a significant part of the morbidity and mortality associated with the disease. A better understanding and management of the haemostatic imbalance associated with the disease therefore seemed essential to optimize patients' management.

Thanks to close work between clinicians and researchers, we were able to contribute to the characterization of the hemostatic disorders associated with severe COVID-19 and their daily evolution during the ICU stay. We have published practical recommendations for the assessment of hemostasis and thrombotic risk in COVID-19 patients. Finally, we are also evaluating the potential value of integrative biomarkers for the assessment and monitoring of the thrombotic risk associated with this disease. Team involved: Hardy Michaël, MD PhD student, Lessire Sarah, MD PhD, Dive Alain, MD PhD, Michaux Isabelle, MD PhD, Bulpa Pierre, MD

Rapidly after the emergence of SARS CoV-2 virus, the rate of pulmonary embolism was questioned. To answer at that specific question, G. Horlait included patients in the COVADIS study. At day 28, 15% of ARDS patients were diagnosed with pulmonary embolism.

Improvement of the perioperative management of anticoagulants and anti-platelet therapy

Studies on the monitoring of residual apixaban level in and outside the perioperative context, the pertinence of using direct oral anticoagulants plasma concentrations as tresholds for clinical-decision making, and the potential interest of andexanet alpha for the reversal of anti-Xa anticoagulants have been published. In a retrospective study using Multiple Electrode Aggregometry, we have analyzed the impact of assessing platelet function in the management of an urgent clinical context of patients on anti-platelet therapy (P2Y12 Inhibitors). A future project concerns the use of viscoelastic tests to manage the perioperative bleeding of patients ongoing complicated lung transplantation in order to improve patient blood management. Team involved: Lessire Sarah, MD PhD, Dincq Anne-sophie, MD, Hardy Michaël, MD, PhD student

Cardiopulmonary resuscitation and the role of cerebral saturation

One of the most challenging aspects in the treatment of a (post-)cardiac arrest patient is the assessment of the extent of brain damage, and its concomitant prognosis. Clinicians are continuously confronted with the optimistic expectations of relatives. Parameters that provide early prognostic information are highly desirable in the (post-)cardiac arrest setting since they would facilitate communication with relatives and would allow better triage of economically burdensome therapies. Reliable, practical measures of intra- and post-arrest neurologic function have potential to guide treatment geared toward reducing neurological damage and providing a basis for accurate prognostication. C. Genbrugge was one of the authors of a manuscript describing the current monitoring parameters during CPR. A persistent candidate measure to fill this role is cerebral oxygen

saturation (rSO2) monitoring, as assessed by near-infrared spectroscopy (NIRS) technology. However, the use by itself in the post-cardiac arrest setting seems limited. Furthermore, C. Genbrugge investigated the effect of elective electrical cardioversion and atrial fibrillation on rSO2 to get a better insight in the effect of different cardiac rhythms and cardiac output on rSO2.

Management of lung and respiratory parameters

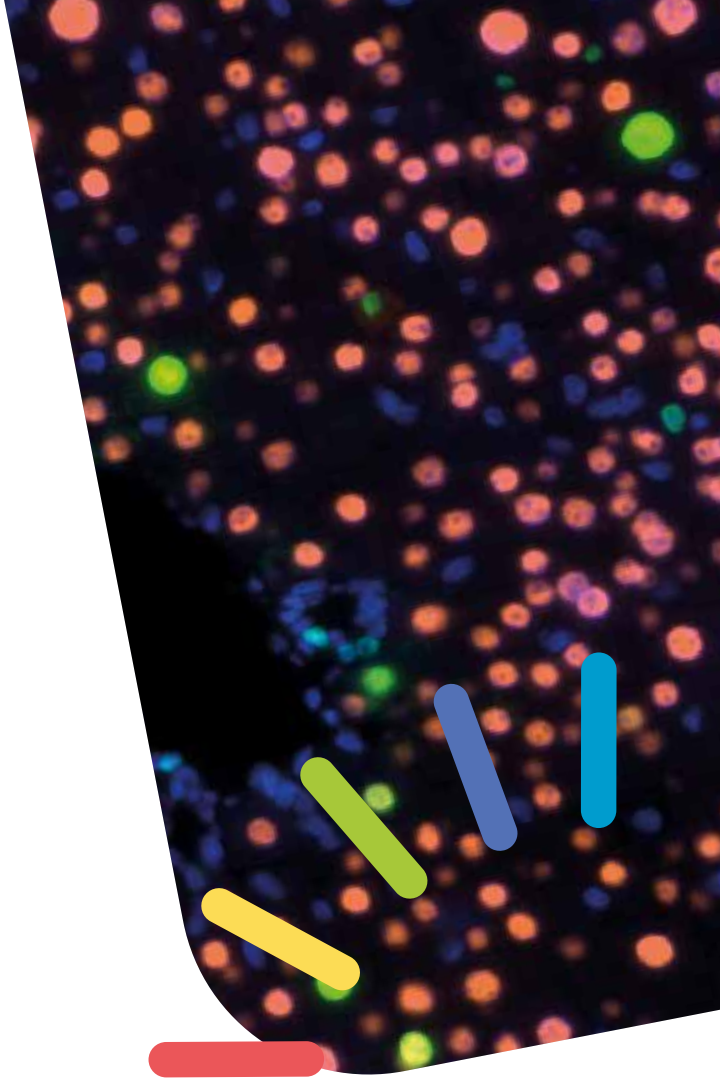
The lung, and more generally the respiratory system, is very frequently failing in patients admitted to the intensive care unit. However, the physiopathological mechanisms involved in this failure are not completely known. Research in respiratory pathology in acute patients is currently articulated over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

Airway stenting offers good palliation and improves the quality of life of patients with judged inoperable bronchotracheal stenosis. During rigid bronchoscopy if high frequency jet ventilation or superimposed high frequency jet ventilation are not enough to ensure adequate oxygenation, a strategy for maintening oxygenation should be anticiped for these critical situations. Extracorporeal membrane oxygenation (ECMO) support placed on local anesthesia is helpful for the high-risk management of bronchotracheal stenting. Anesthesia for endobronchial valve insertion allowing lung volume reduction is another anesthetic challenge: patient suffer from severe emphysema, and are often elderly with multiple comorbidities. Team involved: Laurie Putz, Anne-Sophie Dincq, Sabrina Meyer and Maximilien Gourdin

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 secondary analysis, the study could demonstrate that: 1. hyperoxemia and excess oxygen use were both prevalent in early ARDS but were most often non-sustained. No relationship was found between hyperoxemia or excessive oxygen use and patient outcome;; 2. No evidence was found for benefit or harm with hypercapnia.

P. Bulpa and A. Dive included patients in the INTEREST study with the objective to determine the efficacy and adverse events of IFN-β-1a in patients with moderate to severe ARDS. However, compared with placebo, the administration of IFN-β-1a resulted in no significant difference in a composite score that included death and number of ventilator-free days over 28 days. These results do not support the use of IFN-β-1a in the management of ARDS.

In the Covid 19 area, the St-Luc ICU team reviewed the challenge of ventilator-associated pneumonia diagnosis in COVID-19 patients. The same team investigated in a prospective cohort analysis the respiratory co-infection rate in COVID-19 critically ill through the use of rapid molecular testing and measured its impact on antibiotic management. They also examined whether interleukin 7 (IL-7) was associated with restored host protective immunity in severe coronavirus disease.



Patients suffering from COVID-19 infection may develop severe ARDS. In that context, G. Horlait contributed in the COVADIS study which observed a large and prolonged use of Neuromuscular blocking agent (NMBA). After adjustment, a prolonged course of NMBA was not associated with a lower rate of extubation at day 28. This study also observed that neither hydroxychloroquine nor lopinavir/ritonavir were associated with higher ventilator-free days at day 28 when compared with standard of care.

Ludovic Gerard also participates in collaborative and transversal research activities between the two IREC poles PNEU and MEDA, devoted to acute medicine thematic. He has recently published a retrospective analysis of the prone positioning in spontaneously breathing patients with moderate or severe ARDS under invasive mechanical ventilation, showing that it was well tolerated and achieved significant improvement in arterial oxygenation.

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 confirmed his expertise in the management of severe poisoning. Let us mention the management of a severe trazodone intoxication with the administration of intravenous lipid emulsion.

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REGENERATIVE MEDICINE

Research Poles

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Research Projects

Improving ovarian tissue transplantation using adipose tissue-derived stem cells

L. Cacciottola, M-M. Dolmans

Among fertility preservation techniques, ovarian tissue cryopreservation and transplantation has been shown to restore hormonal cycles and fertility, but a large proportion of the follicle reserve is lost as a consequence of exposure to hypoxia (1).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), which proved effective in mitigating post-transplantation hypoxia, boosting graft revascularization and enhancing follicle survival after short-term grafting. The use of ASCs yielded a larger primordial follicle pool and more physiological follicle distribution after long-term grafting (6 months), with a potential to extend ovarian tissue lifespan and fertility potential (2). Moreover, we demonstrate that ASCs exert positive effects on the ovarian reserve, not only by protecting primordial follicles from apoptosis but also by maintaining their quiescence through modulation of the PI3K/Akt pathway, which is responsible of abnormal follicle activation and depletion (3). We believe that this robust evidence in favor of the two-step ovarian tissue transplantation using ASCs will lead to clinical application in near future.

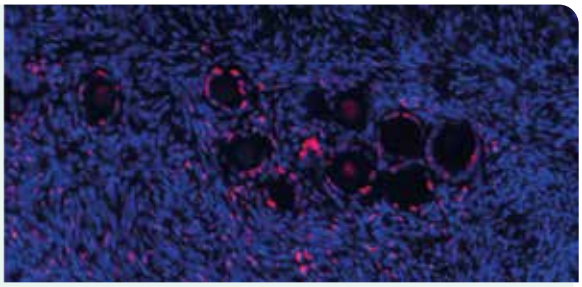

Figure1. Frozen-thawed human ovarian tissue stained with HIF1 (in red) (40X) and DAPI (blue nuclei).

In vitro differentiation of human theca cells

P. Asiabi, E.C.R. Leonel, A. Camboni, M-M. Dolmans, C.A. Amorim

While theca cells (TCs) play a pivotal role in follicle development and production of female steroids, they have never been studied as comprehensively as granulosa cells (GCs). Recently, recruitment and differentiation of TCs were investigated in different animal models. In mice, a subpopulation of cells known as progenitor TCs was reported to differentiate into TCs. On the other hand, in goats and cows, studies revealed that TCs can be converted from ovarian cortical stromal cells. In both cases, the differentiation process was shown to be regulated by factors secreted by GCs and the oocyte. To investigate how TCs differentiate in human ovaries, we first characterized human TCs at different stages of follicle development in relation to steroidogenic enzyme expression and quantification, lipid storage markers and LH/CG-R levels (4). The identification of these markers as well as the proportion of ovarian stromal cells we could isolate (5) from older patients were crucial steps for our TC differentiation study. To investigate how these cells differentiate in human ovaries, we attempted to mimic the in vivo differentiation process by employing different growth factors and adding companion GCs. The resulting TCs closely resembled their ovarian counterparts when investigated by immunohistochemical, ultrastructural and functional analyses (6).

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 and recently improved our MS approach to matrisome characterization (7) 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 glycosaminoglycans (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 (8). 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.

Ovarian tissue cryopreservation and transplantation in patients with central nervous system tumors

T.Y.T. Nguyen, L. Cacciottola, A. Camboni, M-M.Dolmans

Central nervous system (CNS) tumors have the second highest incidence after leukemia in children and often require gonadotoxic treatment, with ovarian tissue cryopreservation remaining the only viable fertility preservation option. Ovarian metastasis potential has been documented in patients with leukemia, borderline ovarian tumors, advanced breast cancer and Ewing sarcoma. Our study is the first study to be conducted in patients with CNS cancers undergoing ovarian tissue cryopreservation and transplantation, and clearly demonstrates no tumor seeding in their frozen-thawed and xenografted tissue (9,10). Indeed, our results indicate that the risk of disseminated disease in CNS patients is minimal (11). This information is vital for doctors to provide patients with meaningful and accurate advice on the possibilities and risks of ovarian tissue reimplantation.

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

D. Kourta, F. Del Vento, J. Poels, MG. Giudice, C. Wyns

We aim to elaborate a porcine bioengineered testicular scaffold to incorporate sorted (free of cancer cells) and propagated human testicular cells with a view to increase knowledge on the SSC niche in vitro, and to achieve in vivo differentiation of SSCs after transplantation (12). By comparing different decellularization protocols of pig 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.

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Research Projects

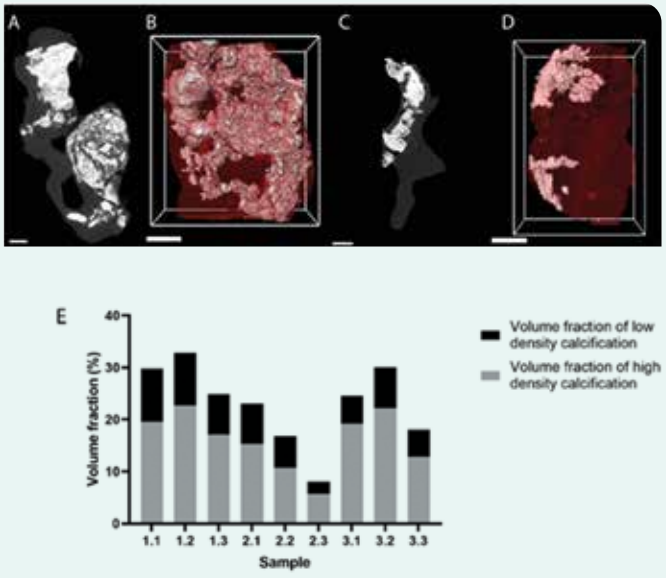
For two decades, Vascularized Composite tissue Allotransplantation (VCA) has represented a true revolution in the field of reconstructive surgery. However, the indications for such transplants remain very limited (fewer than 200 cases for limbs, 45 cases for the face, world-wide) because of the need 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 heart valves, allows to remove cells and antigens from a native tissue by physical and / or chemical agents, while preserving the extracellular matrix (ECM) 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-de-cellularization / 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.

VCE research potentially interests all organs and tissues, while requiring corresponding disciplinary competences. The Regenerative Medicine Against Ageing (RM2A) project aims to develop such research in order to alleviate age-related deficiencies in various organs, such as cardiac valves or bones, for example. In our multidisciplinary consortium, clinicians, biologists, morphologists and engineers collaborate towards (i) microstructural characterization of native and diseased tissues as well as the decellularized ECM, (ii) blood vessel reendothelialization and (iii) matrix recellularization. Different experimental models are tested using human or animal tissues and organs in order to approach gradually the different degrees of the structural, functional and 3-dimensional complexity of the recellularization process.

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 ECM, which 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, native, diseased and decellularized tissues will be used. The PhD of Camille Pestiaux is focused on CE-CT imaging of heart valves, and her aim is to characterize the microstructure and the mechanical behavior of heart valves with this imaging technique. In a first step, diseased tissues have been characterized. For this purpose, human stenotic 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.



Fresh calcified aortic valves (n=3) from human patients explanted for aortic valve replacement. Fresh human aortic valves scanned with a microCT without contrast-enhancement. Soft tissues and calcifications were segmented based on grey values. (A,C) Cross-sectional 2D slice of samples 1.2 and 2.3 respectively after region of interest (ROI) selection, (B,D) 3D rendering of samples 1.2 and 2.3 respectively; calcifications are white and soft tissue red. (E) Volume fraction of the calcifications in the entire valve. Scale bars represent 1mm.

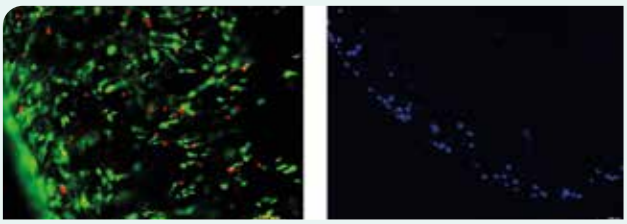
Vascular tree characterization, decellularization and recellularization

Louis Maistriaux, Vincent Foulon, Catherine Behets, Greet Kerckhofs, Benoît Lengelé

Decellularized vascularized composite tissues such as face, ear, nose, hand or finger, have shown cytocompatibility of 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).

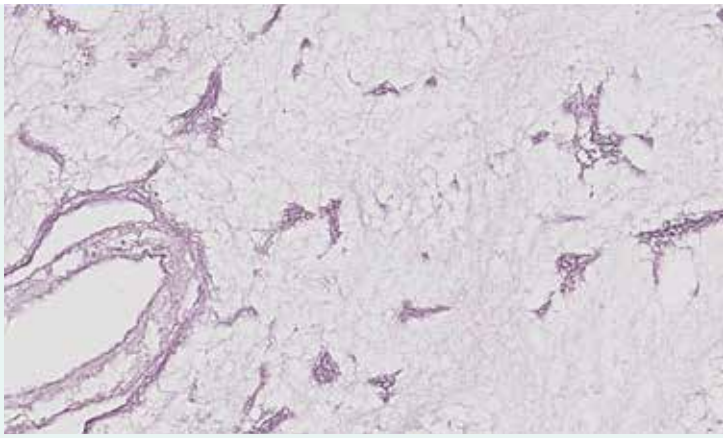


In vitro cytocompatibility test of gastric decellularized matrix with NIH3T3 after 9 days of static cell culture. Left: Live/dead staining (10x). Right: DAPI staining (10x).

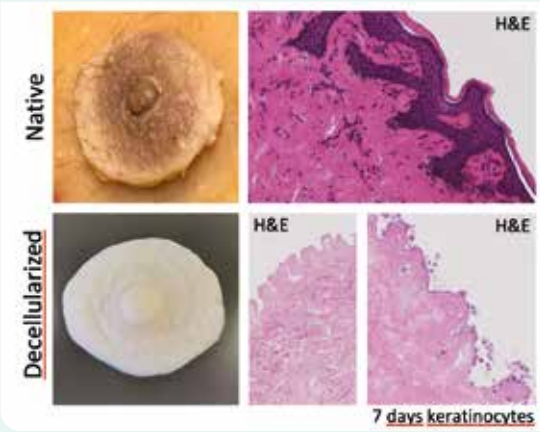
In parallel of the vascular tree regeneration, we are also studying the use of a decellularized vascularized spleen matrix as a cell support of interest cells like endocrine cells (pancreatic, thyroid, adrenal cells).

Finally, we also investigated, on a preclinical model for nipple-areolar complex (NAC) reconstruction, the elementary phenomenons involved in the bidimensional restoration of a living skin cover on a tridimensional decellularized NAC-ECM.

Left: native rat spleen before decellularization
Right: rat spleen after decellularization



Histological assessment of cell clearance and preservation of the extracellular matrix (H&E staining)

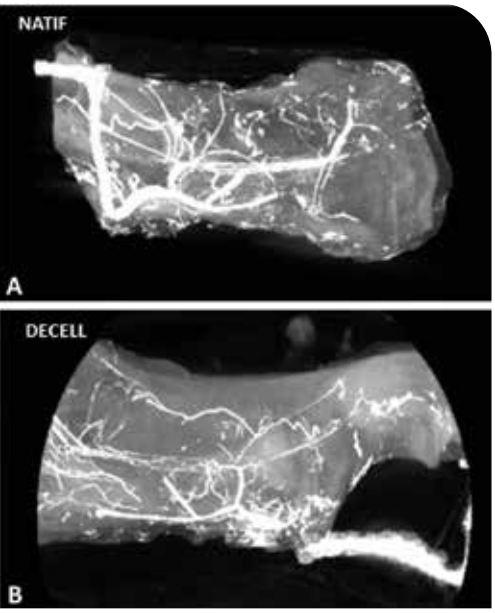


Macroscopic and microscopic (H&E staining) aspects of native (upper row) and decellularized (lower row) NAC. The lower right figure shows keratinocyte spreading 7 days after ECM seeding.

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

Guillaume Rougier, Louis Maistriaux, Robin Evrard, Catherine Behets, Greet Kerckhofs, Raphaël Olszewski, Thomas Schubert, 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.



AngioCT of native (A) and decellularized (B) forelimb bones highlighting vascular tree preservation.

Toward a bio-engineered periosteum

Julie Manon, Robin Evrard, Louis Maistriaux, Catherine Behets, Benoît Lengelé, Thomas Schubert, Olivier Cornu

Since natural bone healing mostly comes from the periosteum, aiming to restore its function is appealing. Native and processed human periosteum (HP) and fascia lata (FL) were assessed by morphological and mechanical analysis and cytotoxicity testing in the prospect of a bio-engineered periosteum.

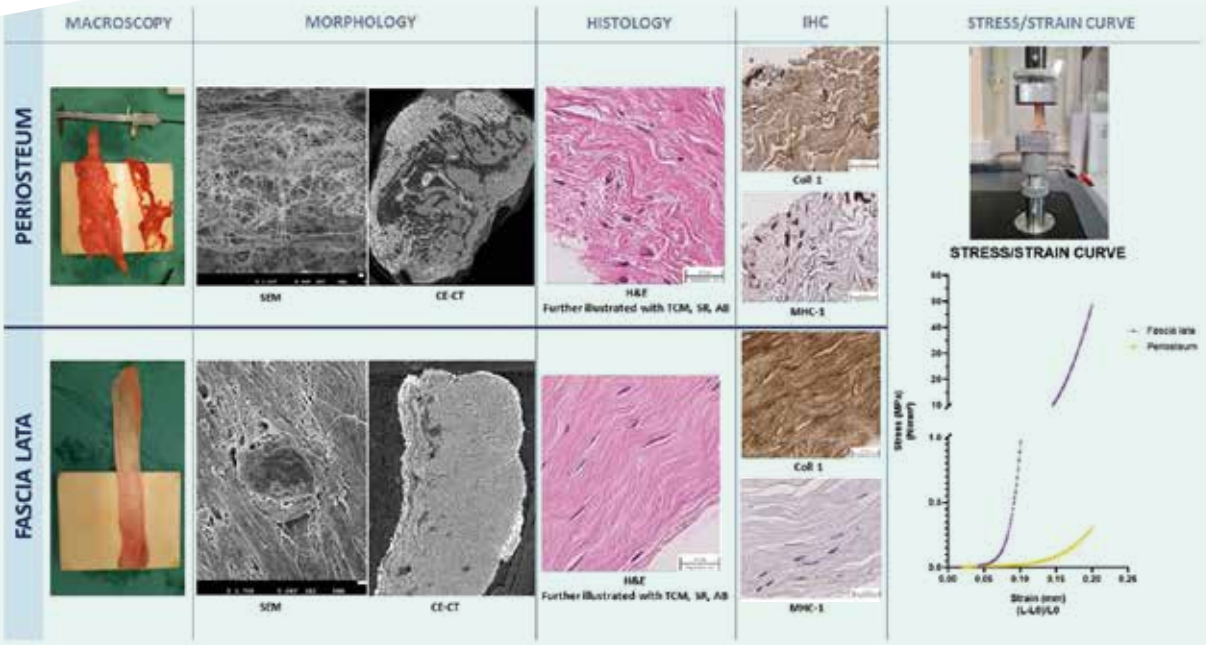
HP and FL were obtained from cadaveric donors and chemically decellularized. Cellular clearance and extracellular matrix (ECM) preservation were assessed by histology (Hematoxylin-Eosin, Masson Trichrome, Sirius Red, Blue Alcian), immunohistochemistry (IHC) for type 1 collagen, DAPI and DNA/Collagen/GAGs quantifications. ECM organization was visualized by electron microscopy (SEM).

Immunogenicity was assessed by IHC for major complex of histocompatibility (MHC-1). Stretch tests underscored differences in mechanical properties. Finally, acellular patches were sterilized by γ-irradiation and seeded with 5x105 human fibroblasts. After 7 days culture, they were analyzed with histology, LDH quan-

tification to evaluate the matrix cytotoxicity and Live/dead staining to assess the cell viability.

Histology and IHC brought out similarities (type I collagen fibers, layer organization) and differences (thickness and compaction of fibers, type of cells) between native tissues confirmed by the SEM. FL can support much more load than HP as attested by a distinct stress/strain curve. Histology and DAPI showed a successful decellularization with a "no man's land" concerning nuclei. DNA concentration statistically fell below the critic threshold (50ng/mg dry weight). Collagen content relatively increased while GAGs one decreased. Immunogenicity derived from nuclei disappeared. The seeded fibroblasts were alive after 7 days as shown by histology and the Live/dead, without significant difference in viability between patches and controls. LDH quantification confirmed the low cytotoxicity.

According to these data, HP and FL present morphological differences. Both offer a biocompatible scaffold after processing. FL was confirmed to be more suitable because of its easier harvesting, its integrity and its mechanical stiffness. Whether FL processed scaffold can further host periosteal stem cells has still to be demonstrated.



Periosteum and fascia lata tissue characterization: Morphological, tissular & mechanical approaches

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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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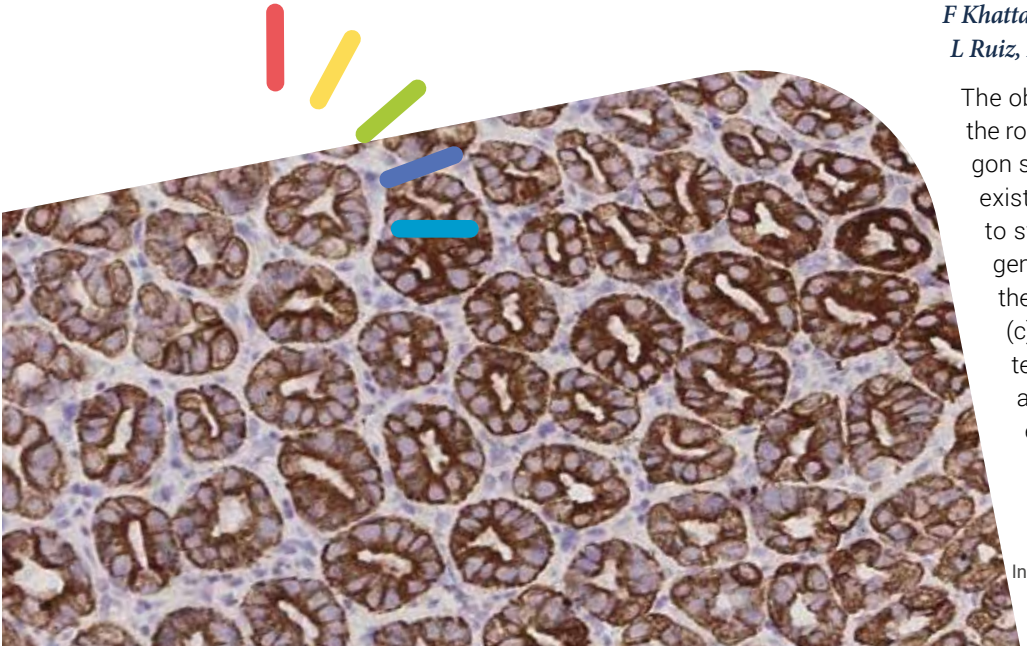
Research Projects

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, M Parambath

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.

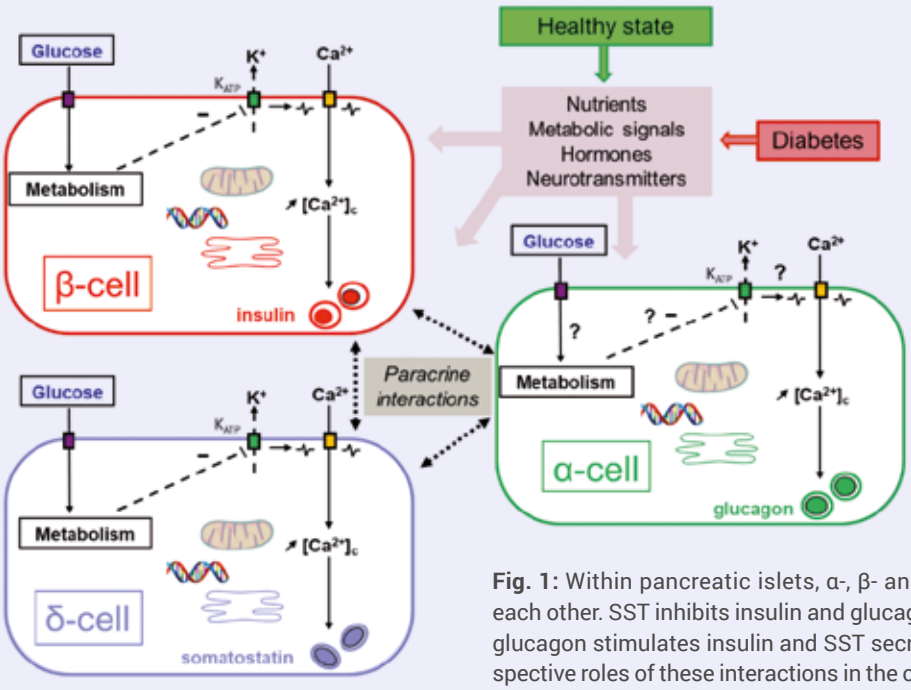


Fig. 1: Within pancreatic islets, α-, β- and δ-cells interact with each other. SST inhibits insulin and glucagon secretion, whereas glucagon stimulates insulin and SST secretion. However, the respective roles of these interactions in the control of islet hormone secretion by nutrients is only partly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

Control of the subcellular redox state in pancreatic β-cells

O Bekhet, AF Close, M Craigie, Y Hajj Hassan, 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).

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

HY Chae, AF Close, P Gilon, Y Hajj Hassan, JC Jonas, M Tariq, B Singh

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.

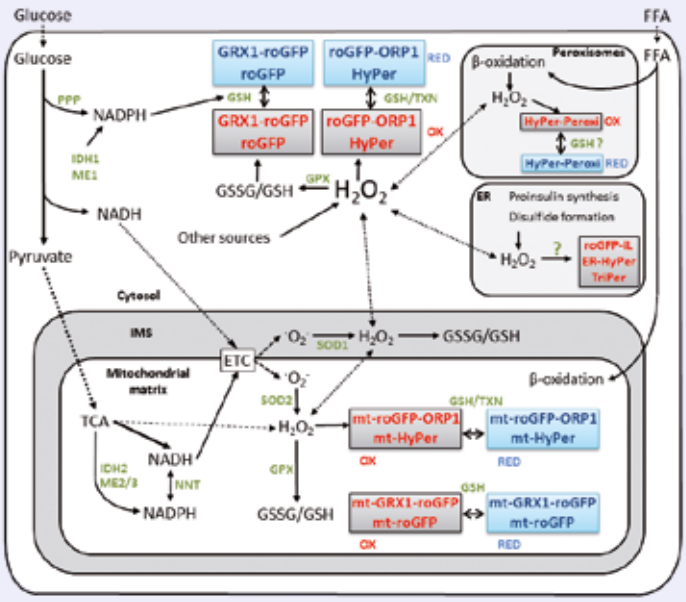


Fig. 2: Compartmentalized redox reactions and the genetically encoded probes used to measure the impact of nutrient metabolism on β-cell subcellular redox state. Schematic representation of the pathways by which nutrients affect NADH, NADPH, and GSH. Enzymes are shown in green, oxidized (OX) probes in 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.

Decreasing inflammation within islets of Langerhans

P Lysy, O Pollé, 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 and in particular the gut-muscle-liver axis: We made the seminal observation that changes in muscle texture anticipate the progression of fatty liver to NASH. We are now exploring the mechanisms underlying the muscle liver cross-talk.

Also we found that the entero-hepatic circulation of BA is perturbed in preclinical models of NASH. Our data support that change in the BA pool contributes to NASH pathogenesis by modulating BA sensors such as TGR5 and FXR.

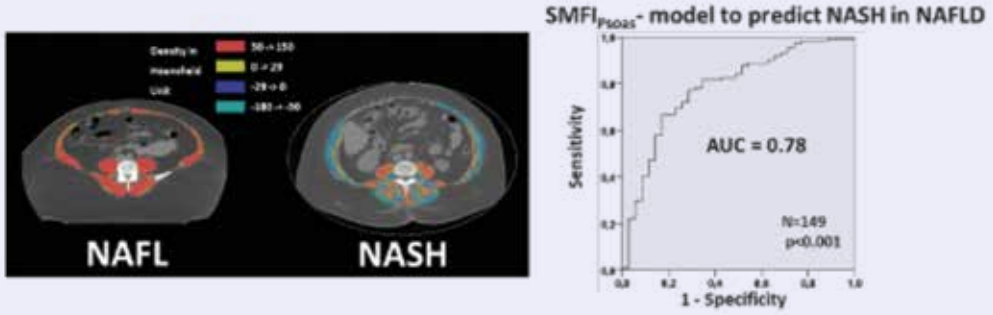


Fig 3: SMFIPsoas = Skeletal Muscle Fat index the psoas muscles (~ absolute fat content based on muscle area and density) measured on Ct-Scan predicts NASH.

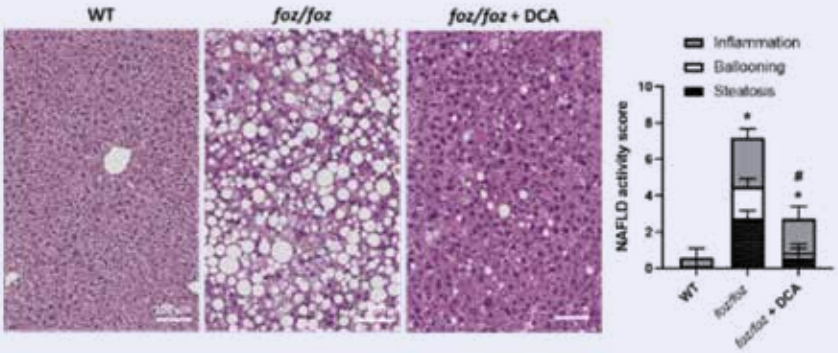


Fig 4: deoxycholic acid (DCA) feeding in high fat diet-fed foz/foz mice, an experimental model of non-alcoholic steatohepatitis, restores the altered bile acid pool and prevents the development of nonalcoholic steatohepatitis (NASH). H&E staining of liver sections and NAFLD activity score of HFD-fed WT, foz/foz, and foz/foz + DCA mice (n=6-7/group). Bar size: 100 µm. Mean ± SD. Statistical significance is represented by * when compared to WT mice and # when compared to foz/foz mice.

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

P Stärkel, 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. We show that changes in the gut microbiome and mycobiome are involved in the development of alcoholic liver disease. In particular, specific bacteria and fungi (e.g. Candida species) and products released by those microbes could play an important role in initiating and/or perpetuating alcoholic liver disease. However, dysbiosis and increased intestinal permeability do not seem to be sufficient for ALD to occur. More recently, we introduced the concept of reduced gut immunosurveillance characterized by profound changes in the gut-associated immune system especially in alcohol use disorder patients with progressive forms of ALD.

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 (Fig. 5).

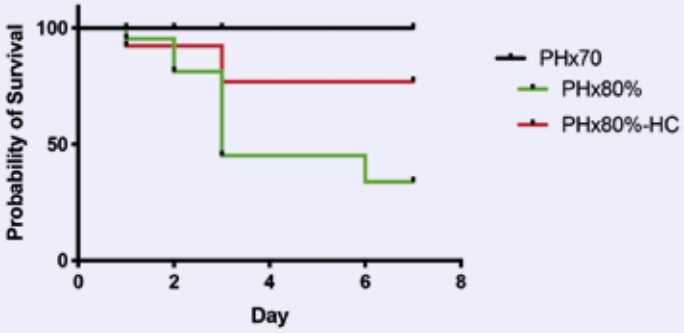
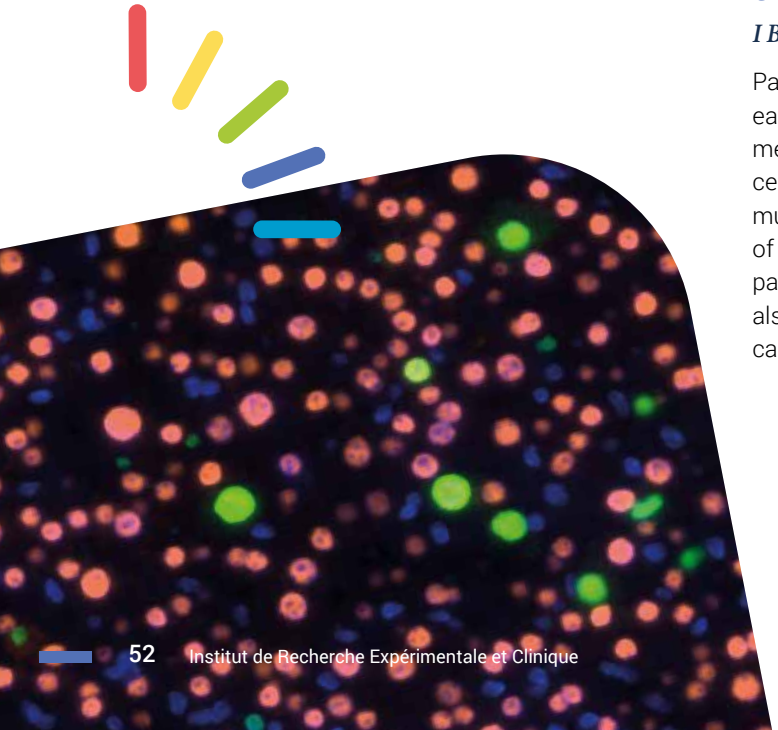


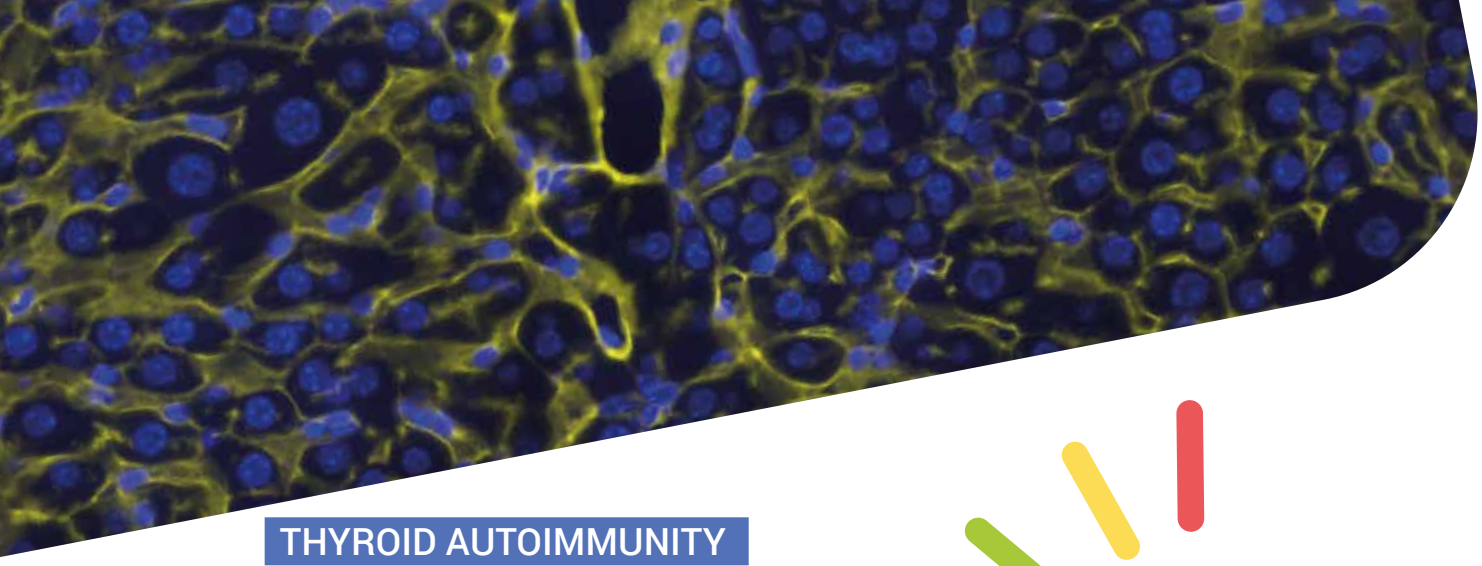
Fig. 5: compared to a 70% partial hepatectomy (PHx70) which induce a rapid and efficient regenerative response with no mortality, resection of 80% of the parenchyma (PHx80) considerably compromises the animals' survival. Hypoxic exposure (PHx80+HC) prevents mortality.

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.





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 Pollé, 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, JP Thissen, B Vandeleene

The Division of Endocrinology and Nutrition at Saint-Luc University Hospital is conducting several clinical studies on type 2 diabetes, obesity, 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

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. Recent work has identified changes in the expression of several myokines known to control glucose homeostasis.

ADIPOKINES IN METABOLIC AND INFLAMMATORY DISEASES

Adiponectin and its mimics on skeletal muscle

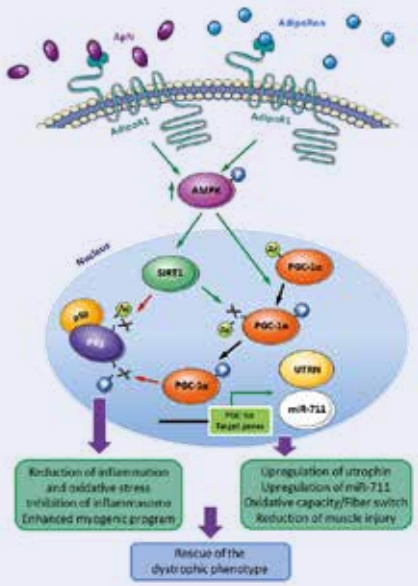
SM Brichard, M. Abou-Samra, N. Dubuisson, C. Selvais and L. Noel

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 (Prix Lagast 2020 to M. Abou-Samra). Adiponectin receptor agonists are now also tested in ageing and age-related sarcopenia (Fig.6.).

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. 6: 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. Recent work has highlighted the role and mechanisms of action of Activin A in the skeletal muscle atrophy observed in 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 focuses on three aspects of tumor metabolism: (1) the oxidative pathway of lactate, (2) the metabolic control of (tissue-specific) metastasis, and (3) metabolic resistance to anticancer chemo- and radio- therapies. The team collaboratively develops new drugs targeting cancer metabolism.

EQUIPMENTS

- **Cell culture and molecular biology**
- **Construction and generation of defective adenovirus (biosecurity level 2)**
- **Evaluation of islet cell biology (dynamic hormone secretion)**
- **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, L Pitance, J Lebleu, N Lambright, A Luc, R Hage, A Nguyen

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, I Doumas, G Everard, C Selves

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.

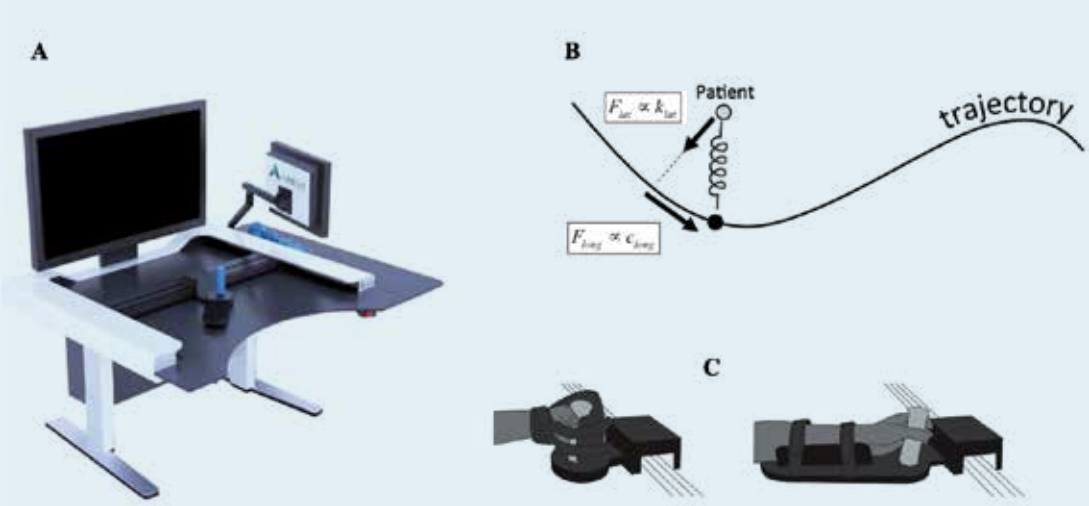

Figure 2. Illustration of (A) the REAplan® robot, (B) the assistance as needed and (C) the positioning of the hand in the glove and the forearm in the gutter.

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

O Cornu, A Englebert, R Evrard, L Fonkoue, E Kouassi, J Manon, H Poilvache

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.

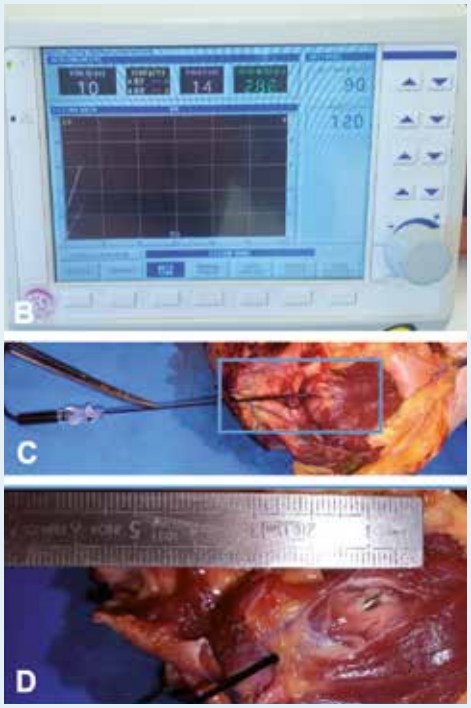

Figure 3. Radiofrequency (RF) lesioning on a cadaveric knee. A, electrodes placement (RFN and IPBSN). B, RF generator. C, RF lesioning of a muscle during the pilot trial. D, dissection around the active tip reveals a clearly visualized RF lesion. RFN, recurrent fibular nerve; IPBSN, infrapatellar branch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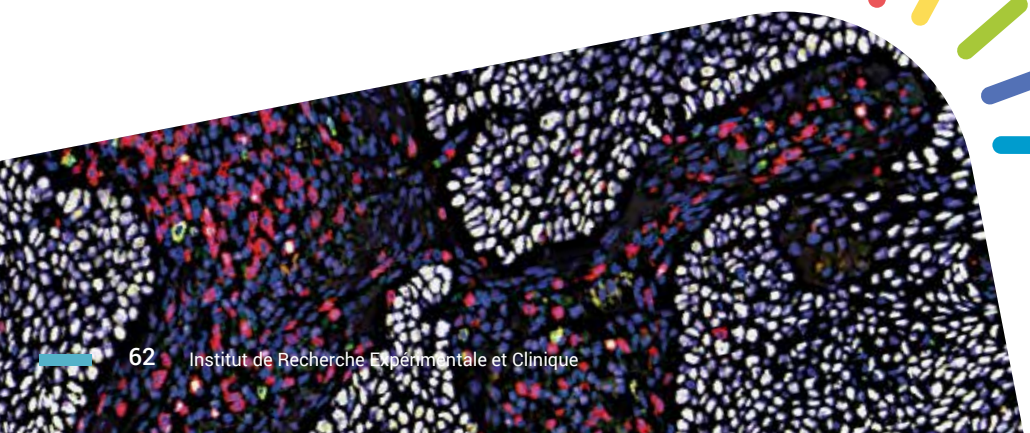

The members of MORF focus on

- **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. (S. Lafont, PhD thesis, defended in November 2020).

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, Antoine Chretien

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.

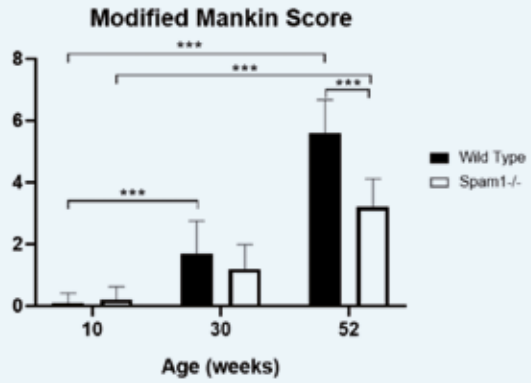

Figure 4. Histological analysis of. (A) Modified Mankin Score assessed in Safranin-O stained frontal sections in the right knee of WT and Spam1-/- mice aged 10, 30 and 52 weeks. Data are expressed as mean + SD. n = 10/age/group. ***: p < 0.001.

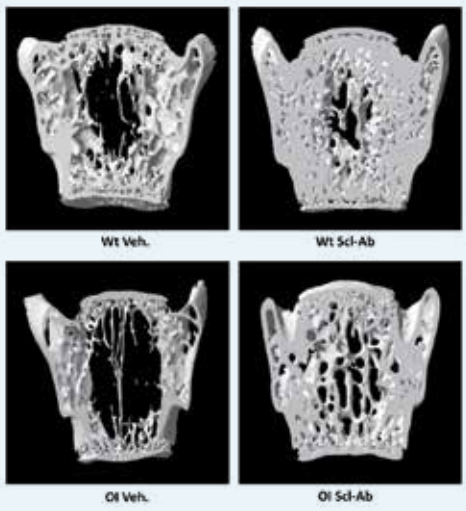

Figure 5. MicroCT analysis of L1 vertebral body of Wildtype (WT) and oim (OI) mice treated with either Vehicle (Veh) or Scl-Ab) from week 5 to 14.

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 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, Catherine Behets, Aleksandar Jankovski, Guillaume Glaudot

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.

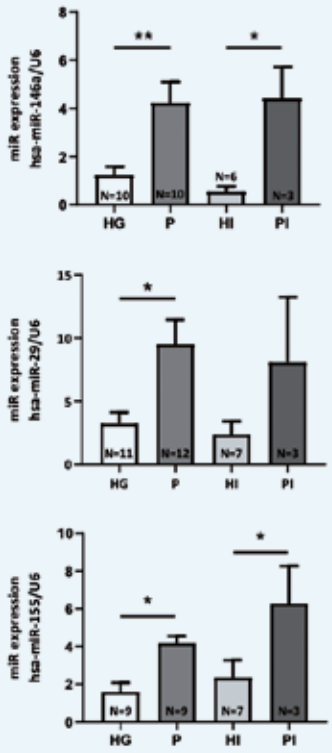

Figure 6. Expression of miR146a, miR155 and miR29b in human gingiva biopsies from patients presenting healthy gingiva (HG), periodontitis (P), healthy periimplant gingiva (HI) and periimplantitis (PI).

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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NMSK

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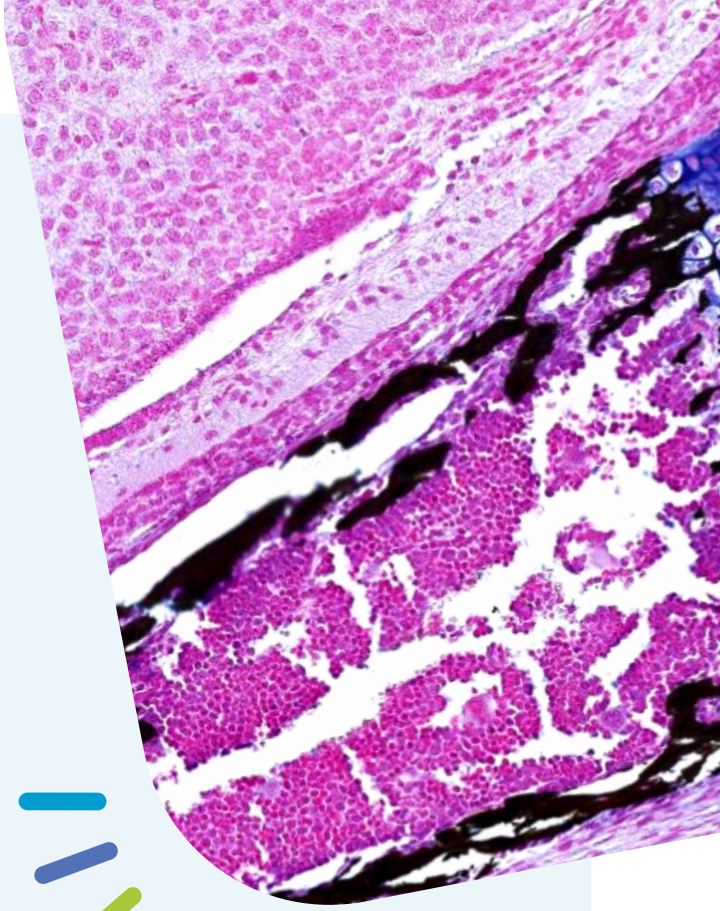

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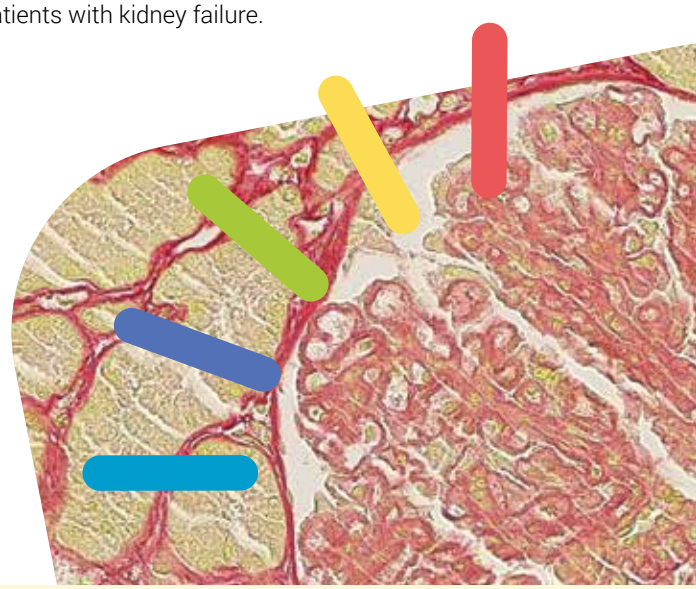
NEPHROLOGY

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 2020 began for the groups of O. Feron and C. Corbet (Pole FATH) with 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 2020 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 and J Clin Oncol ; 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)

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Olivier Feron, PhD

Pierre Sonveaux, PhD

Olivier Feron and Cyril Corbet's teams (*co-supervision):

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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/

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- **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.
- **Action de recherches concertées (ARC) (2019-2024) O. Feron**, L. Bindels, P. Cani, B. Jordan, Y. Larondelle. The role of diet-, microbiota- and adipocyte-derived lipids in cancer progression (LIPOCAN).
- **WALLinov (2018-2022)**. **JP Machiels**. Predictive biomarkers for CDK4 inhibition in cancer.
- **Fondation Belge Contre le Cancer (2019-2022)**: Fundamental Research Grant. FAF-F/2018/1282. **Sonveaux P**, Frédérick R. Lactate dehydrogenase B (LDHB) inhibition for anticancer treatment
- **EU Horizon (2019-2023)**: 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).
- **RW Pôle Biowin: ProTherWal CHARP (2019-2026):** B.Macq & **J.Lee** & **E.Sterpin** Proton thérapie Wallonie, Consensus hospitalier agrégé pour les recommandations en proton thérapie.
- **RW Pôles Biowin & Mecatech ArcPT (2019-2023)**: **E.Sterpin** & **J.Lee**. Arc Proton Therapy.

Research Projects

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 entities, namely, the laboratory of Molecular Imaging and Experimental Radiotherapy led by Prof. John A. Lee, and the laboratory of Medical Oncology led by Prof. J.-P. Machiels.
The driving force of these two laboratories, gathering both clinical and basic scientists, is to bridge the gap between the bench and the clinical applications within their specific research areas.

MIRO (1/2) - Laboratory of Molecular Imaging and Experimental Radiotherapy

Radiation Oncology -delivered as single modality or in combination with surgical, hormonal, or chemical therapies, 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 cause these treatment failures. Within this framework, the Laboratory of Molecular Imaging and Experimental Radiotherapy developed several lines of research aiming :

1) at improving radiation delivery and making it more focused and accurate, by using protons instead of photons, for instance,
2) at a better understanding of radiobiology (tumour micro-environment, high dose rates a.k.a. flash effect),
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.

- **Adaptive treatment in both photon and proton therapies**
- **Audio-video coaching and mechanical ventilation of patients with thoracic and abdominal tumors**
- **Artificial intelligence to automate treatment planning and support clinical decision**
- **Fast Monte Carlo simulations and dose engines in particle therapy**
- **Robust treatment plan optimization for new modalities (arc proton therapy, proton flash, carbon therapy)**
- **Dosimetry and calorimetry in hadron beams**
- **Preclinical in vivo imaging**

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MIRO (2/2) - Laboratory of Medical Oncology

The development of targeted therapies and immunotherapy 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

- **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).**
- **The Prize Jean-Oscar Maes (Health sector-UCLouvain) was awarded to Cyril Corbet for his work on the therapeutic targeting of microenvironment-driven tumor metabolism.**

REPRODUCTIVE MEDICINE

Our research into reproductive medicine focuses on various aspects of human reproduction, both male and female:

- **Fertility preservation: ovarian and testicular tissue cryopreservation and transplantation looking to preserve and restore fertility in cancer patients.**
  Development of artificial gonadal organs (see Regenerative Medicine section).
- **Benign gynecological diseases affecting reproduction: endometriosis, adenomyosis 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 collaboration with the gynecology, hematology and oncology departments of 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 also carry the risk of premature ovarian failure, such as recurrent ovarian cysts and some autoimmune and hematological disorders requiring chemotherapy.

Fertility preservation remains a challenge, whether by medication (1), or cryopreservation of oocytes or ovarian tissue (2-5), or in case of prepubertal patients (6).

The ovarian tissue bank at Cliniques Universitaires St Luc (one of the first and largest in the world) contains tissue from more than 750 patients. The pregnancy rate after autotransplantation is 40%, making it one of the top three global centers (7,8).

This year, our annual workshop on cryopreservation and transplantation of human ovarian tissue and preantral follicle isolation and in vitro culture could not be organized due to the coronavirus pandemic.

Development of optimal transport conditions for human ovarian tissue

J. Vilela, M-M. Dolmans, C.A. Amorim

Recently, we have been concentrating on the influence of the transport procedure on ovarian tissue (9). To this end, we have been analyzing the effects of the most widely used transport media. 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, as well as low rates of necrosis and apoptosis (10), shedding new light on the impact of ovarian tissue transportation media.

New perspectives in the field of ovarian tissue cryopreservation

C. Hossay, M-M. Dolmans

Ovarian tissue cryopreservation and transplantation can be achieved in two different ways, either using ovarian cortical fragments or a whole organ with its vascular pedicle. In theory, the latter technique should maintain endocrine and reproductive functions much longer than grafting of frozen-thawed ovarian cortical fragments thanks to vascular anastomosis (11). However, there is a major risk attached to whole ovary cryopreservation and transplantation, namely the all-or-nothing nature of the procedure. Indeed, if something goes wrong during the operation, it results in loss of all the follicles present in the ovary. Currently, the only technique approved by the American Society for Reproductive Medicine is cryopreservation and transplantation of cortical strips (12). We recently described an original way of managing patients who have had a whole ovary cryopreserved to try to help them avoid the risk of losing the entire organ upon vascular transplantation. We propose dissecting the thawed whole ovary into cortical strips and refreezing the remaining non-grafted fragments, thereby allowing further transplantations and increasing the chances of motherhood and repeated pregnancies. Our study confirmed that refrozen-rethawed ovarian tissue has the same functional characteristics in terms of follicle survival, fibrosis and vascularization as once-only frozen-thawed tissue (13).

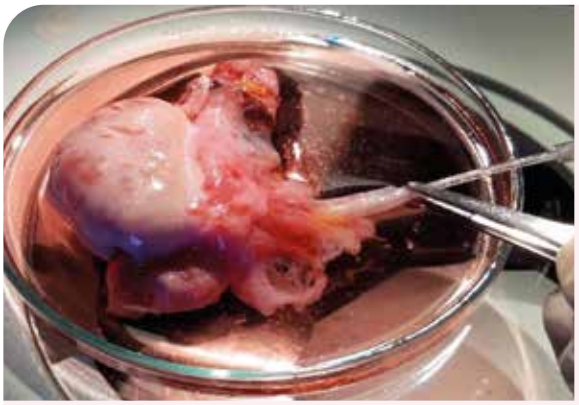

Figure 1. Whole ovary thawing.

Pathways of follicular activation after transplantation

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

Ischemia occurring within the first week of transplantation of frozen-thawed ovarian tissue leads to massive follicle loss through two mechanisms, namely follicle atresia and follicle activation (known as the burnout effect). We focused on understanding the processes and pathways involved in follicle activation. We first confirmed the fact that after just 3 days of grafting, there is a significant fall in the proportion of primordial follicles, together with a significant rise in the proportion of growing follicles, demonstrating the process of follicle activation (14). We then highlighted the roles of the PI3K and Hippo pathways in follicle activation, allowing us to specifically target their effectors (15).

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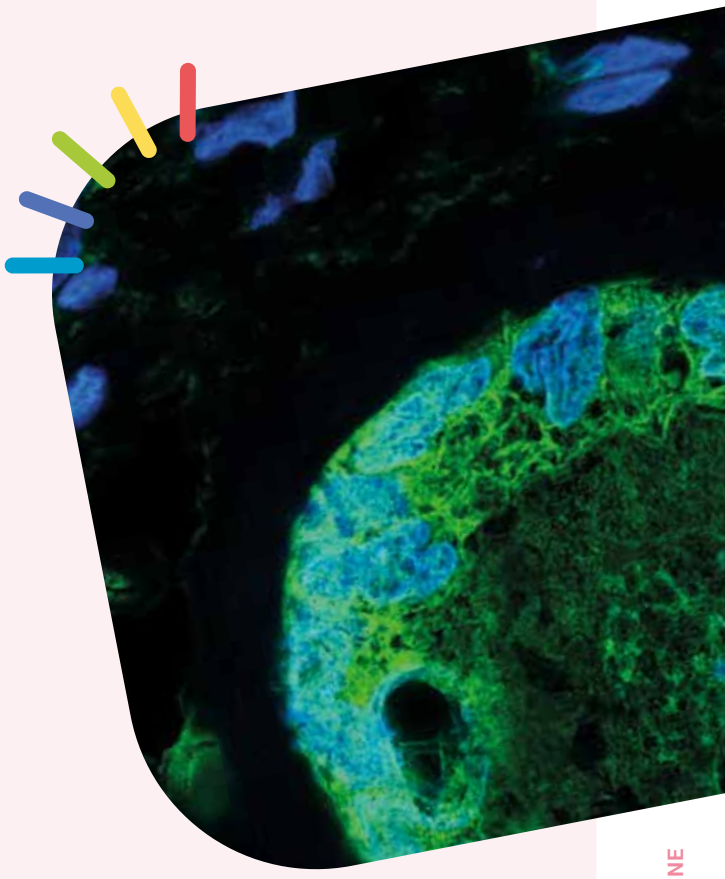

UTERINE FIBROIDS

J. Squifflet, M. Luyckx, M-M. Dolmans

Current treatments for fibroids are mainly surgical and expensive, so alternatives need to be found. It is therefore vital that we investigate and develop other options, especially when fertility preservation is the goal.

When considering less invasive techniques (uterus-sparing procedures 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 (1). There is now a growing body of evidence pointing to the crucial role of progesterone pathways in the pathophysiology of uterine fibroids. Selective progesterone receptor modulators were therefore considered a possible alternative to surgical therapy, but hepatic side effects in some patients led to their withdrawal, leaving room for new medical alternatives (2,3).

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ADENOMYOSIS

C.A. Stratopoulou, S. Mosele, M-M. Dolmans

Adenomyosis (AD) refers to a benign estrogen-dependent gynecological disorder that commonly affects women of reproductive age. There are still no conclusive data on the pathogenesis of this estrogen-dependent condition (1), so our study aimed to delve deeper into its pathogenesis to identify its primary cause. Recent literature points to the potential role of activated platelets and their subsequent aggregation in the development of AD and related fibrosis.

Our results did not detect a primary role for platelet activation or aggregation in the pathophysiological process of AD. Major factors secreted by platelets, namely TGF-β1 and VEGF, were also found to be decreased. We observed higher rates of collagen fibers in adenomyotic lesions, likely to be related to a TGF-β1-independent pathway. Further research is needed to elucidate the mechanism of fibrogenesis in AD (2).

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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 patients suffering from 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 therefore eagerly awaited.

Our research focuses on two main areas:

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 pathophysiology of the spermatogonial stem cell (SSC) niche.

Fertility preservation and restoration from cryopreserved ITT containing SSCs

J. Poels, M. Vermeulen, F. Del Vento, M. Kanbar, D. Kourta, C. Wyns

A slow-freezing protocol for prepubertal human testicular tissue was developed, yielding 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 initiated. As xenotransplantation of thawed ITT resulted in 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 for SSC loss. Fertility restoration with human frozen-thawed ITT has not yet been achieved and our research is therefore investigating two different fertility restoration strategies from cryopreserved ITT:

1) Autotransplantation of stored ITT in patients with no risk of tissue contamination by cancer cells.

Encapsulation of murine ITT in hydrogels supplemented with VEGF nanoparticles was shown to improve vascular density, VEGFR2 activation and endothelial proliferation, doubling spermatogonial survival following encapsulation of ITT in alginate. This was further enhanced by supplementing the hydrogel with anti-necrotic nanoparticles.

2) In vitro maturation of SSCs as a procedure that circumvents the risk of reintroducing cancer cells in cured patients.

An organotypic culture system was developed 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 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 haploid cells. Culture systems based on isolated seminiferous tubules and embedding matrices have been explored and research into systems involving microfluidic technology is ongoing.

Deciphering the physiopathology of Klinefelter syndrome (KS)

J. Poels, M.G. Giudice, C. Wyns

We analyzed functional and morphological alterations to the somatic compartment of KS testes and showed that expression of BTB proteins, i.e. connexin-43 and claudin-11, was significantly reduced and disorganized. Androgen receptors in Sertoli cells and INSL3 in Leydig cells were also significantly reduced.

The ongoing project aims to explore how a testicular organoid (also see section on Regenerative Medicine), applied as a novel investigative tool, could be useful to further elucidate the role of germ and somatic cells in KS.

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MEDICAL 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 Clostridioides difficile Infections (CDI)

Ahalieyah Anantharajah, 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) and are analyzed for virulence genes. Based on the outbreak analysis and the results obtained with the various techniques used, we reported for the first time the emergence of a new hypervirulent strain RT585 that may be as problematic as the notorious 027 strains (NOSOinfo vol. XXIV N°4 - 2020). These finding emphasize the importance of ongoing surveillance for emergent strains. In this context, a typing project by whole genome sequencing (WGS) in collaboration with the French National Reference Center was initiated in 2018 and we participated actively to the European nomenclature harmonization for the PCR-ribotyping.

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 turnaround-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

Hector Rodriguez-Villalobos, Imane Saad Albichr

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 therapeutic strategies to enhance current treatment options for *M. abscessus* infections using a combination of different enzymes and antimicrobials drugs.

Borrelia burgdorferi

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

In 2020, a collaborative project focused on Lyme disease was set up between a Belgian biotechnology company and the medical microbiology research unit of UCLouvain which will conduct a set of experiments on Borrelia burgdorferi sensu lato: identification and species characterization, culture, strain selection, quantification, challenge tests, viability tests.

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. 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).

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 is also investigating 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

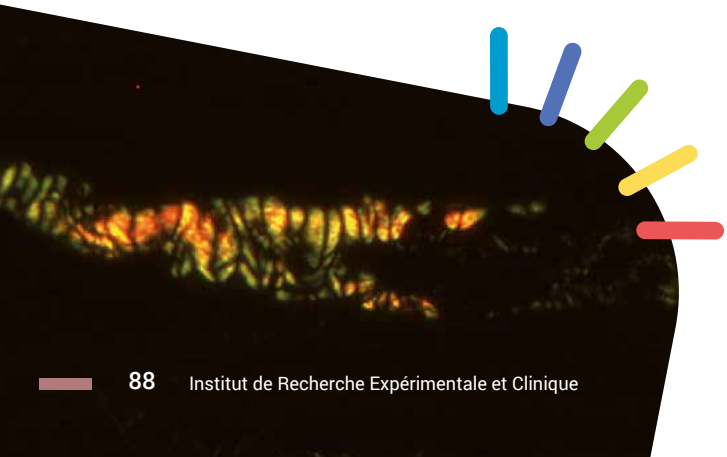
Study on the HIV-1 provirus (Dr Géraldine Dessilly), project having obtained funding from the Louvain Foundation: the objectives of this project consist in carrying out an evaluation of the effectiveness of the NGS platform for sequencing proviral DNA; a comparison of resistance mutations within intracellular 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. In this context, several experiments were carried out in 2020 as part of a master thesis in Biomedical Sciences (Ms. Charlotte Hermanne) to determine if the MX2 proteins were also antagonized by HIV-2, and if there was a difference in efficacy of antagonism between HIV-1 and HIV-2. that may explain, at least in part, differences in pathogenesis of these two viruses.

SARS-CoV-2 and COVID-19

Benoît Kabamba-Mukadi, Jean Ruelle, Géraldine Dessilly, Anne-Thérèse Vandenbroucke, Anne-Thérèse Pâques, Eléonore Ngyuvula Mantu, Kate Soumillion, Lysa Pinsmaye

Following the global COVID-19 pandemic (coronavirus disease 2019) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first identified in December 2019 in Wuhan, China, the medical microbiology (MBLG) research unit of UCLouvain has set up various projects and collaborations targeting this new virus.

From April 2020, full sequencing on the Illumina platform was developed and carried out to answer clinical questions or as part of clinical studies. In addition, it is recently carried out in the context of the Belgian national surveillance of SARS-CoV-2 variants.

The whole genome sequencing (WGS) of SARS-CoV-2 made allowed to launch a research project in collaboration with infectious disease specialists from Cliniques Saint-Luc, with the support of Professor Patrice Cani, aimed at studying the nasopharyngeal microbiota of patients infected with SARS-CoV-2. This project benefited from an urgent research credit granted by the FNRS during summer 2020. The objective is to identify the possible influence of the microbiota, including the interference of an antibiotic treatment, on the clinical phenotype of the disease and its positive or pejorative outcome. In this context, a biobank of clinical samples was consolidated, documented and kept at the MBLG research unit.

Since September 2020, the MBLG research unit has hosted one of the Belgium federal COVID-19 platforms by performing 2,000 to 5,000 SARS-CoV-2 PCR tests per day.

The MBLG unit also carries out the viral culture of SARS-CoV-2 on the cell line VERO 76, clone E6 (Vero ATCC CRL-1586) in the laboratory of security level BSL3. Viral culture is the best indicator of viral infectivity, thus reflecting the infectious potential of an infected person, especially in persisting positive PCR. A seroneutralization test has also been developed. Ongoing collaborations have been initiated to assess the antiviral effect of certain compounds (drug, disinfectant, etc.), the persistence of disinfectants on different surfaces.

Congenital cytomegalovirus infection: correlation between virological and immunological markers and fetal transmission

doctoral thesis project by Ms Anaïs Scohy with Professor Kabamba Mukadi Benoît from UCLouvain as promoter and Professor Arnaud Marchant from the Institute of Medical Immunology - ULB as co-promoter.

In 2020, Anaïs Scohy obtained a doctoral grant as specialist clinician-researcher to start a thesis project aimed at better understanding the mechanisms of cellular immunity that control CMV infection and their role in fetal transmission. A better understanding of these mechanisms is a first step not only towards the development of reliable diagnostic tools for the monitoring of maternal non-primary CMV infections, but also for the development of tools for the prevention of fetal transmission such as vaccines.

EQUIPMENTS

- **Nucleic acid sequencing facilities**
- **Safety laboratory (BL3)**
- **Digital PCR technology**
- **Next-Generation Sequencing (NGS) platforms (Ion Torrent and Illumina).**

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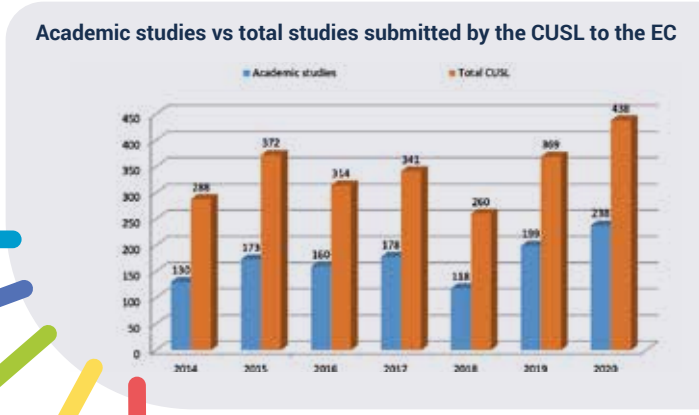
Clinical research at the Cliniques universitaires Saint-Luc (CUSL) :

DEVELOPMENT OF CLINICAL RESEARCH AT THE CUSL

Ethics Committee (EC) submissions at the CUSL: in 2020, academic studies (master theses not included) represented 54% of the total submissions. COVID studies represented 33% of the academic studies.



RESEARCH MANDATES

NEW « FRC » STARTING GRANTS SINCE 2017

	2017	2018	2019	2020	2021	Total
Starting grant	4	4	5	3	**2**	**18**

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

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
TOTAL : Clinical researchers (CUSL)	7	9	13	3	8	5	14	18	13	26	**20**	**137**
Of which renewals :		1	7	0	4	2	5	5	6	11	**6**	**48**
TOTAL : Researchers (UCL)	12	9	9	3	12	11	8	10	7	2	**0**	**83**
Of which renewals :		1	7	1	2	2	3	6	3	2	**0**	**27**

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

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
TOTAL	6	8	8	9	10	12	10	8	6	**6**	**83**

FNRS MANDATES SINCE 2012 (NEW APPOINTMENTS AND RENEWAL)

	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Clinicians (Clinical service)	6	11	11	9	13	13	13	13	**14**	**103**
Researchers (Poles)	5	4	3	3	4	4	2	7	**16**	**48**

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 2020, an additional 0,5FTE was provided at the contract team and the CTC FTE went from 11,3 to 11,8 + 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 2020, the Strategic Council of Clinical Research met once to discuss the CTC annual report but also issues related to the FNRS and public funding of research conducted at the CUSL and UCLouvain.

TASKS AND ACTIVITY REPORT OF EACH CTC COMPONENT

COMMERCIAL AND ACADEMIC CONTRACTS:

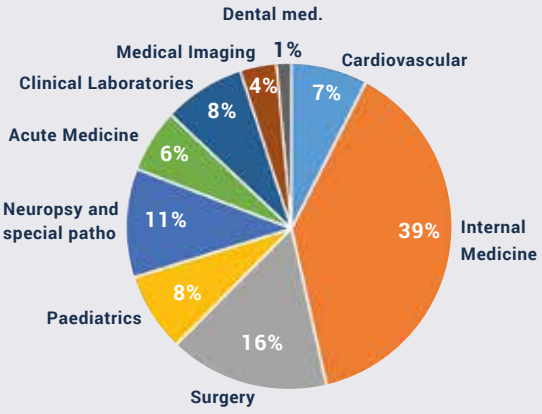
The contracts and finances team manages all the contractual and financial aspects of clinical research.

Type of research contracts	2016	2017	2018	2019	2019	2020
Commercial (new + amendments+ CD+CTR)	291	309	282	343	343	484
Academic (external and internal agreements, MTA, DTA, grants, CTR)	74	76	148	160	160	257

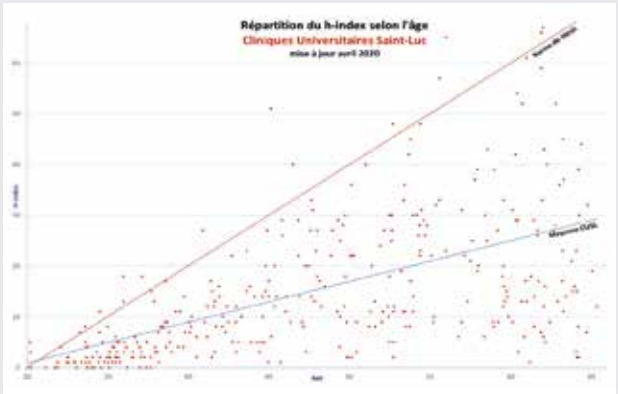
Additionally, 379 contracts divided into 266 consultancies, 108 sponsoring/grants, 5 subsidies have been managed by the CTC and the legal department.

REPORTING AND ACADEMIC INDICATORS FOR THE CUSL MEDICAL DEPARTMENTS

2020 total credits /department

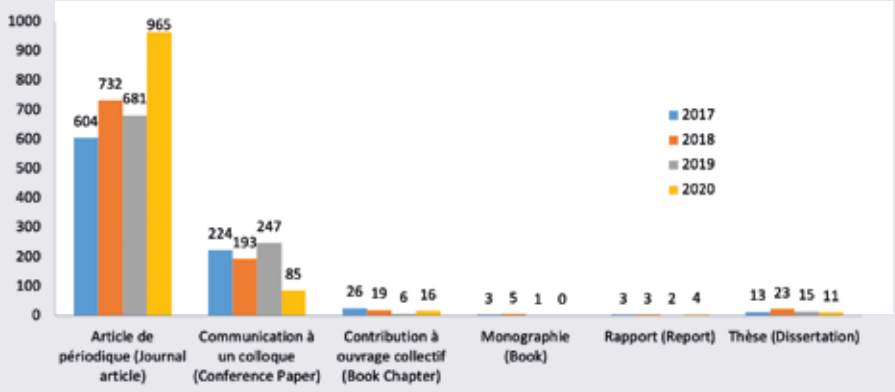


INDIVIDUAL H-INDEX (04/2020 career managerial physicians) BY AGE



Publications CUSL 2017 to 2020

(source: base de données précompte pro des chercheurs)



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, 2020

- Types of projects: 6 H2020/RIA (Research Innovation Action), 4 IMI (Innovative Medicine Initiative)
- Types of contracts : 1 where the CUSL are a linked third party and 9 where the CUSL are direct contractors.

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 2020, 200 commercial studies were submitted to the Ethics Committee. Among them 92 were submitted directly by the central desk. In addition, 81 CTR pilot studies and 27 MNP were submitted directly by the sponsors to the FAHMP.

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 or at the UCLouvain.

B1: ACADEMIC DESKS: Ethics Committee submissions in 2020

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**
31	**81**	**32**	**78**	**16**	6	130	12	**238**

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 (0,7FTE) is supporting UCLouvain researchers performing clinical research at the UCL or at the CUSL.

The UCLouvain central desk provided support to 18 studies and 6 master theses involving UCLouvain researchers performed at the CUSL and 30 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 2020, internal communication was mainly focused on the applicable rules in COVID period and on compliance with drug testing rules in academic research. The website is regularly updated (https://www.saintluc.be/en/research/index.php). Investigators and study coordinators have been trained for clinical research in using the new EPIC EMR.

OPERATIONAL SUPPORT FOR THE STUDY COORDINATORS

The CTC is coordinating the financial aspect of the hiring and the training of the study coordinators.
Forty new study coordinators were hired in 2020: 23 with a permanent contract and 17 with a fixed term contract.

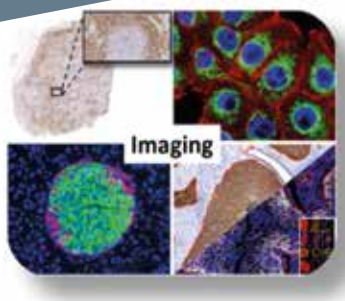
Study coordinators at the CUSL on 31 December 2020:
81 employees: 71 FTE allocated to 24 medical services.

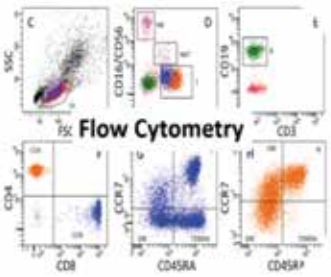
LEGAL SUPPORT

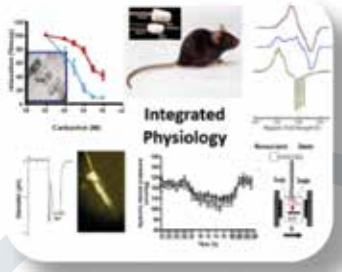
Since August 2018, a half-time legal officer from the legal department of the CUSL is dedicated to the CTC. Together with other members of the legal department, she is involved in the legal review and advices for research contracts, consultancy agreements, master agreements, etc

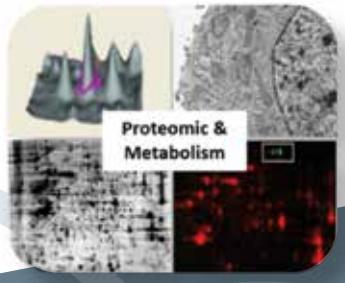
The legal officers provided support for 557 agreements of various types related to clinical research or consultancy and 26 medical legal advice.

IREC TECHNOLOGICAL PLATFORMS









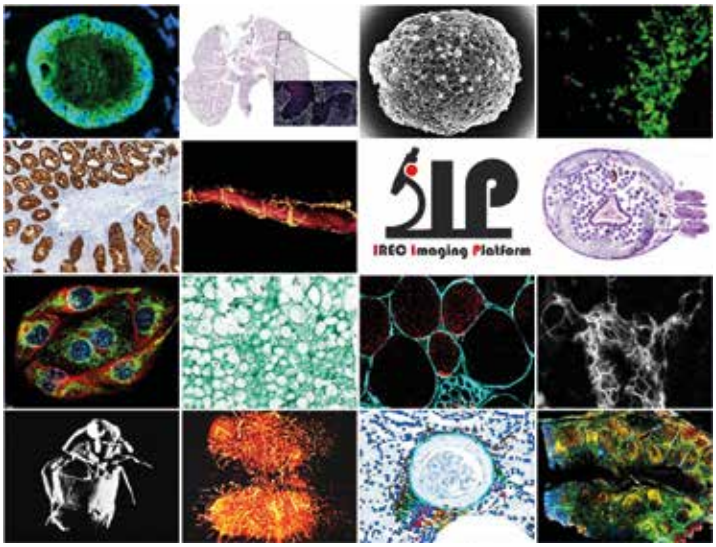
THE OBJECTIVES TARGETED BY OUR TECHNOLOGICAL PLATFORMS:

- 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 2020 AT A GLANCE

183	users
50	research groups
2935	bookings
6776	sections
2655	stainings
5026	immunostainings
1436	hours slide scanning
1459	hours fluorescence imaging
5156	hours image analysis
support	management & user committees
	account manager



PROPOSED SERVICES

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

Sample preparation services (Histo-lab):

- Paraffin embedding
- Paraffin & cryo-sectioning (**NEW** microtome with STS and CoolCut)
- Histological stainings
- Immunostainings (chromogenic-fluorescence-TSA multiplex)

Image acquisition:

- Brightfield, fluorescence **NEW** and polarized light **NEW** whole slide imaging
- 2D fluorescence microscopy (widefield - confocal - structured illumination)
- 3D fluorescence microscopy (lightsheet)

Image analysis:

- 2D images : ImageJ/Fiji support - ZEN Analysis (Zeiss)
- 2D whole slide scans: Author (Visiopharm), Halo (Indicalab) **NEW**, QuPath **NEW**
- 3D images: Arivis (Zeiss)

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

REFERENCES 2020

A multidisciplinary research project initiated within 2IP brought together the GAEN, PNEU, NEFR and LTAP research poles. The objective of this project was to better appraise and describe the accumulation of collagen in several experimental models of fibrosis. The first results of this collaborative study were published in Biomolecules in collaboration with the University of Zurich. We propose a new histological method for quantifying and characterizing fibrosis in models of hepatic, pulmonary and renal fibrosis. This should make it possible to better assess the pathogenic processes of fibrosis and the effectiveness of new therapies.

Digital Image Analysis of Picrosirius Red Staining: A Robust Method for Multi-Organ Fibrosis Quantification and Characterization.

Courtoy GE, Leclercq I, Froidure A, Schiano G, Morelle J, Devuyst O, Huaux F, Bouzin C.
Biomolecules. 2020 Nov 22;10(11):1585.

Through sustained collaborations, 2IP was also involved in the following projects published in 2020:

Slimani et al. **JACC Cardiovasc Imaging.** 2020 Nov 13:S1936-878X(20)30920-7.

Carlier et al. **EBioMedicine.** 2020 Nov;61:103034

Montiel et al. **Sci Transl Med.** 2020 Oct 7;12(564):eaay2176.

Collin et al. **EBioMedicine.** 2020 Oct;60:102974.

Angé et al. **Int J Mol Sci.** 2020 Aug 4;21(15):5581.

Dhooghe et al. **Biol Open.** 2020 Aug 25;9(8):bio053116.

Kandalam et al. **Int J Pharm.** 2020 Sep 25;587:119685.

Demaret et al. **Biochim Biophys Acta Mol Basis Dis.** 2020 Nov 1;1866(11):165900.

Verhaegen et al. **Am J Cardiovasc Dis.** 2020 Jun 15;10(2):72-83. eCollection 2020.

Gourgue et al. **J Cell Mol Med.** 2020 Sep;24(17):10233-10244.

Ouni et al. **Hum Reprod.** 2020 Jun 1;35(6):1391-1410.

Neveu et al. **Mol Imaging Biol.** 2020 Oct;22(5):1324-1332.

Zampieri et al. **Mol Cancer Res.** 2020 Sep;18(9):1379-1391.

Scarcello et al. **Mater Sci Eng C Mater Biol Appl.** 2020 Jul;112:110938.

Grasso et al. **Front Pharmacol.** 2020 Mar 13;11:263.

Trempolec et al. **Cancers (Basel).** 2020 Feb 27;12(3):545.

Acciardo et al. **J Cell Mol Med.** 2020 Jan;24(2):1934-1944.

Mignion et al. **Clin Cancer Res.** 2020 Apr 15;26(8):1932-1943.

Hoffmann et al. **Cancer Immunol Res.** 2020 Jan;8(1):19-31.

Dano et al. **Mod Pathol.** 2020 Mar;33(3):354-366.

de Rudder et al. **Lab Invest.** 2020 Jan;100(1):147-160.

Slimani et al. **JACC Cardiovasc Imaging.** 2020 Feb;13(2 Pt 2):589-600.

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 (RNA-SEQ and scRNA-SEQ)
- 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 (e.g. SARS-COV2) 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.

CTMA 2020 AT A GLANCE

10	Research groups
944	NGS Libraries Preparation/analysis
	ILLUMINA: MiSeq/HiSeq/NovaSeq
90	- TRANSCRIPTOMIC (RNA-SEQ or scRNA-SEQ)
229	- GENOMIC (De NOVO / Resequencing)
80	- METAGENOMIC (Targeted – 16s)
500	- CRISPR Validation
	OXFORD NANOPORE: MinION
15	- GENOMIC (De NOVO / Resequencing)
30	- METAGENOMIC (Targeted / Shotgun)
300	GB of NGS DATA sequenced/analyzed

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

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https://uclouvain.be/fr/instituts-recherche/irec/ctma

REFERENCES 2020

CTMA has been involved in the following IREC collaborative project published in 2020. This list excludes papers that only involves CTMA research activities and papers that only involve biostatistics/bioinformatics analyses.

Demaret T, Roumain M, **Ambroise J**, Evraerts J, Ravau J, Bouzin C, **Bearzatto B**, **Gala JL**, Stepman H, Marie S, Vincent MF, Muccioli GG, Najimi M, Sokal EM. **Longitudinal study of Pex1-G844D NMRI mouse model: A robust pre-clinical model for mild Zellweger spectrum disorder.**
Biochim Biophys Acta Mol Basis Dis 1866(11): 165900, 2020.

Carlier FM, Dupasquier S, **Ambroise J**, Detry B, Lecocq M, Biétry-Claudet C, Boukala Y, **Gala JL**, Bouzin C, Verleden SE, Hoton D, Gohy S, **Bearzatto B**, Pilette C. **Canonical WNT pathway is activated in the airway epithelium in chronic obstructive pulmonary disease.**
EBioMedicine 61: 103034, 2020.

Renoz F, **Ambroise J**, **Bearzatto B**, Baa-Puyoulet P, Calevro F, **Gala JL**, Hance T. **Draft Genome Sequences of Two Cultivable Strains of the Bacterial Symbiont Serratia symbiotica.**
Microbiol Resour Announc 9(10): e01579-19, 2020.

d'Avila-Levy CM, **Bearzatto B**, **Ambroise J**, Helaers R, Butenko A, Yurchenko V, Morelli KA, Santos HLC, Brouillard P, Grellier P, **Gala JL**, Vikkula M. **First Draft Genome of the Trypanosomatid Herpetomonas muscarum ingenoplastis through MinION Oxford Nanopore Technology and Illumina Sequencing.** Trop Med Infect Dis 5(1): 25, 2020.

Asiabi P, **Ambroise J**, Giachini C, Coccia ME, **Bearzatto B**, Chiti MC, Dolmans MM, Amorim CA. **Assessing and validating housekeeping genes in normal, cancerous, and polycystic human ovaries.**
J Assist Reprod Genet 37(10): 2545-2553, 2020.

FLOW CYTOMETRY PLATFORM

CYTOFLUX 2020 AT A GLANCE

62	Users
31	Research groups
10	Trained people
627	Bookings
534	Flow cytometry hours
244	Cell Sorting hours

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UCLouvain - IREC Flow Cytometry Platform
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https://uclouvain.be/en/research-institutes/irec/cytometrie-de-flux.html

PROPOSED SERVICES

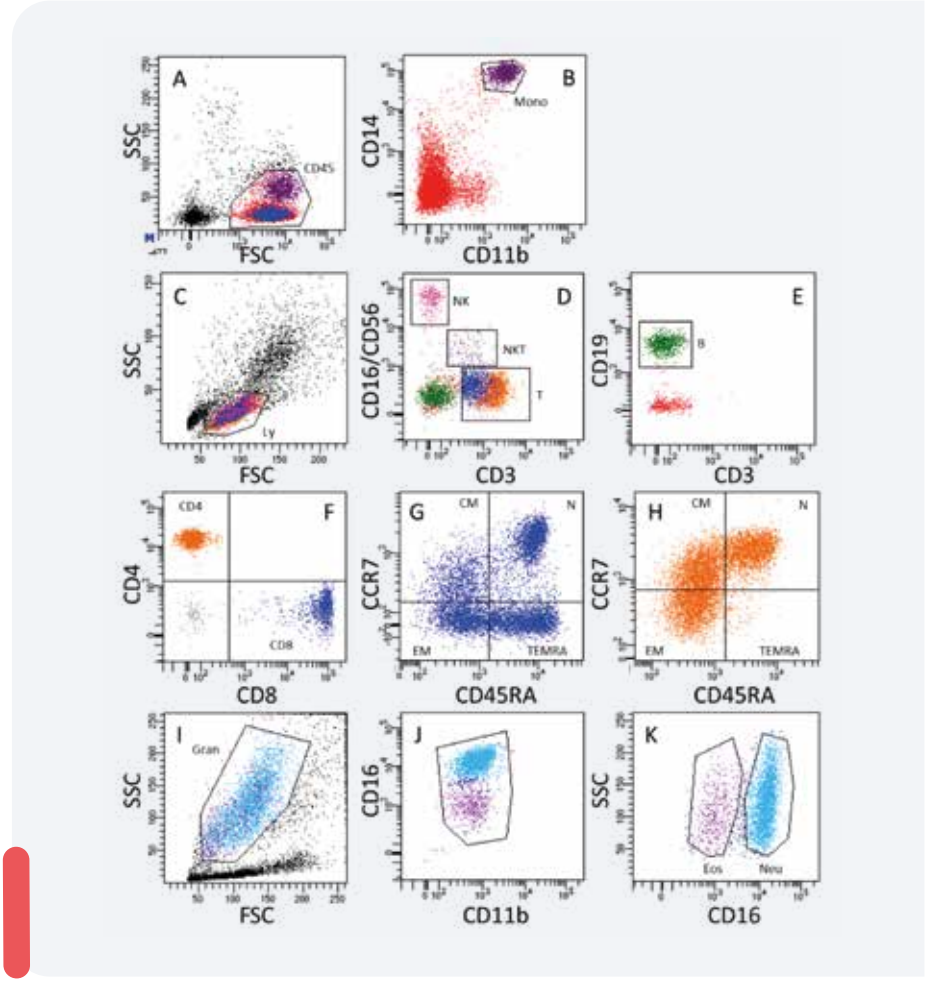
The platform logistician Davide Brusa welcomes you to the CytoFlux platform to discuss about projects involving the use of flow cytometry technology.

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

The platform is equipped with the following instrumentations:

- GentleMACS dissociator with heaters (new acquisition in 2019);
- 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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Chae H, Augustin R, Gatineau E, Mayoux E, Bensellam M, Antoine N, Khattab F, Lai BK, Brusa D, Stierstorfer B, Klein H, Singh B, Ruiz L, Pieper M, Mark M, Herrera PL, Gribble FM, Reimann F, Wojtusciszyn A, Broca C, Rita N, Piemonti L, Gilon P. SGLT2 is not expressed in pancreatic α- and β-cells, and its inhibition does not directly affect glucagon and insulin secretion in rodents and humans. **Mol Metab.** 2020 Sep 4:101071. **JCR 2019/20 6.130**

Verhaegen C, Kautbally S, Zapareto DC, Brusa D, Courtoy G, Aydin S, Bouzin C, Oury C, Bertrand L, Jacques PJ, Beauloye C, Horman S, Kefer J. Early thrombogenicity of coronary stents: comparison of bioresorbable polymer sirolimus-eluting and bare metal stents in an aortic rat model. Am J Cardiovasc Dis. 2020 Jun 15;10(2):72-83. **JCR 2019/20 6.000**

Alevra Sarika N, Payen VL, Fléron M, Ravau J, Brusa D, Najimi M, Pauw E, Eppe G, Mazzucchelli G, Sokal EM, Rieux AD, Taghdouini AE. Human Liver-Derived Extracellular Matrix for the Culture of Distinct Human Primary Liver Cells. **Cells.** 2020 May 30;9(6):1357. **JCR 2019 4.366**

Zampieri LX, Grasso D, Bouzin C, Brusa D, Rossignol R, Sonveaux P. Mitochondria participate in chemoresistance to cisplatin in human ovarian cancer cells. **Mol Cancer Res.** 2020 May 29:1145.2019. **JCR 2019 4.633**

Trempolec N, Degavre C, Doix B, Brusa D, Corbet C, Feron O. Acidosis-Induced TGF-β2 Production Promotes Lipid Droplet Formation in Dendritic Cells and Alters Their Potential to Support Anti-Mesothelioma T Cell Response. **Cancers** (Basel). 2020 May 19;12(5). **JCR 2019 6.102**

Grasso D, Medeiros HCD, Zampieri LX, Bol V, Danhier P, van Gisbergen MV, Bouzin C, Brusa D, Grégoire V, Smeets H, Stassen APM, Dubois LJ, Lambin P, Dutreix M and Sonveaux P. Fitter Mitochondria Are Associated With Radioresistance in Human Head and Neck SQD9 Cancer Cells. **Frontiers in Pharmacology** 2020 Mar 13;11:263. **JCR 2019 4.400**

Trempolec N, Doix B, Degavre C, Brusa D, Bouzin C, Riant O, Feron O. Photodynamic Therapy-Based Dendritic Cell Vaccination Suited to Treat Peritoneal Mesothelioma. **Cancers** (Basel). 2020 Feb 27;12(3). **JCR 2019 6.102**

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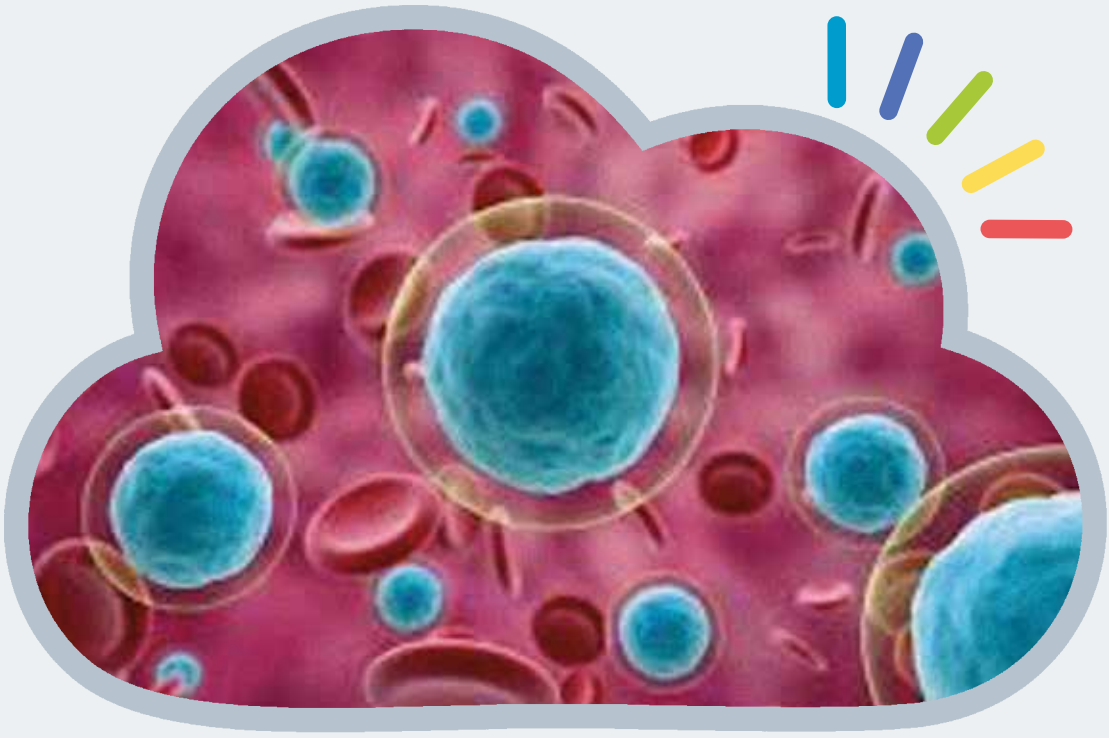

ANIMAL FACILITY

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

THE IREC ANIMAL FACILITY AT A GLANCE

3	Rodent confinement zones: Conventional, Linné-like and SPF-like areas
1	New zone opened in 2020: Linné-Like area
480	Mice cages available in the Conventional area
140	Rat cages available in the Conventional area
560	Mice cages available in the Linné-like area
105	Rat cages available in the Linné-like area
8	Research teams (PIs) using the Facility
68	Users trained to get access to the Facility since its opening

- 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

Contacts

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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 : J.-L. 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)

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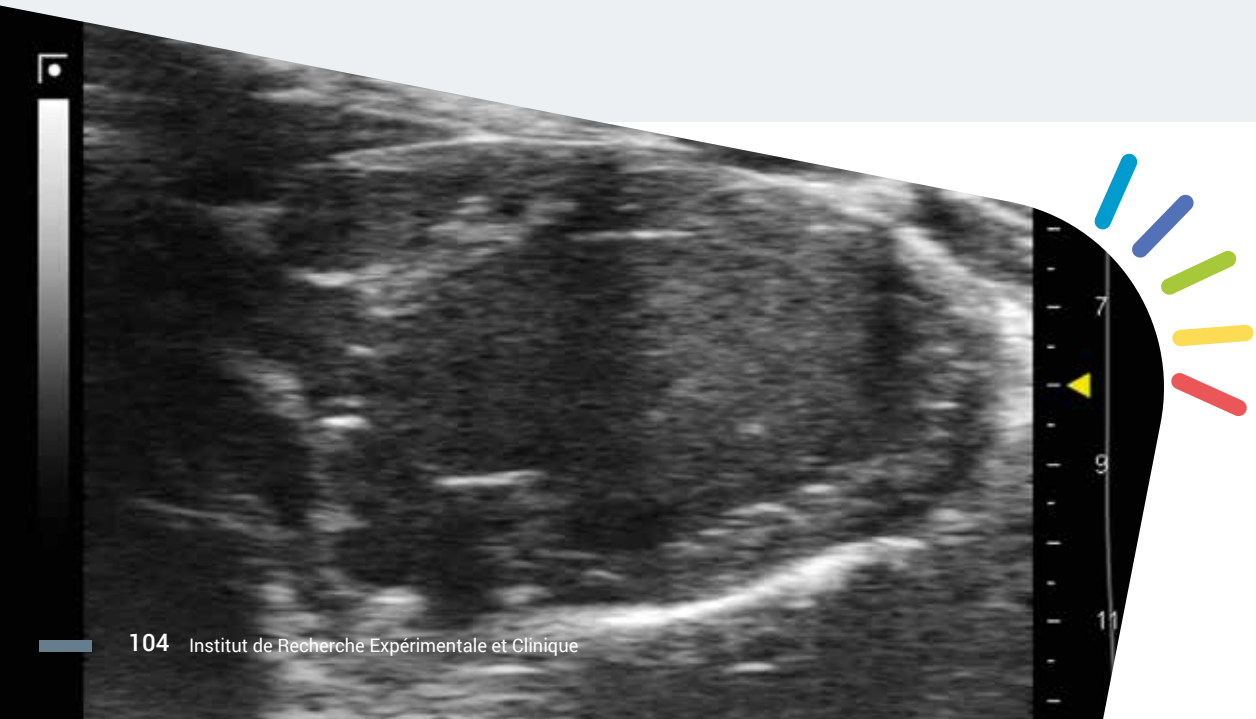

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Ongoing Collaborations

UCLouvain : 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 Prof. 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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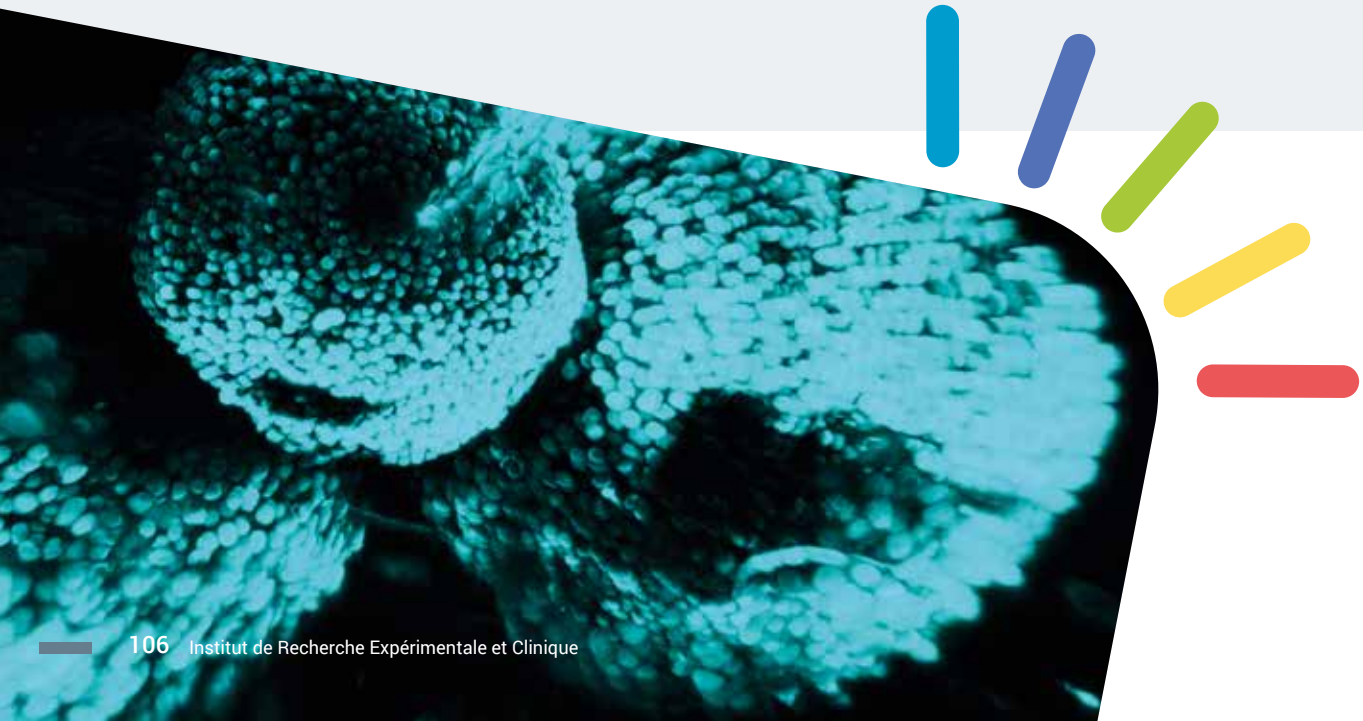

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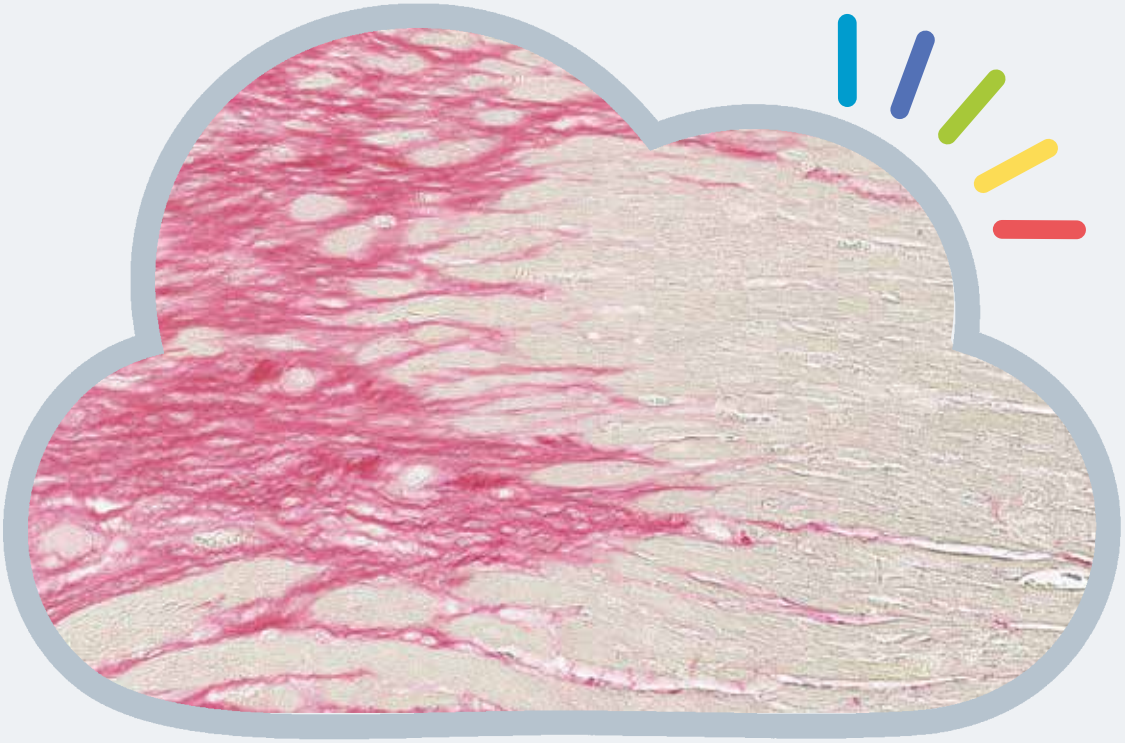

CTMA

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 UCLouvain 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 Improve biosafety and biosecurity unit" defines the full acronym CTMA/DLD-Bio. The cooperation between UCLouvain/CTMA and the Belgian Defense has been formalized in a convention framework signed on 30 August 2016. https://uclouvain.be/fr/sciencetoday/actualites/une-convention-de-recherche-in-edite-entre-la-defense-et-l-rsquo-ucl.html
- 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 is provided.

On the top of this, CTMA actively develops its own proprietary research, following the Russian Dolls strategy, which integrate research applied sciences activities at the 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.

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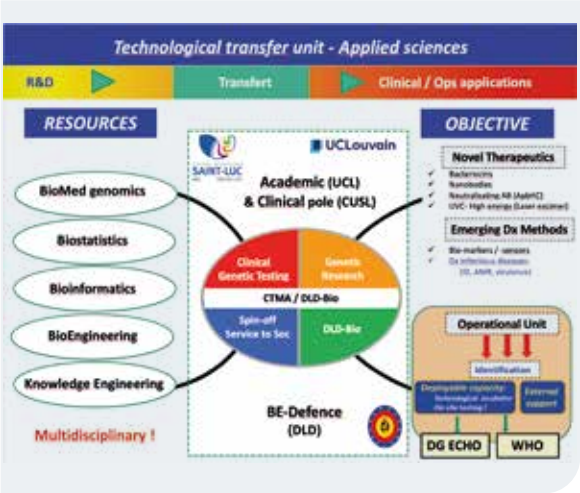
** CUSL: Cliniques universitaires Saint-Luc ** MOD: Ministry of Defense*

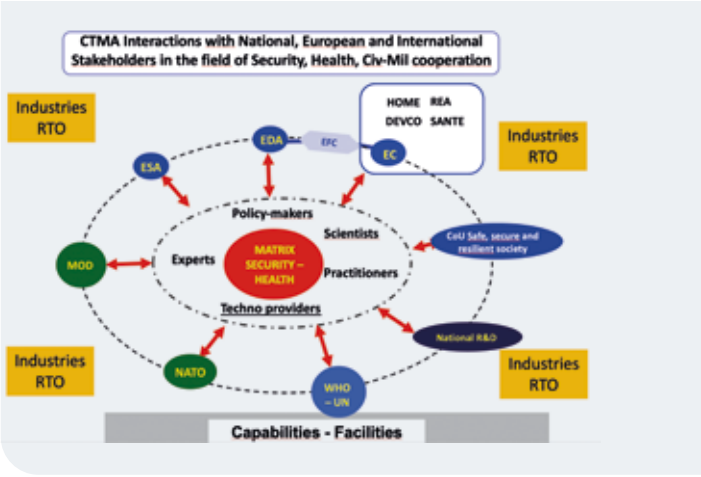
CTMA/DLD-Bio is notably active in microbial research (bacteria, viruses, fungi, helminths…) by developing novel therapeutics and emerging detection methods. Whereas novel therapeutics developments encompass bacteriocins, camelids immunoglobulins, neutralization AB and UVC- High energy (laser excimer), 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 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 (WALinnov and WAL²WIN) 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).

SARS-COV-2 VIRUS AND COVID-19

Since the very beginning of the COVID-19 pandemic in early 2020 CTMA/DLD-Bio launched a lot of R&D studies to contribute to the fight against the Sars-Cov-2 virus and the COVID-19 disease.

SARS-CoV-2 DETECTION

Improving Diagnostic Tests

The viral status of a person suspected of having contracted the SARS-CoV-2 virus is assessed by detecting the presence of RNA and/or virus antigens in the nasal cavities and upper airways. This assessment is obtained by molecular diagnosis, which today occupies a central place in the modern medical paradigm, particularly in health crisis situations such as the current COVID-19 pandemic.

RT-PCR

The in-house RT-qPCR was improved from the original method proposed by Christian Drosten, Charity Hospital, Berlin extraction by QIAamp Viral RNA Mini Kit after inactivation of the sample, followed by an RT-qPCR specifically targeting the gene E (E Sarbeco) common to coronaviruses and the other for the simultaneous detection of the RdRp gene (RNA-dependent RNA polymerase described by Victor M Corman), specific for SARS-CoV-2 and the RNAse P gene (human house-keeping) as an internal control RdRP.

To this end, for each of the two RT-qPCR's, a rigorous development has been carried out which focused on the following points: (1) bioinformatic comparison of the sequences of all coronaviruses to ensure the specificity of the tools developed; (2) development of the RT-qPCRs themselves on positive controls (inactivated viruses) as well as on G-blocks (synthetic gene fragments) in order to determine the limit of detection (LOD) and the efficiency (E) of the two RT-qPCRs; and (3) analysis of RNA extracted from 50 people among those 18% were infected with the SARS-CoV-2 virus with mild COVID-19. The infected viral loads of the infected people was known.

A comparative study has also been conducted between conventional PCR equipment (CFX96 - Biorad) and miniaturized equipment (Mic4 - Sopachem).

The results obtained by the E-gene screening test were then confirmed using the confirmatory RT-PCR assay RdRp. Negative and positive controls were examined in order to assess the validity and reproducibility of the tests between the different RT-PCR series. Interestingly, no amplification signals were detected in the negative controls. Positive controls have highly reproducible values (low standard deviation) within the same RT-PCR experiment and a low coefficient of variation between different RT-PCR runs.

RT-LAMP

In parallel with RT-qPCR, Loop-Mediated Isothermal Amplification (LAMP), an emerging technology for the detection of microorganisms was also evaluated to detect SARS-CoV-2. LAMP makes it possible to considerably reduce the analysis time in comparison with RT-qPCR and thus to make a "first emergency diagnosis", even if a confirmation of the RT-qPCR result is currently essential.

The LAMP method amplifies the genome of the virus at room temperature, and allows to detect it on surfaces, air samples or human samples (nasopharyngeal and salivary swabs) with excellent sensitivity. The chemical reaction is also simpler and faster.

Comparison with the reference technique of RT-qPCR developed at CTMA/DLD-Bio has been realized.

LAMP primer sets have been designed and tested on SARS-CoV-2 E gene RNA and RdRp RNA to select the best sets. The kits from Optigene (UK) and NEB were compared. The NEB kits produce reproducible and reliable data. The study of the sensitivity and specificity of these new RT-LAMP assays is in progress.

The final objective is to multiplex these tests and to integrate the MS2 bacteriophage with RNA as an internal control (IC).

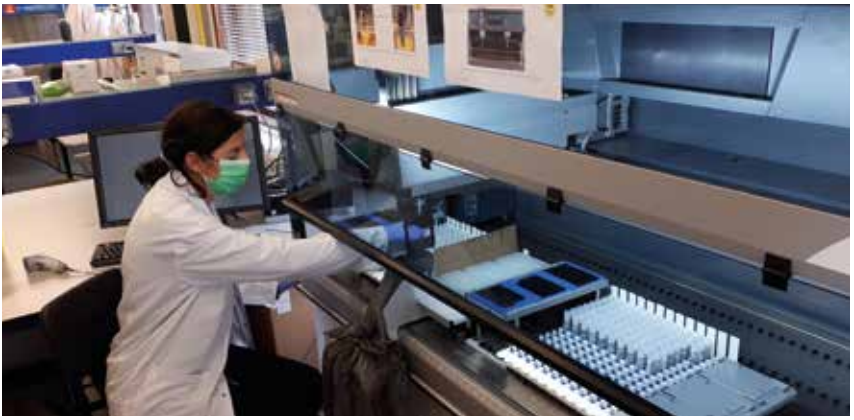
Rapid tests

To address efficiently the need to test a high number of patients in a relatively short period, CTMA/DLD-Bio has devised a smart testing strategy. This strategy is based on the integration of both serological and antigenic lateral flow assays which are fast and easy upfront RT-qPCR testing which are more elaborated and time-consuming. The current approach is very efficient as serological testing based on rapid lateral flow assays permits quick identification of seropositive patients that need further to be tested using antigen lateral flow assay and RT-qPCR. In contrast, seronegative patients can be discharged rapidly.

Rapid test QuickZen COVID-19 IgM/IgG

This is a colorimetric lateral flow assay carried out on drop blood collected by using a prick test. The test is based on the recognition and binding of IgM and/or IgG in the patient's blood to the Spike protein present in the test membrane. The test allows then identification of patients in the acute phase (IgM positive only), the intermediate phase (IgM/IgG positive) and in the convalescent phase (IgG positive only).

CTMA/DLD-Bio participated to the development of this lateral flow assay (test on a nitrocellulose strip). Not being able to go as far as industrial production to meet the real needs of the market, CYMA/DLD-Bio opted for an R&D cooperation with the Liège-based company ZenTech, leader in the rapid test market, to develop their rapid test QuickZen Covid-19 IgM/IgG 25 assay. CTMA/DLD-Bio is cooperating for years with ZenTech in RW-projects focused on the development of rapid tests (ended ALLERT and on-going ToxinEID and DEMASQUE projects).



CTMA/DLD-Bio Laboratories dedicated to Pfed

Scientific and logistical technical support of CTMA/DLD-Bio for the implementation of COVID-19 Federal platform bis (Pfed).

Bertrand Bearzatto

The entire pre-analytical part (sample reception, automated extraction, and preparation for RT-qPCR) of the federal Covid-19 bis platform has been installed in the CTMA's facilities. Several members of the CTMA are involved in the installation and validation of the platform within the CTMA. Over the next 24 months, these scientific staff will also contribute to the management and validation of the qPCR results that will be transmitted to the Belgian federal and regional authorities

COVID-19 FIELD TESTING

ESA IAP Artes 20 B-LiFE COVID-19 Deployment in Italian Piedmont Region (2020)

UCLouvain/CTMA (Prime), EONIX, nazka mapps, ETELM (France), SES Networks (Grand-Duchy of Luxemburg)

From 10 June to 23 July 2020, the B-LiFE mobile laboratory of CTMA/DLD-Bio was deployed in the Italian Piedmont districts of Turin and Novara to provide assistance to the local authorities in combatting the coronavirus pandemic. This mission was supported by the European Space Agency which financed this six-week deployment.

The aim of the mission was to test more than 6.000 first-line health workers (Croce Rossa Italiana), volunteers of the civil protection (Protezione Civile Italiana), Defense (Carabinieri) and volunteers involved in the COVID-19 pandemic fight to assess their past (sero-conversion) and current exposure to the coronavirus. The secondary objective was to detect asymptomatic cases and estimate their real number within this particular cohort. Therefore the B-LiFE team used the Smart Testing Strategy.

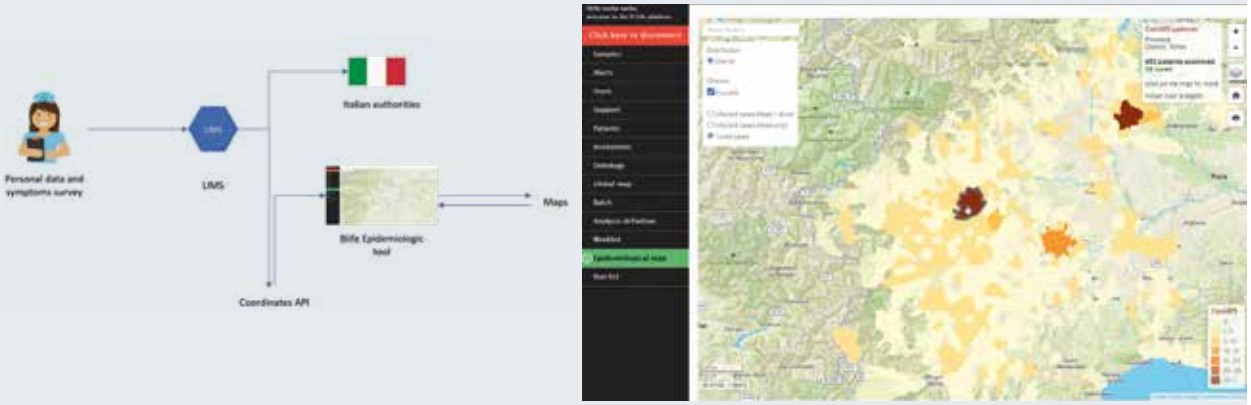
First responders from Novara, a district located nearby the very much affected Lombardy, were more exposed than those working in the more distant Turin; the antibody positive rate was twice as high in first responders from Novara as were those working in Turin. First responders from the Croce Rossa Italiana were obviously and globally more exposed to the coronavirus than first responders from Protezione Civile Italiana.

The deployment successfully confirmed the feasibility of new key operational features determining the success or failure of such rapid intervention in the context of an ongoing major crisis acutely affecting a region or a country, whether inside or outside the European Union. Among those, the concept of mass screening of citizens by deployed mobile laboratories applying a smart testing strategy and the requirements for efficient interconnectivity of laboratory patient database with the host nation (Laboratory Information Management System – LIMS). The concept of scalability and interoperability was also demonstrated through the successful integration within the B-LiFE mobile lab of French scientists from Paris Pasteur Institute and Italian scientists from the University of Torino, all trained by the B-LiFE team.

OVERVIEW OF THE B-LIFE DEPLOYEMENT AND SITE ORGANISATION

1. Patient arrival and registration
2. Attribution of patient identification number
3. Waiting for Prick tests
4. Prick test (serological testing)
5. Test reading and communication of result
6. Patient waiting for test result

B-LiFE Deployment in the ESA Exomars Hangar in Torino



Data Transmission from B-LiFE LIMS to Piedmont Authorities DataBase and to nazka mapps for Production of Epidemiological Maps. nazka mapps produced Epidemiological Map of Piedmont Region Torino and Novara Districts

EC H2020 CORDIAL-S Portable and fast surface plasmon resonance Point-of-Care test for COVID-19 (2020 – 2021)

Aleksandr Vybornov

The ongoing pandemic of severe acute respiratory syndrome SARS-CoV-2 infections, has morphed into a more permanent and long-lasting pan-epidemic outbreak. One efficient manner to limit COVID-19 spreading and an adequate mean of better managing the COVID-19 outbreak is through unrestrained availability of fast, efficient, accurate and cost-effective point-of-care tests (POCT).

The project consortium proposes C-POCT-S, a rapid (< 20 Euros) solution to address this medical need. C-POCT-S is based on a combination of several technologies such as the use of COVID-19 specific nanobodies (VHH), magnetic nanoparticles with high magnetic strength and a VHH modified interfaces, all integrated in a a hand-held surface plasmon resonance (SPR) based POC test (CPOCT-S) for the screening of the presence/absence of the SARS-CoV-2 virus in nasal and salvia samples.

The aim of this project is to complete product optimization, performance validation in a clinical setting and manufacturing quality control for C-POCT-S and completion of its technical file, to enable declaration of conformity and affixing of CE mark.

CTMA/DLD-Bio has a role as a technology validator and developer of the international LIMS interface in order to transfer data to national eHealth platforms, the European Commission and WHO. This rapid COVID-19 diagnostic test will be deployable on the field on mobile laboratory like our B-LiFE.

The EU faces growing lth of EU 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).

EU H2020 eNOTICE: European Network Of CBRN Tralning Centers: (2017-2022)

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 2020 eNOTICE organized a joint activity – a simulation and serious gaming CBRN exercise in Ankara, Turkey, and other events were held online – a webinar on Just-in-time training of first responders, a workshop for training centres on COVID-19 procedures trained by first responders as a consequence of the current pandemics, and a Policy meeting with the network stakeholders with the discussion dedicated to the network sustainability. 49 CBRN training centres are currently in the network.

EC H2020 ENCIRCLE: EuropeaN CBRN Innovation for the maRket CLustEr - (2017-2021)

Olga Vybornova, Aleksandr Vybornov, Omar Nyabi, Jérôme Ambroise, Bertrand Bearzatto

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.

The community now has 259 registered organisations in the Technological community and 211 practitioner organisations. There are 310 tools, 34 finished and running projects, and 259 organisations listed in the ENCIRCLE dynamic catalogue.

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

EC H2020 RKI Germany EuroBioTox: Validation of Biological Toxins Measurements after an Incident – Development of Tools and Procedures for Quality Control. (2018-2023)

CTMA/DLD-Bio 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 organizations, 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

Due to the COVID-19 pandemic and problems related to shipping test materials, CTMA/DLD-Bio did not participate to the in planed in 2020 proficiency tests.

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

Mostafa Bentahir

A panel of assays based on high-speed isothermal genomic amplification will be used to identify highly pathogenic biological agents in a field setting rapidly. 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 assays were developed and validated to detect Bacillus anthracis bacterium in simple and complex matrices, including soil and powders. Lamp assays development and validation are ongoing for rapid and specific detection and identification of viral pathogens such as the Zika, the middle east coronavirus (Mers-Cov), and severe acute respiratory syndrome coronavirus-2 (Sars-CoV-2) virus, which is the causative agent of COVID-19 pandemic.

Additionally, a multiple target LAMP assay for detecting Vibrio Cholerae was developed and is currently under validation on a panel of DNA samples obtained from strains isolated from patients. These assays are presently thoroughly validated for their specificity and sensitivity before their lyophilization. Following stability testing, these assays will be tested and validated for use under field conditions in the B-LiFE mobile laboratory

Belgian Defense Research Program 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. (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 CTMA/DLD-Bio team to carry out NGS analysis in the B-LiFE fieldable bio-laboratory in case of deployment for 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 two well-described simulants the MS2 and the AcNPV will be used.

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

Jamal Badir, Auxane Ladang, Mostafa Bentahir, Benjamin Smits, Olga Mineeva-Swango, Florencia Linero, Omar Nyabi

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.

The team succeed to generate a bench of polyclonal antibodies against most of the toxins described in the project (Clostridium Botulinum (Toxin A & B) staphylococcus Aureus; and nanobodies for Ricin detection.

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

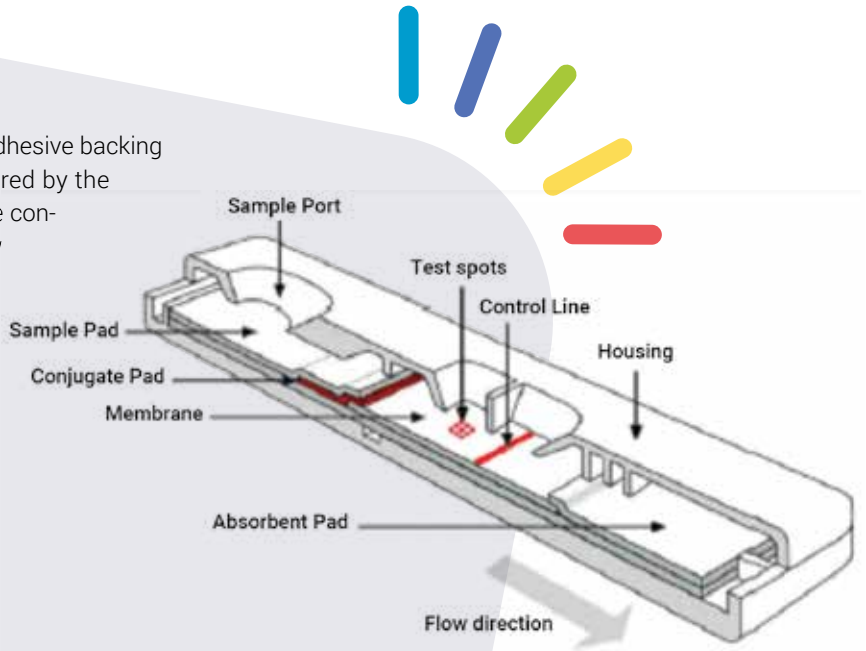
Mostafa Bentahir, Jamal Badir, Omar Nyabi, Nawfal Chibani, Pierre Vandenberghe

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. The assay will be robust and must achieve 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 development is far away conducted either on antigenic or genomic detection. For the first part of the assay, nanobodies required for the establishment of the diagnostic assay are under investigation and characterization before the assembly of the test. While, the second part, meaning the genomic detection, is on good path by bringing into focal, isothermal amplification, LAMP, towards detection the pane flavivirus (Zika, Dengue and Yellow fever viruses).

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.

Belgian Defense Research Program MSP16-4: Development of procedures for biological agent inactivation to enhance biosafety conditions during the procedure of identification under field conditions. (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 significantly interfering with PCR identification. The combination with UV exposure at specific wavelengths and exposure times has proven to be very effective for inactivation. However, this inactivation has been associated, due to DNA/RNA degradation, with a reduction in PCR detection sensitivity. Exposure conditions are further fine-tuned, evaluated and compared to the commercial kits to identify the best inactivation procedure associated with the most accurate PCR assay for the detection of bio-agents in environmental and clinical sample matrices.

Belgian Defense Research Program HFM 18-10: Assessment of water quality prior and after decontamination under field conditions. (2018-2022)

Project Team Cooperation with Laboratory for Hydrology, Bromatology and Air (LHBA) of the Veterinary Service of the Military Hospital (MHKA), Léonid Mwana Wa Bene Irenge, Antoine Cartier

The presence of life-threatening pathogens in water is a major healthcare issue, especially in developing countries. Waterborne diseases caused by parasites, bacteria or viruses are responsible of diseases which can be fatal. 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 related to these parasitic agents 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 of this 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.

The following developments have been achieved:

1) Development and validation of a rapid molecular assay for detection of Vibrio cholerae, the bacteria responsible for the pandemic diarrheal disease called cholera. It consists in a quadruplex real-time PCR assay which allows the detection and discrimination between V. cholerae causing the current pandemic and other V. cholerae strains, and also other closely-related agents which are present in water, like Aeromonas, Escherichia coli, Klebsiella and Salmonella.

The assay has been validated on a collection of 96 isolates from DR Congo collected from patients suspected of having contracted cholera (among which 78 isolates are of V. cholerae and 16 isolates of Aeromonas which had previously been misidentified as V. cholerae). Subsequent analysis by whole genome sequencing confirmed the identification provided by our quadruplex real-time PCR assay.

2) Development and validation of a molecular assay for the detection of the most prevalent parasites associated with diarrheic diseases, namely Entamoeba histolytica, Giardia intestinalis and Cryptosporidium spp. Similar to the V. cholera test, this assay is also a quadruplex PCR that targets the multi-copy gene 18S rDNA. The specificity of the assay was achieved by testing the quadruplex against human DNA and against DNA from Gram positive and negative bacteria available in the collection of CTMA/DLD-Bio.

The assay has been used to detect the presence of these parasites in fecal samples of cats infected with Cryptosporidium. It is known that the cysts of the parasites we are looking for have a thick wall which might hamper DNA extraction and thus reduce the sensitivity of the PCR. Two DNA extraction kits for fecal samples were compared: 1) the QIAmp Fast DNA Stool Mini Kit (Qiagen) and 2) the Quick-DNA Fecal/Soil Microbe Miniprep Kit (Zymo Research). The second one gave better DNA yield and was associated with lower Cq values upon real-time PCR. So far, the presence of Cryptosporidium has been confirmed in the fecal samples analysed. Similarly, the analysis of water samples from Mali has confirmed the presence of Cryptosporidium spp.

3) Development of a molecular assay for detection of Cyclospora cayetanensis, Toxoplasma gondii and Schistosoma. This assay has been tested on engineered plasmids harboring the 18S rDNA plasmids

Belgian Defense Research Program 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. (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 and characterization of relevant infections) 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.

Belgian Defense Research Program HFM 20-11: RICIn Detection, Identification and Verification of the biological activity (RICIDIV) (2020 – 2024)

Zacharie Paquet, Steven Verberckmoes

Toxins are molecules produced by living organisms among which some are of the most toxic chemicals for humans when inhaled, ingested, or absorbed. A lack of medical countermeasures and relatively easy procurement make toxins, especially ricin, a praised bioweapon candidate, as illustrated in recent past. This study aims to combine the complementary know-how of two laboratories of the Belgian Defence Laboratories (DLD), the chemical analysis laboratory (DLD-CA) located at Peutie (Vilvoorde) and the biological laboratory (DLD-Bio) part of the the CTMA/DLD-Bio, to provide Belgian Defence with a robust ricin detection and identification laboratory pipeline, including a new on-site screening technique, reach back cross-confirmation methods and an optimized sample preparation protocol for the LC-MS/MS reference method. Developing, assessing and validating this analytical panel requires to have high standard controls that are safe, easily accessible and available in ample amounts: they will be produced by genetic engineering in collaboration with the University of Ghent.

In 2020 genetic engineering of microbial cell factories to produce reference material has been started.

Belgian Defense Research Program HFM 20-13: CANDY-DATE – CANDida Yeasts Detection and resistance Analysis: a Triple hElix project (2020 – 2024)

Béatrice Sulka

Aside bacteria, fungal species can also cause invasive infections, especially in immunocompromised and critically ill patients. Most fungal agents associated with these conditions belong to the Candida genus. While Candida albicans is the most prevalent, Candida auris, an emerging Candida is often cited as a potential new "super bug", due to its association with high drug resistance and high mortality rates. It is being frequently reported as the cause of severe infection, especially in regions where Belgian military personnel are deployed.

The objective of this study is to develop a marketable (TRL 8) rapid detection assay of pathogenic Candida species based on a DNA-amplification method combined with lateral flow immunochromatographic assay, in triple helix partnership with the Belgian company CORIS BioConcept. In addition, the virulence and anti-fungal resistance of the detected pathogens will be analyzed through genomic characterization using NGS.

Belgian Federal Government – Académie de Recherches et d'Enseignement Supérieur (ARES) Sustaining the capacity to detect diarrheal infectious diseases: focus on reducing morbidity and mortality due to cholera in South Kivu Province (Democratic Republic of Congo). (2019 – 2021 with possible prolongation up to 2025)

Léonid Mwana Wa Bene Irenge

This project aims to contribute to the reduction of mortality and illness related to cholera in the province of South Kivu (DRC) through the strengthening and optimization of diagnostic tools (rapid diagnosis, confirmatory diagnosis) of this diarrheal disease in the high-prevalence health areas of the province.

This project is part of an ambition to improve the effectiveness of the intervention of national and international partners involved in the fight against cholera in DRC. In addition, these tools for rapid and specific diagnosis of the causal agent of cholera (Vibrio cholerae) will be used to search for potential reservoirs of V. cholerae that may explain the persistence of this disease over the past decades in the province of South Kivu.

The project also aims to strengthen collaboration between the different actors of the Congolese health structures in the province of South Kivu who are involved in the fight against cholera, through frequent consultations and exchanges of information. This group of actors will include the Provincial Division of Health (DPS) of South Kivu, the Provincial Ministry of Health (MPS), doctoral stu-

dents working on cholera within the framework of this project, academics from the universities and institutes of the province, especially Institut Supérieur des Techniques Médicales (ISTM) Bukavu, managers of health zones affected by cholera, NGOs, both international and local, members of the WASH and Health clusters as well as the local network of Congolese researchers active in the health field, which has emerged from the activities of the PIC 2012-2016 project in South Kivu.

FPS-Euphresco-2017-A-243-VIRFAST: Faster, cheaper identification of emerging virus problems (2018 - 2021)

Bertrand Bearzatto

The development, validation and implementation of fast, reliable and affordable on-site detection and identification tools for viral pathogens is a key challenge for a safer trade of plants and plant goods. The project will develop a scaled and efficient approach to evaluate the potential of Oxford Nanopore Technologies ONT for fast and cheap identification of viruses on plants, and plant products. In addition to the technology development, the project aims to create a community of stakeholders in order to identify the advantages and disadvantages of current on-site diagnostic tools (Lateral Flow Devices, LAMP…) and to highlight the gaps and opportunities for routine on-site diagnostic. This community will also co-design the development of ONT technologies to make them fit-forpurpose.

CTMA is also working for the industry to find new drugs against antimicrobial resistance and to produce fungal mass for vaccines at his Myco premises.

Antimicrobial resistance: bacteriocins in the fight against M20 acterium tuberculosis and Vibrio cholerae Funding: Syngulon

Anandi Martin (SYNGULON researcher), Jérôme Ambroise, Léonid Mwana Wa Bene Irenge

With the increase in antimicrobial resistance and the lack of development of antibiotics, solutions are urgently needed to combat antibiotic resistant bacteria. Different sets of molecules are therefore being studied aiming to develop new drugs. Among these, bacteriocins, antimicrobial peptides naturally produced by bacteria, appear particularly promising and continue to attract the attention of scientists. They are of great interest in the food industry as a bio-preservative due to their antibacterial effects. Bacteriocins could be an alternative to antibiotics in the health sector. SYNGULON owns a unique collection of bacteriocins (PARAGEN collection) which allows us for the first time to test bacteriocins but also to combine them with antibiotics against bacteria known to be multi-drug resistant (such as Mycobacterium tuberculosis responsible for tuberculosis).

There is a demand for this market since broad-spectrum antibiotics have shown their limits with the emergence of resistant microbes. There is an internationally recognized urgency to find alternatives or strengthen the arsenal of antibiotics currently available to the medical world. Syngulon therefore decided to explore this potential based on its knowledge of bacteriocins and its PARAGEN collection. Exploring this new market requires Syngulon to acquire new skills in the area of microbial infection control. This project fits into this strategy through collaboration with CTMA. The aim is to explore the use of bacteriocins in the fight against Mycobacterium tuberculosis and Vibrio cholerae infections as a new alternative to antibiotics.

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Irenge LM, **Ambroise J**, Mitangala PN, **Bearzatto B**, Kabangwa RKS, **Durant JF**, **Gala JL**. Genomic analysis of pathogenic isolates of Vibrio cholerae from eastern Democratic Republic of the Congo (2014-2017). PLoS Negl Trop Dis 14(4): e0007642, 2020.

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PHD THESES

Date: 09-01-2020 Name: **GRASSO Debora** **Lab: FATH**
Thesis: Common metabolic alterations in cancer chemoresistance and radioresistance
Promotor: SONVEAUX Pierre Copromotor: GREGOIRE Vincent

Date: 27-01-2020 Name: **SCARCELLO Eleonora** **Lab: LTAP**
Thesis: Cytotoxicity and endothelial dysfunction induced by iron-containing bioresorbable materials
Promotor: LISON Dominique

Date: 31-01-2020 Name: **DILI Alexandra** **Lab: GAEN**
Thesis: Small-for-size syndrome and hypoxia - A lesson learned from the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) rapid liver regeneration model in rats
Promotor: LECLERCQ Isabelle Copromotor: BERTRAND Claude

Date: 04-02-2020 Name: **LAI Bao Khanh** **Lab: EDIN**
Thesis: The role of somatostatin and KATP channels in the control of glucagon secretion by glucose
Promotor: GILON Patrick

Date: 10-02-2020 Name: **GALOT Rachel** **Lab: MIRO**
Thesis: Personalized biomarker-based treatment strategy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck
Promotor: MACHIELS Jean-Pascal

Date: 11-02-2020 Name: **RENGUET Edith** **Lab: CARD**
Thesis: Protein acetylation, a new player in the regulation of cardiac metabolism
Promotor: BERTRAND Luc Copromotor: BEAULOYE Christophe

Date: 02-03-2020 Name: **LACROIX Olivia** **Lab: EPID**
Thesis: Statins and Metformin in digestive tract cancers: Pattern of use and its association with disease progression
Promotor: ROBERT Annie

Date: 06-03-2020 Name: **MASCIANGELO Rossella** **Lab: GYNE**
Thesis: Ovarian tissue cryopreservation and transplantation in adult and prepubertal patients
Promotor: DOLMANS Marie-Madeleine Copromotor: ANDRADE AMORIM Christiani

Date: 16-03-2020 Name: **KIRCHGESNER Thomas** **Lab: Service d'imagerie médicale CUSL**
Thesis: Dixon MRI sequences in hands with early rheumatoid arthritis
Promotor: VANDE BERG Bruno Copromotor: STOENOIU Maria Simona

Date: 09-06-2020 Name: **VAN OOTEGHEM Geneviève** Lab: MIRO
Thesis: Non-invasive ventilation techniques to serve respiratory-related motion management strategies in radiotherapy
Promotor: GEETS Xavier Copromotor: BORBATH Ivan

Date: 19-06-2020 Name: **SANTIAGO DE JESUS João Pedro** **Lab: FATH**
Thesis: TGF-β2 at the crossroads between tumor acidosis, lipid metabolism and epithelial-to-mesenchymal transition
Promotor: FERON Olivier Copromotor: CORBET Cyril

Date: 16-07-2020 Name: **ABOUBAKAR NANA Frank** **Lab: PNEU**
Thesis: Role of Focal Adhesion Kinase in the invasive phenotype of small-cell lung cancer
Promotor: OCAK Sebahat Copromotor: PILETTE Charles

Date: 27-08-2020 Name: **JORIS Virginie** **Lab: FATH**
Thesis: MiR-199a family members: new actors of cardiovascular functions in health and disease
Promotor: DESSY Chantal

Date: 01-09-2020 Name: **LAMBERT Catherine** **Lab: Service d'hémostase, CUSL**
Thesis: Non-substitutive strategies to improve hemophilia care in developing countries. Experience in Côte d'Ivoire.
Promotor: HERMANS Cédric Copromotor: DE MOERLOOSE Philippe (CHU Genève)

Date: 03-09-2020 Name: **SELDRUM Stéphanie** **Lab: CARD**
Thesis: Left ventricular remodeling after correction of aortic or mitral regurgitation
Promotor: VANOVERSCHELDE Jean-Louis Copromotor: GERBER Bernhard

Date: 04-09-2020 Name: **VERHAEGEN Carole** Lab: CARD
Thesis: New degradable biomaterials for endovascular stents: In vitro and in vivo evaluation of the biological response
Promotor: KEFER Joëlle Copromotor: HORMAN Sandrine

Date: 07-09-2020 Name: **DEMARET Tanguy** Lab: PEDI
Thesis: Liver-targeted therapies in Zellweger Spectrum Disorders
Promotor: SOKAL Etienne

Date: 09-09-2020 Name: **SIRONVAL Violaine** Lab: LTAP
Thesis: Evaluating and predicting the respiratory hazard of particles used in Li-ion batteries, for a safe and sustainable development
Promotor: LISON Dominique Copromotor: VAN DEN BRULE Sybille

Date: 10-09-2020 Name: **DUPREZ Frédéric** Lab: PNEU & CUSL
Thesis: Oxygen therapy in hypoxaemic failure to subjects who breathe spontaneously: How can we improve oxygen supplementation?
Promotor: REYCHLER Gregory

Date: 15-09-2020 Name: **VERMEULEN Maxime** Lab: GYNE
Thesis: Development of an artificial testis free from neoplastic cells and transplantable to the patient
Promotor: WYNS Christine Copromotor: POELS Jonathan

Date: 23-09-2020 Name: **LEBLEU Julien** Lab: CARS
Thesis: Quantitative mobility assessment in patients with knee osteoarthritis: From lab to an ecological approach by means of wearable technology
Promotor: DETREMBLEUR Christine Copromotor: MAHAUDENS Philippe

Date: 24-09-2020 Name: **SLIMANI Alisson** Lab: CARD
Thesis: Physiopathological mechanisms of severe paradoxical low gradient aortic stenosis
Promotor: VANOVERSCHELDE Jean-Louis Copromotor: GERBER Bernhard

Date: 01-10-20 Name: **COPPIN Louise** Lab: PEDI
Thesis: Tissue factor related thrombogenesis induced by heterologous human adult liver-derived progenitor cell infusion: modulation by cell dose escalation and anticoagulant drugs. Clinical application and relevance
Promotor: STEPHENNE Xavier Copromotor: SOKAL Etienne

Date: 02-10-2020 Name: **DARIUS Tom** Lab: CHEX
Thesis: Exploring Different Preservation Strategies in a Pig Kidney DCD Autotransplant Model
Promotor: MOURAD Michel Copromotor: GIANELLO Pierre

Date: 06-10-2020 Name: **ROY Clotilde** Lab: Pathologies cardiovasculaires
Thesis: Phenotyping Heart Failure with Preserved Ejection Fraction: Focus on markers of fibrosis (extracellular volume by cMRand biomarkers) and their prognostic impact
Promotor: POULEUR Anne-Catherine Copromotor: GERBER Bernhard

Date: 23-10-2020 Name: **COMBRET Yann** Lab: PNEU
Thesis: Physical capacities in children with cystic fibrosis. From muscle to functional assessment.
Promotor: REYCHLER Gregory

Date: 06-11-2020 Name: **LAFONT Sébastien** Lab: MORF
Thesis: The influence of hyaluronidase Spam1 in the pathogenesis of osteoarthritis
Promotor: BEHETS WYDEMANS Catherine Copromotor: MANICOURT Daniel

Date: 09-12-2020 Name: **HAGE Renaud** Lab: CARS
Thesis: Kinematic characterization of fast and accurate cervical rotations during point-to-point test in healthy and neck pain individuals
Promotor: DETREMBLEUR Christine Copromotor: PITANCE Laurent

Date: 18-12-2020 Name: **BIHOUN Biébo** Lab: EPID
Thesis: Age-related factors associated with placental malaria and adverse pregnancy outcomes in rural Burkina Faso
Promotor: ROBERT Annie Copromotor: TINTO Halidou (Université polytechnique de Bobo Dioulasso, Burkina Faso)

PHD DAY

PROGRAM

The 2020 edition of IREC PhD Day took place entirely remotely in compliance with anti-COVID measures.

DECEMBER 17TH

9h00-10h20 First session

Welcome

POILVACHE Hervé (NMSK) - Synergistic effect of an enzymatic solution with multiple classes of antibiotics against methicillin-resistant Staphylococcus aureus (MRSA) biofilms in an in-vitro model relevant to prosthetic joint infections

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

OCTAVE Marie (CARD) - Pharmacological ACC inhibition decreases thrombin-induced platelet aggregation by a mechanism independent of lipid content

VANDER LINDEN Catherine (FATH) - Pre-challenge with 3-bromopyruvate renders MCT4 inhibition synthetically lethal in cancer cells

Moderators: Laurent Bultot (CARD) & Natacha Fourny (CARD)

10h20-10h40 Coffee Break.

10h40-12h00 Second session

COHILIS Marie (MIRO) - Comparison of various dual-energy CT calibration methods for proton SPR estimation in animal soft tissues

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

SAWADOGO Salam - Difference in the distribution of blood group phenotypes between blood donors and other population sub-groups or the « universal blood donors and recipients » concept bias

WAUTIER Delphine (NMSK) - Aseptic loosening and lucent line under the tibial base plate in primary total knee arthroplasty: origin and evolution, a new understanding approach

Moderators: Laurent Dumas (FATH) & Alice Marino (CARD)

Sponsor Talk (Promega)

DECEMBER 18TH

9h00-10h20 Third session

PETTINARI Matteo (CARD) - Annular dynamics and not diameter, predict later tricuspid regurgitation after mitral valve surgery: results from a prospective randomized trial

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

NACHIT Maxime (GAEN) - Non-invasive detection of myosteatosis predicts NASH in the context of metabolic syndrome and obesity

VAN GOETHEM Nina (EPID) - The added value of viral genomic data for predicting the severity of influenza infection

Moderators: Laura Ferté (CARD) & Ana Barragan Montero (MIRO)

10h20-10h40 Coffee Break

10h40-12h00 Fourth session

DIERGE Emeline (FATH) - Cancer cell addiction to fatty acids in tumor acidic compartment supports a link between dietary lipids and cancer progression

D'ABADIE Philippe (MIRO) - Antireflux catheter improves tumor targeting in liver radioembolization

PLANTÉ-BORDENEUVE Thomas (PNEU) - The pIgR-IgA system: A new player in idiopathic pulmonary fibrosis?

HUYGHE Nicolas (MIRO) - Interim analysis of the avetuxiri trial : Avelumab combined with cetuximad and irinotecan for treatment of refractory microsatellite stable (MSS) metastatic colorectal cancer (mCRC) – Correlative study with immunoscore

TRIAILLE Clément (RUMA) - Comparison of paired synovial biopsies shows conserved T cell organization across joints from the same RA patients.

Moderators: Matias Ramirez (CHEX) & Cécile Dufeys (CARD)

12h00 CorSci presentation and Award Ceremony

The Award committee: Alice Marino (CARD), Cécile Dufeys (CARD), Laurent Dumas (FATH), Laura Ferté (CARD), Natacha Fourny (CARD), Matias Ramirez (CHEX), Ana Barragan Montero (MIRO) and Laurent Bultot (CARD)

POSTERS

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

Elena Lucia Borderias Villarroel (MIRO) Dose restoration in lung cancer patients: an on-line adaptive strategy to fight against density changes in proton therapy

Gregory Buti (MIRO) Fast robust optimization using a patient-specific scenario selection methodology

Luciana Cacciottola (GYNE) Adipose tissue-derived stem cells to enhance early revascularization and follicle survival rates in human ovarian tissue long-term xenotransplants

Arthur Colson (OBST) Hypoxia-inducible factor-2α impairs human placental development in fetal growth restriction

Louise Declerck (NMSK) Adaptive sports following motor disability from acquired central neurological lesion: A systematic review on feasibility and effectiveness according to the ICF framework

Julien De Poortere (CARD) The role of α1AMP-activated protein kinase (α1AMPK) in vascular dysfunctions induced by sepsis

Justine Gillard (GAEN) Alterations in bile acids and TGR5 activation in nonalcoholic steatohepatitis

Camille Hossay (GYNE) Is ovarian tissue able to withstand refreezing-rethawing?

Giulia Jannone (PEDI) Bile duct resection in the rat: a model of liver senescence

Marc Kanbar (ANDRO) Implementing a Microfluidic culture system to improve spermatogenesis efficiency in a porcine prepubertal model

Céline Khalifa (STLUC) Electroencephalographic signals as predictable markers of postoperative delirium: a study protocol in elective cardiac surgery

Sibille Lejeune (CARD) Heart failure with preserved ejection fraction in Belgium: baseline characteristics and outcome of a real life cohort

Luca Maccioni (GAEN) The link between the gut and the liver during early alcoholic liver disease

Juliana Macedo (PNEU) Distance from Home to Rehabilitation Center did not Influence Adherence to Pulmonary Rehabilitation Program: A Retrospective Study

Louis Maistriaux (MORF) Perfusion-decellularization of vascularized pig stomachs

Massart Isabelle (EDIN) Cancer cachexia is associated with a marked increased production of acute-phase reactants by skeletal muscle

AnhPhong Nguyen (NMSK) Effect of age on the wrist's viscoelasticity in healthy participants from 3 to 90-years-old

Olivier Pollé (PEDI) Multilevel longitudinal approach to identify new biomarkers in pediatric new-onset type 1 diabetes: DIATAG study

Lucie Ruiz (EDIN) Regulation of pancreatic ð-cell [Ca2+]c and somatostatin secretion by glucose

Tshikongo Arsene Kabamba (MBLG) Evaluation de la performance de deux tests de diagnostic rapide (TDR) par rapport à l'automate Liaison XL dans le diagnostic des hépatites virales B et C en RDC

Julien Van Damme Comparison of Whole-body MRI and 68Ga-PSMA-PET for the detection of metastases in prostate cancer: preliminary results of a prospective diagnostic accuracy study

Marie Vanderputten (MIRO) Phosphoproteome profiling of small-cell lung cancer in response to focal adhesion kinase inhibition

Sophie Welsch (PEDI) GENEPEDIAB study: multicenter screening of genetic forms of diabetes in cohorts of children and adolescents with type 1 diabetes

Luca Zampieri (FATH) Mitochondrial alterations associated to cisplatin resistance in ovarian cancer

Serge Henri Zango (EPID) Malaria and curable sexually transmitted infections in pregnant women in rural Burkina Faso

Timothée Cayrol (FSM) Near perfect within- and between-session reliability of secondary hyperalgesia induced by electrical high-frequency stimulation. ERROR?

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IREC SEMINARS 2020

DATE	SPEAKER	INSTITUTION	TITLE/THEME
13/01/20	Pr Dr. Ulf Nehrbass	CEO, Luxembourg Institute of Health	Clinnova - Unlocking the potential of data science and artificial intelligence in health care
20/01/20	Dr Pauliina Damdimopoulou	Unit of Obstetrics and Gynecology, Department of Clinical Sciences, Karolinska Institute, Sweden	Deconstructing human ovaries: from single cell analysis to environmental pollutants
27/01/20	Pr Bernard Van Beers	University Paris Diderot, Beaujon University Hospital Paris Nord Researcher at INSERM, France	Quantitative MRI in Fatty liver disease
24/02/20	Pr Norbert Stefan	University of Tübingen and researcher at the German Center for Diabetes Research (DZD); Germany	Metabolically healthy and unhealthy normal weight and obesity
25/05/20*	Pr Christoph Maack	Universitätsklinikum Würzburg, Germany	Mitochondrial redox regulation in heart failure
21/09/20	Dr Caroline Bouzin	2IP Platform, IREC, UCLouvain	Dive into 2IP's new equipments
26/10/20*	Pr Virginie Montiel	FATH, IREC, UCLouvain	Inhibition of aquaporin-1 prevents myocardial remodeling by blocking the transmembrane transport of hydrogen peroxide
23/11/20*	Pr Antoine Froidure	PNEU, IREC, UCLouvain	Epithelial and immune crosstalk in lung fibrosis
21/12/20*	Pr Laurent Gatto	de Duve & IREC, UCLouvain	Where and with whom: using Bayesian inference and deep learning to study protein localisation and protein-protein interactions

** Webinar*

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SCAN TO WATCH IREC VIDEO:

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