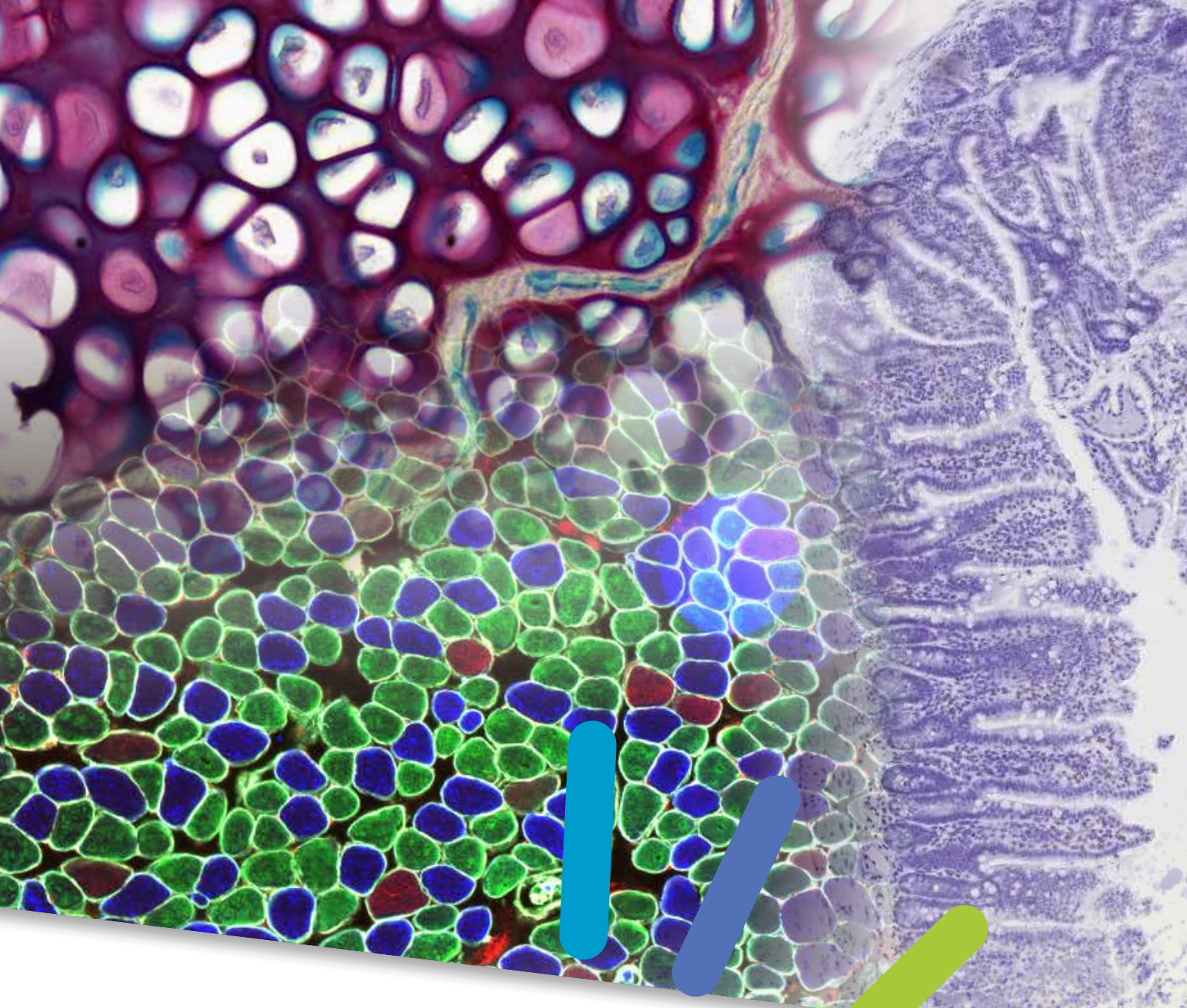


IREC

ACTIVITY REPORT

2022

« 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.

As in past years, and despite the COVID-19 pandemic, we enjoyed the (mostly virtual) visits of prominent national and international scientists at our monthly Seminars (now held in the new "G. Cori" Auditorium in the Laënnec building), and held highly praised networking events, such as the "IREC lunch" and "IREC PhD day".

Through this year 2022, we have enjoyed the company and collaboration of many international young scientists, a number of whom defended their PhD thesis, others competitively obtained research Fellowships and more senior ones obtained an exceptionnally high number of competitive research grants or were promoted to permanent -including academic- positions. Many members of our technical and administrative staff were also promoted in their career tracks. This is a tribute to their, as well as their supervisors'dedication to our common mission: building knowledge together to combat diseases. This year was also my last year as IREC president; I'm happy to now hand the institute over to professor Isabelle Leclercq.

Jean-Luc Balligand

IREC President

SCAN TO WATCH IREC VIDEO:

The mission of

IREC

Institut de Recherche Expérimentale et Clinique

Building kowledge together to combat diseases

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.

ADMINISTRATIVE COORDINATOR:

Veronica Curto / Caroline Dutry

LOGISTICS AND ACCOUNTING:

Maimouna Elmjouzi
MBLG/PNEU/CTMA

Nadtha Panin
LTAP

Deborah Morrens
FATH/RUMA/2IP/Cytoflux

Dora Ourives Sereno
GAEN/GYNE/CARD

IREC GENERAL ADDRESS:

Avenue Hippocrate, 55 bte B1.55.02
1200 Woluwe-Saint-Lambert

INTERNET ADDRESS:

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

INDEX

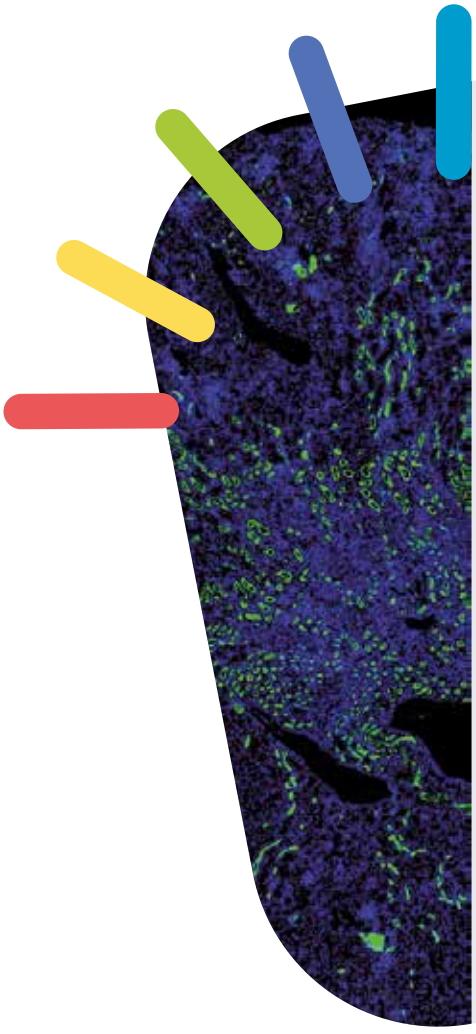
SCIENTIFIC ADVISORY BOARD

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.

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 NEXT VISIT OF THE SCIENTIFI ADVISORY BOARD IS SCHEDULED ON MAY 2023. WE WILL WELCOME :



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. M. Goldman,
Professor emeritus at Faculty of Medicine,
ULB, Brussels, Belgium

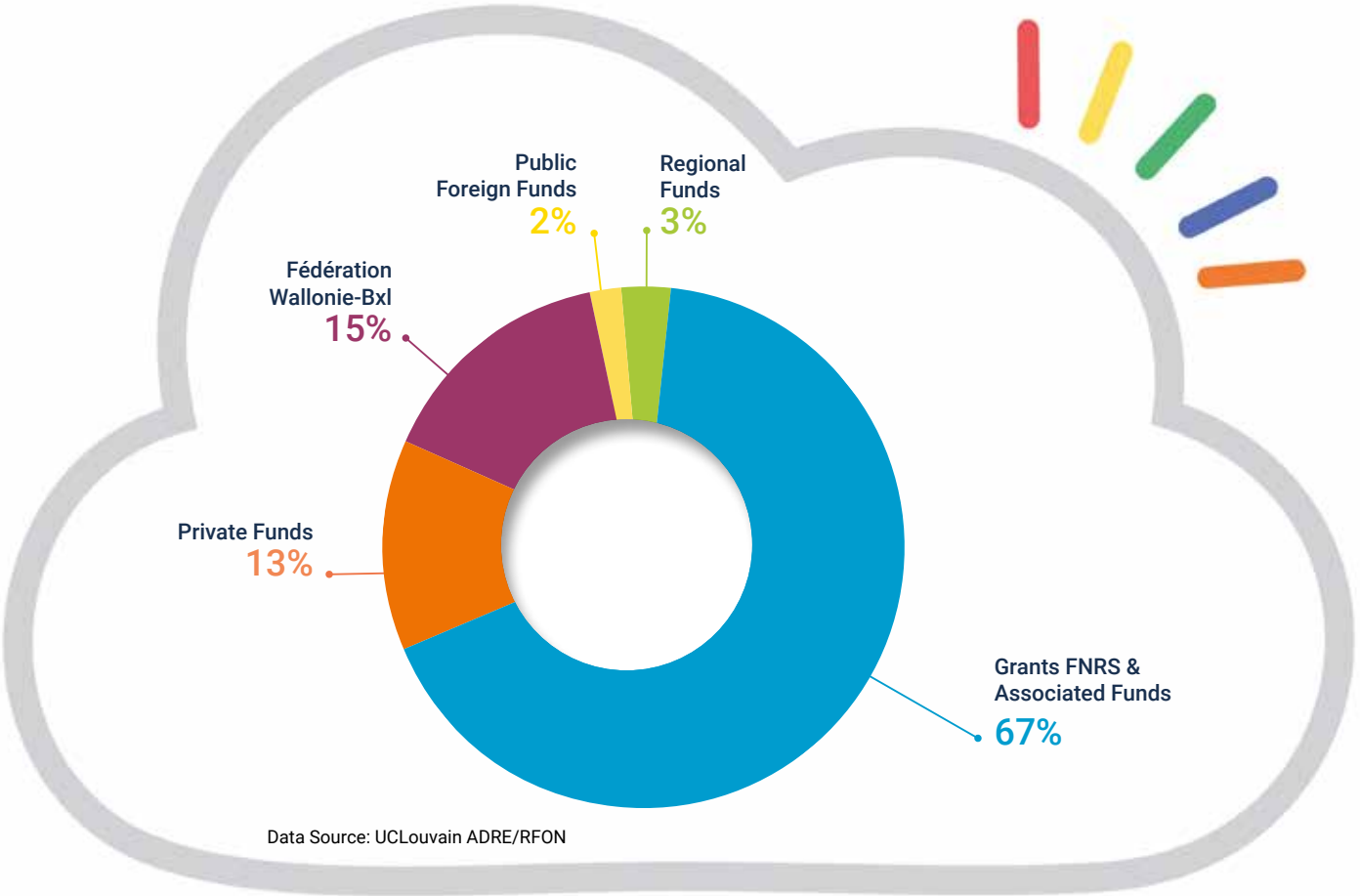
Prof. J Zuckman Rossi
Director, centre de Recherche des Cordeliers,
Paris, France

Prof B Staels
INSERM, Pasteur Institute and University of Lille,
Lille, France

NEW RESEARCH AGREEMENTS AND CONTRACTS CONCLUDED IN 2022

Funding Sources	N. of agreements	Funding Amount
Grants FNRS & Associated Funds	82	€ 5.546.751
Private Funds	16	€ 3.328.183
Fédération Wallonie -Bxl	18	€ 1.486.490
Public Foreign Funds	2	€ 722.570
Regional Funds	4	€ 612.294
Other Public Belgian Funds	1	€ 35.539
Federal Funds	1	€ 18.153
Total	**124**	**€ 11.749.980**

SIGNED FUNDING AGREEMENTS PER FUNDING SOURCE (%) 2022



Data Source: UCLouvain ADRE/RFON

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)

Parla Astarci, MD, PhD

Christophe Beauloye, MD, PhD

Luc Bertrand, PhD

Laurent De Kerchove, MD, PhD

Gébrine El Khoury, MD, PhD

Bernhard Gerber, MD, PhD

Sandrine Horman, PhD

Joëlle Kefer, MD, PhD

Agnès Pasquet, MD, PhD

Alexandre Persu, MD, PhD

Sophie Piérard, MD, PhD

Anne-Catherine Pouleur, MD, PhD

David Vancraeynest, MD, PhD

Jean-Louis Vanoverschelde, MD, PhD

Members:

Claire Baufays, MD, PhD student
Julie Bodart, PhD student
Laurent Bultot, Postdoctoral Fellow
Marin Boutte, MD PhD student
Julien Cumps, PhD student
David de Azevedo Coutinho Pereira, Md, PHD Student
Emma de Cartier d'Yves, PhD student
Mélanie Dechamps, MD, PhD student
Marine De Loof, PhD student
Julien De Poortere, PhD student
Justine Dontaine, PhD student
Cécile Dufeys, Postdoctoral Fellow
Natacha Fourny, Postdoctoral fellow
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
Anais Lotens, PhD student
Sebastien Marchandise, MD, PhD student
Alice Marino, Postdoctoral fellow
*Nassiba Menghoum,*MD PhD Student
Marie Octave, PhD student
Laurence Pirotton, PhD student
Nour Rahnama, MD, PhD student
Valentine Robaux, PhD student
Emmanuel Vandenhooft, Technician
Dora Ourives, Grants and Contracts Administrator

Pole Contact Persons

For basic research:

Christophe Beauloye
Christophe.beauloye@uclouvain.be
Luc Bertrand
Luc.bertrand@uclouvain.be
Sandrine Horman
Sandrine.horman@uclouvain.be

For clinical research:

Christophe Beauloye
Christophe.beauloye@uclouvain.be
Bernhard Gerber
Bernhard.gerber@uclouvain.be

POLE OF PHARMACOLOGY AND THERAPEUTICS (FATH)

Chantal Dessy, PhD

Jean-Luc Balligand, MD, PhD

Members:

Sultan Al-Siyabi, PhD student
Ramona Bella, Postdoctoral Fellow
Hasnae Boughaleb, PhD student
Lorena Cascarano, PhD student
Clara Chivasso, Postdoctoral Fellow
Delphine De Mulder, Technician
Hrag Esfahani, Research Scientist
Irina Lobysheva, Senior Scientist, Research collaborator
Dorothée Marchand, PhD student
Lauriane Michel, Post-doctoral Fellow
Virginie Montiel, Postdoctoral Fellow
Gopinath Muruganandam, Postdoctoral Fellow
Lucie Pothen, PhD Student
Delphine Thibou, Technician
Roxane Verdoy, Technician
Deborah Morrens, Grants and Contracts Administrator

Pole Contact Persons

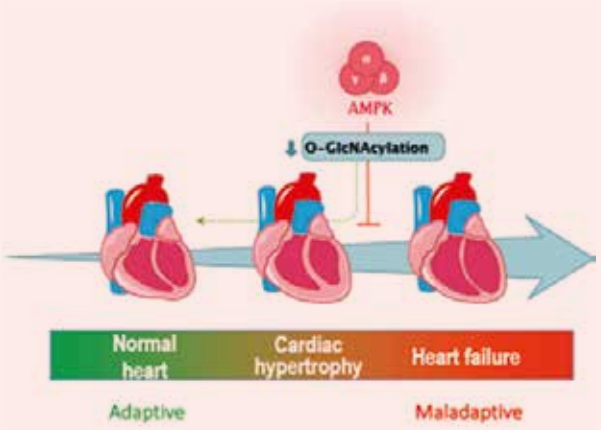
Jean-Luc Balligand
Jean-Luc.balligand@uclouvain.be
Chantal Dessy
Chantal.dessy@uclouvain.be

CARDIAC HYPERTROPHY

AMPK and O-GlcNAcylation, two partners intimately connected to reverse cardiac hypertrophy development, improving cardiac function

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

We previously showed that AMPK activation blocks cardiac hypertrophy development by reducing a particular post-translational modification called O-GlcNAcylation. Using several models of cardiac hypertrophy, we recently showed that AMPK activation can also reverse cardiac hypertrophy once already developed. This reversibility protects the heart improving systolic function. In parallel, we established an unbiased mass spectrometry approach, identifying more than 1400 different O-GlcNAcylated proteins in the hypertrophic heart, several of them being currently investigated with the goal to find new therapeutic targets.



Sodium myo-inositol cotransporter 1 (SMIT1) affects cardiac hypertrophy in pressure-overloaded mouse hearts

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

Sodium myo-inositol cotransporter 1 (SMIT1) accounts for intracellular accumulation of myo-inositol, an important cyclic polyol precursor of inositol phosphates. Our group demonstrated that SMIT1 is expressed in the heart where it could have a significant contribution in the development of cardiac hypertrophy during left ventricular remodeling. Using an in vivo model of cardiac hypertrophy, induced by chronic pressure overload, we demonstrated that lack of SMIT1 prevents the development of cardiac hypertrophy, and preserves cardiac function in pressure overloaded mouse hearts. We confirmed the protective effects of SMIT1 deletion against hypertrophy using isolated mouse cardiomyocytes. We are currently investigating what mechanisms may be involved in the hypertrophic response. Our preliminary results indicate that the lack of SMIT1 attenuates O-GlcNacylation, a key hypertrophic pathway. Altogether, this work provides important insights into the role of SMIT1 in the onset of heart failure and opens new avenues for the development of therapeutic approaches.

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

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

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

Aquaporin-1 (AQP1), microcardia and hypertropic remodelling

V. Montiel, R. Bella, G. Muruganandam, H. Esfahani, D. De Mulder, O. Devuyst, J.-L. Balligand

We have serendipitously observed a microcardia in mice with genetic deletion of the water channel, Aquaporin-1 (AQP1) (Montiel et al.). Deletion or inhibition of this channel also attenuates the hypertrophic remodelling in vitro/vivo. Among underlying mechanisms, we found that AQP1 mediates the localized transport of H2O2, driving oxidant-dependent hypertrophic signaling in cardiac myocytes. AQP1 also regulates tissue fibrosis. Orally administered Bacopaside inhibitors of AQP1 prevent adverse remodeling in mice submitted to infusion of Angiotensin II, as well as oxidation of erythrocytes in human volunteers. In a translational endeavor, similar Bacopa extracts are being tested vs. placebo in a RCT (BacOxy trial) in volunteers to test its ability to protect the vasculature against oxidant stress.

In collaboration with colleagues from the NEFR Pole, an association was demonstrated between clinical outcomes in peritoneal dialysis and a polymorphism in the promoter sequence of the gene encoding AQP1, that impacts AQP1 expression in endothelial cells of the peritoneum (Morelle et al). Similar associations are being examined between this polymorphism and human cardiac hypertrophy.

Ongoing studies examine the structural determinants of the gating of the AQP1 tertramer using cryo-EM in combination with small molecule modulators of its permeability, as well as functional correlates in a new clonal cell line expressing human wild-type AQP1 or mutants on specific residues (part of a WELBIO project funded by the WEL-Research Institute, Walloon Region).

HEART FAILURE WITH PRESERVED EJECTION FRACTION

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

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

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

Plasma myo-inositol elevation in heart failure with preserved ejection fraction; Results from the BElgian and CAnadian MEtabolomics in HFpEF (BECAME-HF) research project

A.-C. Pouleur - N. Menghoum - J. Cumps, A. Marino, S. Lejeune, L. Bertrand, S. Horman and C. Beauloye

This study reveals that plasma myo-inositol, a metabolic factor, is elevated in HF patients. Elevated myo-inositol is associated with the HFpEF status and renal dysfunction. Among HFpEF patients, plasma myo-inositol correlates positively with biomarkers of congestion (NT-proBNP), myocardial injury (cardiac troponin T), and cardiac fibrosis (FGF-23), and is an independent predictor of poor prognosis. Moreover, using cultured HCFs, we show that myo-inositol addition promotes their migration, proliferation, and myodifferentiation, further supporting its role in cardiac fibrosis.

Mean platelet volume: a prognostic marker in heart failure with preserved ejection fraction

N. Menghoum, C. Beauloye, S. Lejeune, A. Pasquet, D. Vancraeynest, B. Gerber, L. Bertrand, S. Horman and A.-C. Pouleur

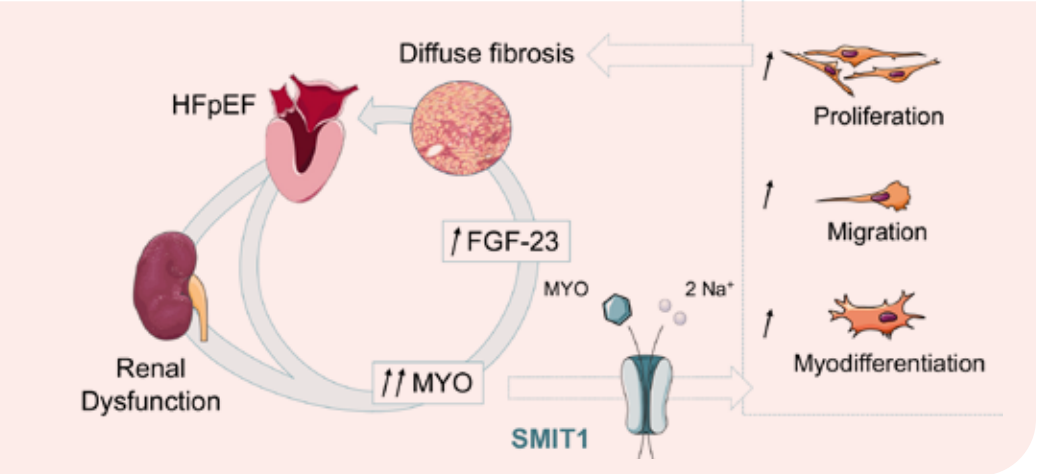
This study has demonstrated MPV to be significantly higher in HFpEF patients compared with controls of similar age and gender. Furthermore, HFpEF patients with elevated MPV exhibited the presence of ischemic heart disease. High MPV levels were not associated with renal function, inflammation markers, myocardial injury, and congestion markers, which are usually observed in HFpEF. However, they were associated with high levels of intact FGF-23, which is a marker of cardiac fibrosis. These results imply that MPV might be linked to atherosclerosis and cardiac fibrosis, independently of renal function and congestion markers.

In addition, elevated MPV turned out to be both a strong and independent marker of poor outcome in HFpEF, whereas prior ischemic cardiomyopathy did not. According to our results, platelets might play an essential role in4 HFpEF's pathology.

Animal model of HFpEF

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

We developed a mouse model recapitulating some features of the morphometric and echocardiographic phenotype of human heart failure with preserved ejection fraction. The model is used to characterize 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.



Cross-talk between adipose tissue and the heart

L. Cascarano, L. Michel, H. Esfahani, D. De Mulder, C. Dessy, J.-L. Balligand

The different components of the adipose tissue mediate a rich and complex cross-talk with remote organs, including cardiovascular tissues. In mice, adrenergic activation of the brown adipose tissue protects against the development of atherosclerosis, but effects on the heart are less well known. The beta3-adrenergic receptor (B3AR) is markedly expressed in murine adipocytes and was more recently clearly identified in the brown and white adipose tissue in man, where it can be activated with specific agonists such as mirabegron. Here, we study the effect of the specific activation of the adipocyte B3AR on myocardial hypertrophy and fibrosis, by developing a murine genetic model with conditional deletion of Adrb3 (coding B3AR) restricted to adipocytes. Myocardial remodeling and function during a high fat diet are compared between these mice and their appropriate genetic controls, treated or not with B3AR agonists.

Future treatments, translational perspectives

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

A study of 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 was recently completed . This investigator-initiated, European multicentric RCT, subsidized by a Horizon2020 grant, was coordinated at UCLouvain (Beta3-LVH). A publication of the results is pending.

DIABETIC CARDIOMYOPATHY

Increased level of O-GlcNAcylation found in the diabetic heart, a major actor of cardiac diabetic dysfunction

N. Fourny, L. Bultot, M. De Loof, S. Horman, C. Beauloye, L. Bertrand

We found that cardiac O-GlcNAcylation is increased in different mouse models of diet-induced type 2 diabetes. Of interest, the increase in protein O-GlcNAcylation nicely correlates with the severity of cardiac dysfunction. Via an unbiased mass spectrometry approach, we currently map the O-GlcNAcylated proteins potentially involved in the development of the disease.

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 *(Hermida et al)*.

Fibrotic remodelling after myocardial infarction/Platelet GARP-TGFβ signalling

J. Bodart - C. Dufeys, A. Ginion, 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. Indeed, the generation of active TGFβ is drastically impaired in the serum of platelet specific GARP knockout mice, while the amount of total TGFβ is not affected. We are investigating the role of platelet GARP in cardiac inflammation and fibrosis after myocardial infarction.

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

J. Cumps, A. Marino, C. Dufeys, A.-C. Pouleur, L. Bertrand, C. Beauloye and S. Horman

Clinical studies reported a rise in plasmatic myo-inositol in patients with severe heart failure. Additionally, we showed that SMIT1 (Sodium Myo-Inositol Transporter 1) mRNA expression was increased in human failing hearts and correlated with fibrotic markers. We aim to evaluate the role of SMIT1 and myo-inositol in fibroblasts properties regulation. Using human CF (HCF) and mouse CF (MCF) isolated from SMIT1 wild type and knock-out mice, we demonstrated that SMIT1 controls myo-inositol uptake in CFs and influences proliferation, migration and 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 *(De Pauw et al.)*

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

CONTROL OF CARDIAC METABOLISM

Protein acetylation, including the acetylation of tubulin, participates in the reduced glucose uptake induced by fatty acids

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

Type 2 diabetes is characterized by elevated plasma levels of fatty acids, leucine and ketone bodies. More generally, fatty acids are known to reduce glucose metabolism on what is known as the Randle cycle. We recently demonstrated that these three acetyl-CoA-generating metabolites promote protein acetylation in cardiomyocytes. Consequently, this increase in acetylation is responsible for the inhibition of insulin-stimulated glucose uptake by reducing translocation of the glucose transporter Glut4. In our search for acetylated proteins potentially responsible for this inhibition, we found tubulin as significant player. Acetylated tubulin characterized diabetic hearts as well as fatty acids-treated cardiomyocytes. More significantly, pharmacological, and genetic modulation of tubulin acetylation level reveals that it correlates well with the level of glucose transport inhibition. This provides new clue in the elucidation of the molecular mechanisms involved in the Randle cycle as well as in the metabolic inflexibility of the diabetic heart.

Connection between beta3-AR and glucose uptake

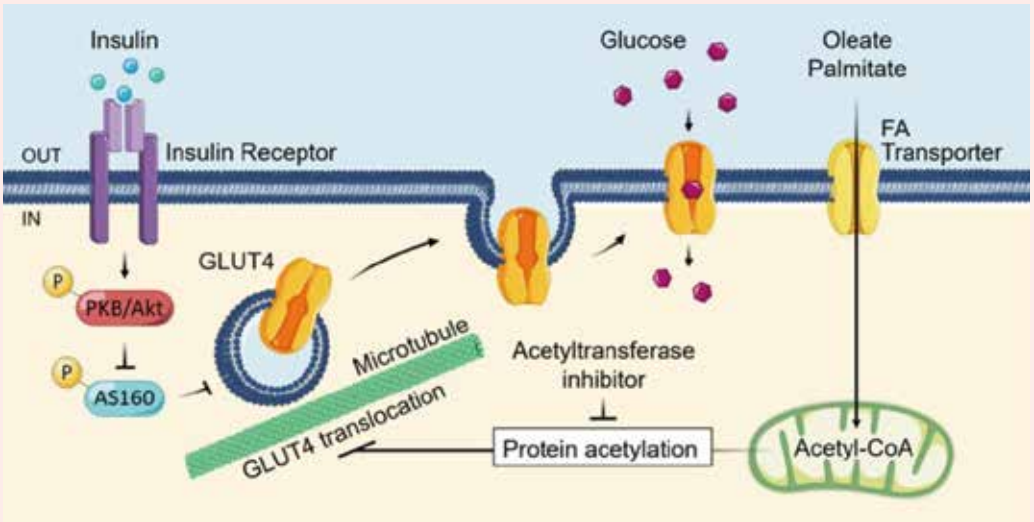
L. Michel, H. Esfahani, C. Dessy; L. Bertrand, J.-L. Balligand

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, using unbiased metabolomics and measurements of metabolic fluxes using radiolabeled subtstrates (collab. with M. Ruiz and C. Des Rosiers, Montréal, Canada)

Evaluation of pregnancy outcomes in patients with congenital heart diseases

N. Rahnama, S. Pierard

Our work focusses on evaluating the pregnancy outcomes of patients with grown up congenital heart diseases (GUCH) in comparison to patients having no congenital heart disease. Other work focusses on evaluating placenta histopathology and signs of chronic placental hypoperfusion in such patients with GUCH.



Valvular heart disease

V. Hanet, M. Boutte, D. De Azevedo, A. Pasquet, J.-L. Vanoverschelde, D. Vancraeynest, B. Gerber

Our research aims at studying the pathophysiology and prognosis of different valvular heart diseases. In aortic regurgitation we studied prognostic markers and guideline criteria for surgery. We evaluated postoperative outcomes of 1890 patients operated for aortic regurgitation in the AVIATOR registry and observed that patients operated with meeting class I guideline criteria have worse survival than patients operated earlier, suggesting the surgery should be performed earlier.

Also, in aortic stenosis we perform work evaluating the influence of guideline parameters such as valve surface, gradients and flow on natural history and survival to better understand the optimal timing in that disease. Ongoing works consists in evaluating the differences in left ventricular remodeling in aortic and mitral valve regurgitation according to gender and on on studying the development of myocardial fibrosis relative to myocardial remodelling by cardiac imaging in mitral and aortic regurgitation before and after surgery. Other ongoing works focusses on characterization of mechanisms of progression of aortic valve stenosis and of valvular bioprosthetic degradation using NaF positron emission tomography.

Cardio-oncology

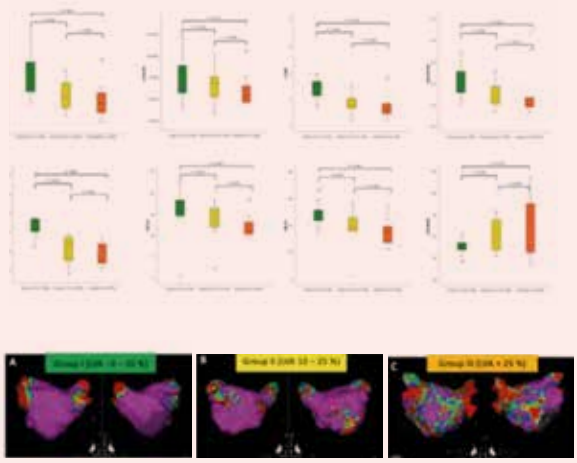
P. Krug, A.-C. Pouleur, B. Gerber

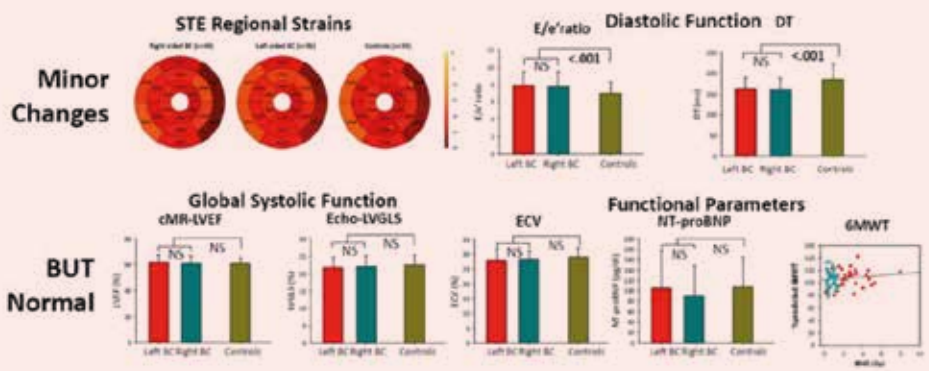
We evaluated the consequences of radiation exposure during radiotherapy for breast cancer on the heart on development of coronary artery disease, valvular heart disease and myocardial fibrosis in 76 patients with breast cancer 11 years after treatment. We also started work in patients undergoing acute radiotherapy for thoracic cancers the possible effects on high dose radiation exposure to the heart on development of myocardial inflammation fibrosis and on coronary flow reserve.

Atrial Fibrillation

S. Marchandise, B. Gerber

Research consisted in characterization atrial glucose metabolism by PET vs atrial function and atrial fibrosis by MRI in patients with atrial fibrillation before and after return to sinus rhythm. We also evaluated the predictive value of atrial function by speckle tracking echocardiography to predict success of catheter ablation in this setting.





Resistant Hypertension, Fibromuscular Dysplasia and Spontaneous Coronary Artery Dissection

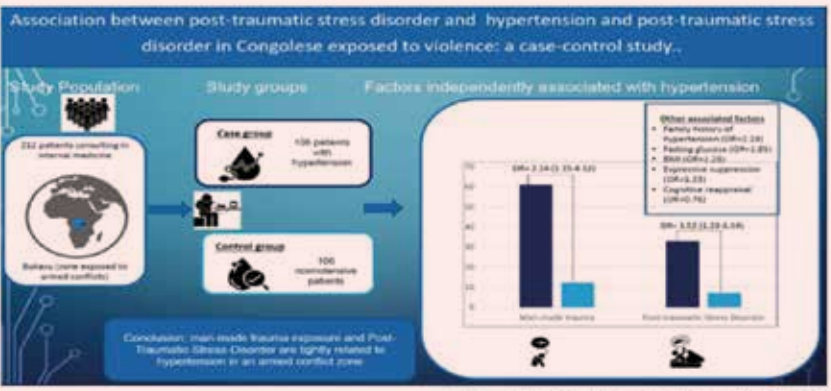
C. Georges, ML. Lopez-Sublet, F. Maes, D. Adlam, A. Persu

Resistant hypertension, renal denervation and drug adherence:

We contributed to evaluate the safety and blood-pressure lowering effects of ultrasound- (1) and alcohol infusion-based (2-4) renal denervation and the impact of drug adherence on blood-pressure lowering effects of renal denervation.

Furthermore, we documented associations between post-traumatic stress disorder, altered expression of emotions and somatization on one side, poor drug adherence and true drug resistance on the other side in patients with resistant hypertension, particularly young patients without a history of cardiovascular disease (refs). Similar factors were also strongly associated with hypertension, over and above classical factors, in patients from Bukavu, i.e. living in a region of East-Congo exposed to war and chronic violence for 25 years.

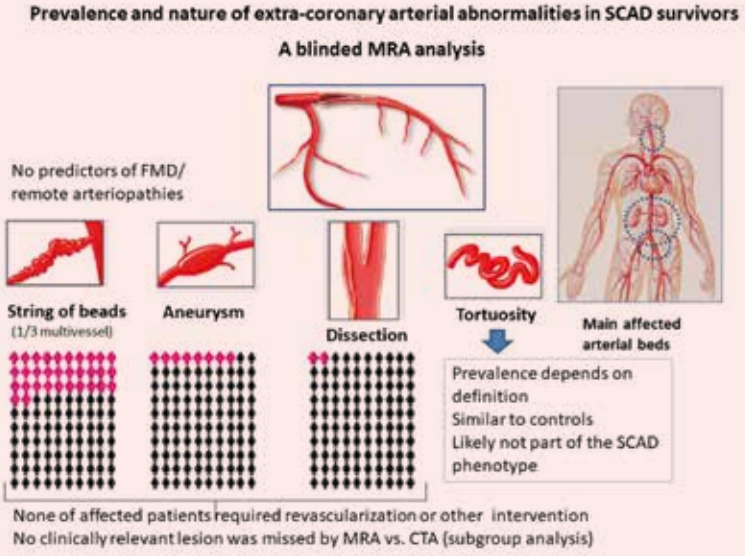
The contribution of the group is further highlighted by participation to the European Society of Hypertension (ESH) position paper on renal denervation (5) and an international position paper on chemical drug adherence testing.



Fibromuscular Dysplasia and Spontaneous Coronary Artery Dissection:

Research consisted in in-depth characterization of Fibromuscular Dysplasia (FMD) lesions associated with Spontaneous Carotid (6) and Coronary Artery Dissection (7) and contribution to identification of new loci associated with FMD within an international research consortium (8).

The results of the study performed in patients with Spontaneous Coronary Artery Dissection (SCAD) (7) are summarized in the figure and the text below.



SCAD is a cause of acute myocardial infarction, mainly affecting women. It is known to be associated with extra-coronary arteriopathies and in particular FMD. We sought in a blinded analysis with healthy controls to assess the prevalence, extent and severity of non-coronary arteriopathies in SCAD.

The findings of a somewhat lower prevalence of arteriopathies in our study was expected as we used MRA, strict definitions based on the international FMD consensus and blinded analysis with healthy controls.

The most striking findings were that severe manifestations (multi-vessel FMD, aneurysms and dissections) were much less common than reported in patients with primary FMD, and clinical consequences of SCAD-associated arteriopathies (renovascular hypertension or vascular events) were very rare.

Therefore, clinicians are recommended to continue to screen patients for SCAD-associated arteriopathies from brain to pelvis, but patients can be reassured that clinically important findings are uncommon and from what is currently known, the prognosis of FMD in SCAD appears to be very good.

ENDOTHELIAL FUNCTION

MiR-199a and the NOS/NO pathway

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

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

MiR-199a, oxidative stress and angiogenesis

J. Craps, V. Joris , L. Baldeschi , C. Daumerie , A. Camboni , A. Buemi, B. Lengelé , C. Behets, A. Boschi , M. Mourad , M.-C. Many, C. Dessy

Interestingly, the impact of miR-199a on angiogenesis and oxidative stress, extends beyond the cardiovascular system stricto senso. Using human biopsies of thyroids from patients suffering from Grave's disease (DG), and adipose tissues from patients with Grave's orbitopathy (GO), we have shown that both tissue types are characterized by a downregulation of miR-199a3p/5p. This correlated with an up regulation of direct targets of miR-199a-5p, namely NOX4 that contributes to oxidative stress, and HIF1a and VEGFA, key players of angiogenesis. Our work points to STAT-3-dependent regulation of miR-199a as a common driver leading to these events in GD thyroids and GO orbital fats.

From gut to the endothelium

V. Joris, L. Dumas, C. Dessy

Lifestyle and food choices dramatically impact cardiovascular health. Our research focusses on the impact of inulin type fructans (an example of probiotics) enriched diet on endothelial dysfunction in a mice model of hypercholesterolemia (Catry et al. 2016). Our current work proposes to further document the mechanisms underlying the improvement in endothelial function.

Mechanisms for the "memory" of cardiovascular risk factors

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

Cardiovascular risk factors such as diabetes, dyslipidemia or hypertension have long-lasting effects on cardiac and vascular tissues that drive clinical events even after removal or correction of the initial risk factor. This project established a new mouse model of the "memory" effects of temporary exposure to angiotensin II, a key mediator of hypertension and cardiovascular remodeling. Unbiased RNAseq analysis of the vascular wall transcriptome combined with bioinformatic construction of a disease network unveiled *Acta2 as* a pathogenic "node". Subsequent validation experiments *in vitro* and *in vivo* in a replication cohort identified transcription factors and putative epigenetic regulators responsible for the sustained downregulation of Acta2 associated with the long-lasting phenotype. The work opens potential new avenues for the reversal of "memory" effects in cardiovascular diseases *(Pothen et al.)*.

Clinical assessment of endothelial (dys) function

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

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

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

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

Vascular dysfunction and haemostatic disorders during sepsis - AMPK signalling

J. De Poortere, M. Angé, M. Octave, L. Bertrand, S. Horman and C. Beauloye

Hyperpermeability is one of the microvascular dysfunctions observed during sepsis. Our group previously demonstrated that α1AMPK deficiency is associated with an increase in vascular permeability in a model of LPS-induced endotoxemia, while its activation by AICAr or canagliflozin is protective. Apart from increasing permeability, sepsis also activates haemostasis, which involves coagulation, fibrinolysis, platelet activation, and NETosis. In this study, we are investigating the link between a1AMPK and haemostatic alterations during sepsis, using both α1AMPK KO mice and AMPK pharmacological activators.

Endothelial dysfunction associated with COVID-19

V. Montiel, I. Lobysheva, R. Verdoy, J-L Balligand

SARS-CoV-2 targets endothelial cells through the angiotensin-converting enzyme 2 receptor. The resulting endothelial injury induces widespread thrombosis and microangiopathy. We developed an observational study including ICU and non-ICU adult COVID-19 patients admitted in hospital for acute respiratory failure, compared with control subjects matched for cardiovascular risk factors similar to ICU COVID-19 patients, and ICU septic shock patients unrelated to COVID-19. We found that early SARS-CoV-2 infection was associated with an imbalance between an exacerbated oxidative stress and a reduced nitric oxide bioavailability (measured as 5-α-nitrosyl-hemoglobin, HbNO) proportional to disease severity. HbNO levels correlated with oxygenation parameters (PaO_2/FiO2 ratio) in COVID-19 patients. Plasma levels of angiotensin II, aldosterone, renin or serum level of TREM-1 ruled out any hyper-activation of the renin-angiotensin-aldosterone system or leucocyte respiratory burst in ICU COVID-19 patients, contrary to septic patients. Endothelial oxidative stress with ensuing decreased NO bioavailability appears as a likely pathogenic factor of endothelial dysfunction in ICU COVID-19 patients. As a correlation between NO bioavailability and oxygenation parameters is observed in hospitalized COVID-19 patients, our study highlights an urgent need for oriented research leading to a better understanding of the specific endothelial oxidative stress that occurs during SARS-CoV-2 *(Montiel et al)*.

Dexamethasone and covid-19-induced coagulopathy in critically ill

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

Severe forms of coronavirus 2019 (COVID-19) disease are caused by an exaggerated systemic inflammatory response and subsequent inflammation-related coagulopathy. Anti-inflammatory treatment with low dose dexamethasone has been shown to reduce mortality in COVID-19 patients requiring oxygen therapy. Here, we have investigated the mechanisms of action of corticosteroids in critically ill patients, in the context of COVID-19. Plasma biomarkers of inflammatory and immune responses, endothelial and platelet activation, neutrophil extracellular trap formation, and coagulopathy were compared between patients treated or not by systemic dexamethasone for severe forms of COVID-19. We showed that dexamethasone treatment significantly reduced the inflammatory and lymphoid immune response in critical COVID-19 patients but had little effect on the myeloid immune response and no effect on endothelial activation, platelet activation, neutrophil extracellular trap formation, and coagulopathy. The benefits of low dose dexamethasone on outcome in critical COVID-19 can be partially explained by a modulation of the inflammatory response but not by reduction of coagulopathy. Future studies should then explore the impact of combining dexamethasone with other immunomodulatory or anticoagulant drugs in severe COVID-19.

PLATELETS AND THROMBOSIS

PLinking platelet lipid metabolism and platelet functions

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

We recently discovered that systemic activation of acetyl-CoA carboxylase (ACC) increases the platelet content of arachidonic acid (AA)-containing phosphatidylethanolamine plasmalogen (PEP) and influences platelet reactivity to collagen. We thus hypothesized that platelet ACC was a key enzyme in regulating platelet lipid levels and functions. Using platelet-specific ACC1 knockout mice (ACC1 pKO), we reveal that this enzyme is a tight regulator of saturated and polyunsaturated fatty acyl chain levels contained in platelet phospholipids. In particular, ACC1 pKO platelets have a decrease in AA-containing PEP content. These arachidonylated plasmalogens represent a main source of thromboxane and other eicosanoids, respectively involved in platelet activation and bioenergetics. Accordingly, we demonstrate that ACC1 deletion impairs mitochondrial respiratory capacity, thromboxane generation and dense granule secretion in activated platelets. This results in a reduced thrombus formation on collagen-coated surfaces under flow conditions. Collectively, our data demonstrate that ACC1 is essential to maintain specific phospholipid pools required for platelet energy and reactivity and might therefore constitute a novel potential target for pharmacological anti-thrombotic applications.

α-tubulin acetylation in platelets from coronary artery disease patients

V. Robaux, A. Ginion, M. Dechamps, S. Lejeune, S Horman, C. Beauloye

Platelet inhibition is the main treatment strategy to prevent atherothrombotic complications after acute coronary syndrome or percutaneous coronary intervention. Despite dual antiplatelet therapy (DAPT) combining aspirin and a $P2Y_{12}$ receptor inhibitor, high on-treatment platelet reactivity (HPR) persists in some patients due to poor response to treatment and is associated with ischemic risk. We hypothesized that circulating platelets in these high-risk patients could have distinct morphological characteristics, potentially influencing their pro-thrombotic effect. Knowing the key role of α-tubulin acetylation in regulating platelet shape change, we investigated whether this post-translational modification could differ according to antiplatelet therapy and on-treatment platelet reactivity. Platelets were isolated from arterial blood samples of 240 patients admitted for coronary angiography, and α-tubulin acetylation on lysine 40 (α-tubulin K40 acetylation) levels were evaluated

by immunoblotting. This study highlights the role of high platelet α-tubulin K40 acetylation as a marker of platelet inhibition in response to DAPT, which can contribute to maintain resting morphology of circulating platelets.

Linking platelet lipid metabolism and inflammatory responses in septic patients

E. de Cartier d'Yves, M. Dechamps, J. De Poortere, L. Bertrand, C. Beauloye, S. Horman

Platelet activation can influence the inflammatory response via cytokines secretion. Platelets also produce lipids, some of which are also inflammatory mediators (including Specialized Pro-resolving Mediators). We previously observed that platelet acetyl-CoA carboxylase 1 (ACC1), responsible for de novo lipid synthesis, is phosphorylated and thus inhibited by AMP-activated protein kinase (AMPK) upon thrombin stimulation, which leads to changes in the platelet lipidome. However, the role of AMPK-ACC signaling in the regulation of the platelet lipidome during sepsis, and its potential impact on inflammation, has never been investigated. In this work, our aim to investigate whether changes in ACC phosphorylation can influence the platelet lipidome and the inflammatory response of patients during sepsis. We believe that a comprehensive analysis of intraplatelet lipids and of their regulation might offer novel diagnostic or therapeutic options.

REFERENCES 2022

MAJOR REFERENCES

Boughaleb H, Lobysheva I, Dei Zotti F, Balligand JL, Montiel V. Biological Assessment of the NO-Dependent Endothelial Function. Molecules. 2022 Nov 16;27(22):7921

Craps J, Joris V, Baldeschi L, Daumerie C, Camboni A, Buemi A, Lengelé B, Behets C, Boschi A, Mourad M, Many MC, Dessy C. miR-199a Downregulation as a Driver of the NOX4/HIF-1α/VEGF-A Pathway in Thyroid and Orbital Adipose Tissues from Graves' Patients. Int J Mol Sci. 2021 Dec 23;23(1):153

Dechamps M, De Poortere J, Martin M, Gatto L, Daumerie A, Bouzin C, Octave M, Ginion A, Robaux V, Pirotton L, Bodart J, Gerard L, Montiel V, Campion A, Gruson D, Van Dievoet MA, Douxfils J, Haguet H, Morimont L, Derive M, Jolly L, Bertrand L, Dumoutier L, Castanares-Zapatero D, Laterre PF, Horman S, Beauloye C. Inflammation-Induced Coagulopathy Substantially Differs Between COVID-19 and Septic Shock: A Prospective Observational Study. Front Med. 2022;8;780750

Dechamps M, De Poortere J, Octave M, Ginion A, Robaux V, Pirotton L, Bodart J, MS, Gruson D, Van Dievoet MA, Douxfils J, Haguet H, Morimont L, Derive M, Jolly L, Bertrand L, Laterre PF, Horman S, Beauloye C. Dexamethasone modulates the cytokine response but not COVID-19-induced coagulopathy in critically ill. In Press

Dontaine J, Bouali A, Daussin F, Bultot L, Vertommen D, Martin M, Rathagirishnan R, Cuillerier A, Horman S, BeauloyeC, Gatto L, Lauzier B, Bertrand L, Burelle Y. The intra-mitochondrial O-Glcnacylation system rapidly modulates OXPHOS function and ROS release in the Heart Commun Biol. 2022;5;349

Ferté L, Cumps J, Battault S, Esfahani H. Balligand JL, Horman S, Bertrand L, Beauloye C., Marino A. Letter regarding the article - Chronic Pressure Overload Induces Cardiac Hypertrophy and Fibrosis via Increases in SGLT1 and IL-18 Gene Expression in Mice. Int Heart J. 2022;63;184-186

Georges CMG, Ritscher S, Pappaccogli M, Petit G, Lopez-Sublet M, Bapolisi A, Di Monaco S, Wallemacq P, Rabbia F, Toennes SW, de Timary P, Persu A. Psychological determinants of drug adherence and severity of hypertension in patients with apparently treatment-resistant vs. controlled hypertension. Blood Press. 2022 Dec;31(1):169-177.

Georges CMG, Pappaccogli M, Fanelli E, Petit G, Ritscher S, Lopez-Sublet M, Bapolisi A, Wallemacq P, Rabbia F, de Timary P, Toennes SW, Persu A. Drug adherence and psychological factors in patients with apparently treatment-resistant hypertension: Yes but which ones? J Clin Hypertens (Greenwich). 2022 Nov;24(11):1436-1443.

Gruson D, Pouleur AC, Hermans MP, Ahn SA, Rousseau MF. Treatment with sodium-glucose cotransporter-2 inhibitors in heart failure patients: The potential benefits of monitoring FGF-23 levels? Ann Endocrinol (Paris). 2022 Feb;83(1):78-80

Hermans C. Haemophilia gene therapy: experiences and lessons from treated patients. Orphanet J Rare Dis. 2022 Apr 4;17(1):154

Kefer J, Carbonez K, Pierard S, Mouthuy FP, Peeters A, Hermans C, Lambert C, DeMeester C, Sluysmans T, Pasquet. Antithrombotic Therapy Duration after Patent Foramen Ovale Closure for Stroke Prevention: Impact on Long-Term Outcome. A. J Interv Cardiol. 2022 Oct 27;2022:6559447

Lambert C, Meité N, Kouassi GK, Dohoma AS, Bognini Akou SA, Sanogo I, Hermans C. Nonreplacement therapy for hemophilia in low-income countries: experience from a prospective study in Ivory Coast. Res Pract Thromb Haemost. 2022 Dec 28;7(1):100033

Lane D, Lawson A, Burns A, Azizi M, Burnier M, Jones DJL, Kably B, Khunti K, Kreutz R, Patel P, Persu A, Spiering W, Toennes SW, Tomaszewski M, Williams B, Gupta P, Dasgupta I. Nonadherence in Hypertension: How to

Develop and Implement Chemical Adherence Testing ; Endorsed by the European Society of Hypertension (ESH) Working Group on Cardiovascular Pharmacotherapy and Adherence.Hypertension. 2022 Jan;79(1):12-23

Larossi M, Lambert C, Hermans C. Absence of Effect of Emicizumab on D-Dimer Concentrations in Adult Patients with Severe Hemophilia A. Clin Appl Thromb Hemost. 2022 Jan-Dec;28:10760296221143382

Maes A, Pestiaux C, Marino A, Balcaen T, Leyssens L, Vangrunderbeeck S, Pyka G, De Borggraeve W, Bertrand L,Beauloye C, Horman S, Wevers M, Kerckhofs G. Cryogenic Contrast-Enhanced MicroCT Enables Nondestructive 3D Quantitative Histopathology of Soft Biological Tissues Nat Comm. 2022;13:6207

Marchandise S, Garnir Q, Scavée C, Varnavas V, le Polain de Waroux JB, Wauters A, Beauloye C, Roelants V, Gerber BL. Prediction of Left Atrial Fibrosis and Success of Catheter Ablation by Speckle Tracking Echocardiography in Patients Imaged in Persistent Atrial Fibrillation. Front Cardiovasc Med. 2022 May 25;9:856796

Menghoum N, Vos JL, Pouleur AC, Nijveldt R, Gerber BL. How to evaluate cardiomyopathies by cardiovascular magnetic resonance parametric mapping and late gadolinium enhancement. Eur Heart J Cardiovasc Imaging. 2022 Apr 18;23(5):587-589

Montiel V, Lobysheva I, Gérard L, Vermeersch M, Perez-Morga D, Castelein T, Mesland JB, Hantson P, Collienne C, Gruson D, van Dievoet MA, Persu A, Beauloye C, Dechamps M, Belkhir L, Robert A, Derive M, Laterre PF, Danser AHJ, Wittebole X, Balligand JL. Oxidative stress-induced endothelial dysfunction and decreased vascular nitric oxide in COVID-19 patients. EBioMedicine. 2022 Mar;77:103893

Morimont L, Dechamps M, David C, Bouvy C, Gillot C, Haguet H, Favresse J, Ronvaux L, Candiracci J, Herzog M, Laterre PF, De Poortere J, Horman S, Beauloye C, Douxfils J. NETosis and Nucleosome Biomarkers in Septic Shock and Critical COVID-19 Patients: An Observational Study. Biomolecules. 2022 Jul 27;12(8):1038

Persu A, Lopez-Sublet M, Al-Hussaini A, Pappaccogli M, Radhouani I, Van der Niepen P, Adair W, Beauloye C, Brillet PY, Chan N, Chenu P, Devos H, Escaned J, Garcia-Guimaraes M, Hammer F, Jackson R, Jebri S, Kotecha D, Macaya F, Mahon C, Natarajan N, Neghal K, Nicol ED, Parke KS, Premawardhana D, Sajitha A, Wormleighton J, Samani NJ, McCann GP, Adlam D. Prevalence and Disease Spectrum of Extracoronary Arterial Abnormalities in Spontaneous Coronary Artery Dissection. JAMA Cardiol. 2022;7:159-166

Persu A, Maes F, Toennes SW, Ritscher S, Georges C, Wallemacq P, Haratani N, Parise H, Fischell TA, Lauder L, Mahfoud F. Impact of drug adherence on blood pressure response to alcohol-mediated renal denervation. Blood Press. 2022 Dec;31(1):109-117.

Peugnet V, Chwastyniak M, Mulder P, Lancel S, Bultot L, Fourny N, Renguet E, Bugger H, Beseme O, Loyens A, Heyse W, Richard V, Amouyel P, Bertrand L, Pinet F, Dubois-Deruy E. Mitochondrial-targeted therapies require mitophagy to prevent oxidative stress induced by SOD2 inactivation in hypertrophied cardiomyocytes. Antioxidants 2022;11;723

Pothen L, Verdoy R, De Mulder D, Esfahani H, Farah C, Michel LYM, Dei Zotti F, Bearzatto B, Ambroise J, Bouzin C, Dessy C, Balligand JL. Sustained Downregulation of Vascular Smooth Muscle Acta2 After Transient Angiotensin II Infusion: A New Model of "Vascular Memory". Front Cardiovasc Med. 2022 Mar 14;9:854361

Renguet E, De Loof M, Fourny N, Ginion A, Bouzin C, Poüs C, Horman S, Beauloye C, Bultot L, Bertrand L. α-Tubulin acetylation on Lysine 40 controls cardiac glucose uptake Am J Physiol Heart Circ Physiol. 2022;322;H1032–H1043

Rodriguez J, Neyrinck AM, Van Kerckhoven M, Gianfrancesco MA, Renguet E, Bertrand L, Cani PD, Lanthier N, CnopM, Paquot N, Thissen JP, Bindels LB, Delzenne N. Physical activity enhances the improvement of body mass index and metabolism by inulin: a multicenter randomized placebo-controlled trial performed in obese individuals BMC Med. 2022;20;110

Spadaccio C, Nenna A, Henkens A, Mastrobuoni S, Jahanyar J, Aphram G, Lemaire G, Vancraeynest D, El Khoury G, De Kerchove L. Predictors of long-term stenosis in bicuspid aortic valve repair. J Thorac Cardiovasc Surg. 2022 Apr 30:S0022-5223(22)00502-5.

van der Velden J, Asselbergs FW, Bakkers J, Batkai S, Bertrand L, Bezzina CR, Bot I, Brundel B, Carrier L, ChamuleauS, Ciccarelli M, Dawson D, Davidson SM, Dendorfer A, Duncker DJ, Eschenhagen T, Fabritz L, Falcão-Pires I, Ferdinandy P, Giacca M, Girao H, Gollmann-Tepeköylü C, Gyongyosi M, Guzik TJ, Hamdani N, Heymans S, Hilfiker A, Hilfiker-Kleiner D, Hoekstra AG, Hulot JS, Kuster DWD, van Laake LW, Lecour S, Leiner T, Linke WA, Lumens J, Lutgens E, Madonna R, Maegdefessel L, Mayr M, van der Meer P, Passier R, Perbellini F, Perrino C, Pesce M, Priori S, Remme CA, Rosenhahn B, Schotten U, Schulz R, Sipido K, Sluijter JPG, van Steenbeek F, Steffens S, Terracciano CM, Tocchetti CG, Vlasman P, Yeung KK, Zacchigna S, Zwaagman D, Thum T. Animal models and animal-free innovations for cardiovascular research: current status and routes to be explored. Consensus document of the ESC working group on myocardial function and the ESC Working Group on Cellular Biology of the Heart. Cardiovasc Res. 2022;118;3016-3051

van Dievoet MA, Brusa D, Octave M, Horman S, Stephenne X. Anti-GPVI (HY101) activates platelets in a multicolor flow cytometry panel. Platelets. 2022 Oct 3;33(7):1096-1099

IMAGING

IMAG IS THE MEDICAL IMAGING RESEARCH POLE 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 pole 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

Frédéric Lecouvet, MD, PhD

Thierry Duprez, MD

Nicolas Michoux, PhD

Frank Peeters, PhD

Perrine Triqueneaux

Philippe Clapuyt, MD

Dana Dumitriu, MD

Emmanuel Coche, MD, PhD

Contact Persons

Frédéric Lecouvet
frederic.lecouvet@uclouvain.be

Members:

Thomas Kirchgesner, MD-PhD
Frédéric Lecouvet, MD-PhD
Laurence Annet, MD-PhD
Emmanuel Coche, MD-PhD
Etienne Danse, MD-PhD
Benoît Ghaye, MD-PhD
Vasiliki Perlepe, MD-PhD
Bruno Vande Berg, MD-PhD
Vasiliki Pasoglou, MD-PhD
Nicolas Michoux, PhD
Frank Peeters, PhD
Gaetan Duchêne, PhD
Sandy Van Nieuwenhove, MD-PhD student
Souad Acid, MD
Nadia Amini, MD
Philippe Clapuyt, MD
Anca Cristina Dragean, MD
Dana Dumitriu, MD
Thierry Duprez, MD
Ikram El Hamrouni, MD
Latifa Fellah, MD
Pierre Goffette, MD
Ariane Gregoire, MD
Frank Hammer, MD
Sana Jamali, MD
Isabelle Leconte, MD
Chiara Mabiglia, MD
Jacques Malghem, MD
Renaud Menten, MD
Pierre Montigny, MD
Marie Navez, MD
Pierre Trefois, MD
Pierre Vincke, MD
Guido Wilms, MD

Contact Persons

Frédéric Lecouvet
frederic.lecouvet@saintluc.uclouvain.be

Nicolas Michoux
nicolas.michoux@saintluc.uclouvain.be

Perrine Triqueneaux
perrine.triqueneaux@saintluc.uclouvain.be

EQUIPMENTS

- **4 IRM**
  GE signa Premier 3T (full research)
  GE MR450 1,5T, Siemens Skyra 3T,
  Philips Ingenia 3T
- **5 CT scanners**
  Philips Iqon And ICT
  Siemens Somatom X. Cité and Definition AS,
  Cone beam iCAT
- **13 conventional X-rays**
  Philips (x4), Fuji (x5), GE (x2), Siemens (x2)
- **2 interventional X-rays**
  Philips Allura, SiemensAxiom
- **17 Ultrasound systems**
  Philips US Affinity (x2), US EPIQ 7 (x10),
  Philips EPIQ 7G (X2), Philips CX 50,
  Philips SPARQ, Philips SEQUOIA

(GE, Siemens, Philips). IMAG investigators also provide expert advice in the various fields of medical imaging techniques.

Research Projects

POLYCYSTIC KIDNEY DISEASE IN MRI

Limited Performance of Estimated Total Kidney Volume for Follow-up of ADPKD

Demoulin N, Nicola V, Michoux N, Gillion V, Ho TA, Clerckx C, Pirson Y, Annet L

Introduction: Total kidney volume (TKV) is a qualified biomarker for disease progression in autosomal dominant polycystic kidney disease (ADPKD). Recent studies suggest that TKV estimated using ellipsoid formula correlates well with TKV measured by manual planimetry (gold standard). We investigated whether the ellipsoid formula could replace manual planimetry for follow-up of ADPKD patients. Methods: Abdominal magnetic resonance images of patients with ADPKD performed between January 1, 2013, and June 31, 2019, in Saint-Luc Hospital, Brussels, were used. Two radiologists independently performed manual TKV (mTKV) measures and kidney axial measures necessary for estimating TKV (eTKV) using ellipsoid equation. Repeatability and reproducibility of axial measures, mTKV and eTKV, and agreement between mTKV and eTKV were assessed (Bland-Altman). Intraclass correlation coefficient (ICC) was used to assess agreement on Mayo Clinic Imaging Classification (MCIC) scores. Results: 140 patients were included with mean age 45±13 years, estimated glomerular filtration rate (eGFR) 71±31 ml/min per 1.73 m2, and mTKV 1697±1538 ml. Repeatability and reproducibility were superior for mTKV versus eTKV (repeatability coefficient 2.4% vs. 14% in senior reader, and reproducibility coefficient 6.7% vs. 15%). Intertechnique reproducibility coefficient (95% confidence interval [CI]) was 19% (17%, 21%) in senior reader. Intertechnique agreement on derived MCIC scores was very good (ICC = 0.924 [0.884, 0.949]). Conclusion: TKV estimated using ellipsoid equation demonstrates poor repeatability and reproducibility compared with that of mTKV. Intertechnique agreement is also limited, even when measurements are performed by an experienced radiologist. Estimated TKV, however, accurately determines MCIC score.

BREAST IMAGING USING SPECTRAL CT-DATASETS

Possibility to discriminate benign from malignant breast lesions detected on dual-layer spectral CT-evaluation

Demirler Şimşir B, Krug KB, Burke C, Hellmich M, Maintz D, Coche E

Objectives: Intramammary mass lesions are reportedly present in up to 5.8% of all contrast enhanced CT-examinations of the female chest. We aimed to assess whether their biological relevance can be estimated using spectral CT-datasets. Methods: In this bicentric retrospective study patients with breast masses visualized on spectral CT-examinations from 07/2017 to 06/2019 were included. Lesions were characterized as malignant or benign based on histology and/or a stable follow-up of >2 years. Conventional CT-images, iodine density-maps, virtual monoenergetic-images (40 keV, 100 keV) and Zeffective-maps were evaluated by two independent readers. Statistical analysis derived from

the Regions of interest (ROIs) was done by calculating the Areas under the Receiver operating characteristic (ROC) curve (AUC) and Youden-indices. Results: 106 breast masses (malignant/benign: 81/25, 76.4%/23.6%) were included. The mean AUCs of the variables "iodine content" (reader 1/2:0.97;0.98), "monoenergetic curve-slope" (0.97;0.96) and "Zeffective" (0.98;0.98) measured in the target lesions (TL) showed superior results compared to those derived from the variable "density" (0.92;0.93) ($p < 0.001$). The ratios "TL to aorta" calculated for the variables "iodine content", "monoenergetic curve-slope" and "Zeffective" showed superior results compared to normal breast tissue and muscle ($p < 0.001$). The optimal cutpoint for the "iodine content" in the TL was 0.7–0.9 mg/ml (sensitivity 96.6%, specificity 91.7%). The best diagnostic results were achieved by normalizing the iodine content in the TL to that in the aorta (optimal cutpoint 0.1, sensitivity 95.5%, 98.9%, specificity 91.7%). Conclusions: Our preliminary results suggest that spectral CT-datasets might allow to estimate the biological dignity of breast masses detected on clinically indicated chest-examinations.

PERTHES DISEASE IMAGING USING X-RAY

Transient synovitis of the hip: is systematic radiological screening necessary for the detection of Perthes disease?

Heylen CE, Dovquier P-L, Dumitriu D

Current imaging guidelines in Belgium advise a systematic X-ray screening of the hips after an episode of transient synovitis of the hip, in order to detect Perthes disease. The aim of this study was to analyze whether systematic radiological screening is necessary for all children or whether the X-ray indication could be guided by clinical symptoms. A retrospective single center study including all children with the diagnosis of transient synovitis of the hip between 2013 and 2018 was performed. 242 patients with the diagnosis of one or more transient synovitis episodes were included, 102 of whom underwent a follow up X-ray. Persistence or recurrence of symptoms were recorded for all patients, as well as the results of follow-up hip X-rays. 12 children did not remain symptom-free after the episode of transient synovitis. Of these patients 10 had a normal follow-up X-ray and 3 were diagnosed with Perthes disease. 1 patient of those 3 had a normal X-ray but was diagnosed with Perthes disease on MRI. Of the children which remained symptom-free after the episode of transient synovitis, none were diagnosed with Perthes disease afterwards. A follow-up X-ray to exclude Perthes disease after a diagnosis of transient hip synovitis appears to be necessary only in patients with persistent or recurrent symptomatology.

BRAIN MAGNETIC RESONANCE IMAGING

Progressive hemiparesis reveals X-linked adrenoleukodystrophy in a 3.5-year-old boy

Kosseifi CE, Seddiki K, Dumitriu D, Nassogne M-C

X-linked adrenoleukodystrophy (X-ALD) is caused by a defect in the ABCD1 gene, encoding the transmembrane ALDP protein and is characterized by progressive nervous system demyelination and adrenal gland dysfunction. While several phenotypes were described in boys and females, the two most important ones include childhood cerebral ALD (CCALD) and adult onset adrenomyeloneuropathy in males. CCALD classically occurs in boys, at 6–9 years of age, presenting with mild neurological or psychiatric signs, with a decline in cognitive performance and school achievement. Later, neurological impairment appears to be leading to death within 3 years. In most CCALD cases, the initial demyelinating lesion is in the splenium of the corpus callosum, progressing towards the adjacent parieto-occipital white matter. Upon brain MRI, abnormal symmetrical signal intensities (increased T2 signal and FLAIR sequences; decreased T1 sequence signal) are found in the corpus callosum, parieto-occipital or frontal white matter, or pyramidal tracts within the brainstem, pons, and internal capsules. Peripheral gadolinium enhancement of demyelinating lesions occurs in the case of rapid disease progression, reflecting severe inflammation and blood brain barrier disruption.

NEUROSURGERY

Holmes tremor in a monocentric series of resected brainstem cavernomas

Del Gaudio N, Vaz G, Duprez T, Raftopoulos C

Several scientific papers report clinical symptoms, indications, complications and outcomes of brainstem cavernous malformation (BSCM) surgery without reporting on the occurrence of postoperative Holmes tremor (HT). Our purpose is to report our experience with HT in a monocentric series of resected brainstem cavernomas. Methods: We reviewed all the BSCM surgical records between 2002 and 2018 at Saint-Luc University Hospital's Department of Neurosurgery, Brussels and selected patients developing HT postoperatively. Patients' demographics, symptoms, pre- and postoperative imaging, recurrence and complications were analysed. A PubMed literature review was performed to compare our results with those in the existing literature. Results: In a total series of 18 resected BSCM, 5 patients: 1 male and 4 females, with a median age of 51 years (range 29–59 years), developed HT. The median preoperative mRS score was 2 (range 1–4). GTR was achieved in all patients without surgery-related death. BSCM were located in the mesencephalon in 4 patients (80%) who developed HT. Tremor was noticed between

ten days and one year after surgery. One patient saw significant improvements to the point of stopping treatment. The median follow-up period was 2 years (range 1–14 years). At the last follow-up, 40% of our patients showed a worse mRS score, 40% stayed unchanged, and 20% improved. Conclusion: We are reporting an original single-center series of patients suffering from HT after BSCM surgery. The risk for HT after surgery is significant for midbrain BSCM. A spontaneous favorable evolution is possible.

NEURO-OPHTHALMOLOGY USING MRI

Optic Neuropathy Revealing Severe Superficial Siderosis in the Setting of Long-standing Low-grade Intracranial Neoplasm

Hemptinne C, Coche A, Duprez T, Demaerel P, Raftopoulos C, Boschi A

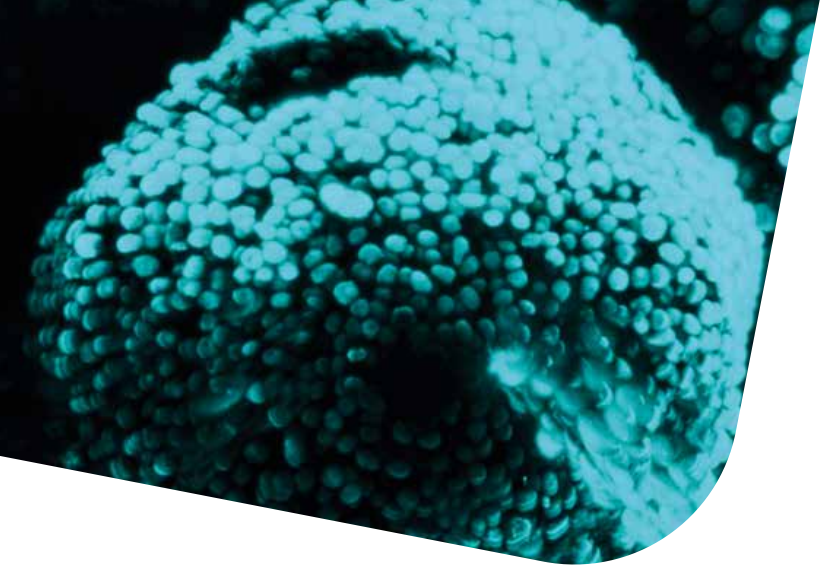
Two cases of optic neuropathy due to superficial siderosis (SS) are reported in two patients, aged 29 and 38 years, operated for intracranial neoplasms, the first one with a desmoplasic infantile ganglioglioma excised in 1991, and the other one with a pilocytic astrocytoma, operated on in 1997, 1998 and 2016. Both patients presented with progressive loss of visual acuity, as a result of bilateral optic nerve atrophy, as well as unsteadiness, ataxic gait and hearing loss. Magnetic resonance imaging (MRI) of the brain and spine, including gradient echo (GRE) T2-weighted acquisitions, revealed thin optic nerves and strong hypointensity with susceptibility artefacts corresponding to haemosiderin deposits within the meningeal layers of the spine, the infra- and supratentorial spaces of the brain and the peri-optic sheaths in both patients. The cerebrospinal fluid (CSF) was macroscopically haemorrhagic in one patient, who underwent a dynamic myelography, which failed to reveal any trans-dural CSF leakage. Neuro-ophthalmological symptoms due to SS, such as visual acuity loss, have been scarcely reported. MRI using GRE T2-weighted sequences highlighting the presence of haemosiderin deposits plays a key role in the diagnosis of this condition. Treatment should aim at preventing haemosiderin deposition by treating the cause of the subarachnoid bleeding.

LUNG HIGH-RESOLUTION CT

Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae

Froidure A, Mahsouli A, Liistro G, De Greef J, Belkhir L, Gérard L, Bertrand A, Koenig S, Pothen L, Yildiz H, Mwenge B, Aboubakar F, Gohy S, Pilette C, Reychler G, Coche E, Yombi J-C, Ghaye B

Background: COVID-19 pandemic resulted in an unprecedented number of hospitalizations in general wards and intensive care units (ICU). Severe and critical COVID-19 patients suffer from extensive pneumonia; therefore, long-term respiratory sequelae may be expected. Research question: We conducted a cohort study to determine respiratory sequelae in patients with severe and critical COVID-19. We aimed at evaluating the proportion of patients with persisting respiratory symptoms and/or abnormalities in pulmonary function tests (PFT) or in lung imaging. Study design: and methods: This is a single center cohort study including COVID-19 survivors who underwent a three-month follow-up with clinical evaluation, PFT and lung high-resolution computed tomography (HRCT). All clinical, functional, and radiological data were centrally reviewed. Multiple linear regression analysis was performed to identify factors associated with residual lesions on HRCT. Results: Full clinical evaluation, PFT and lung HRCT were available for central review in 126, 122 and 107 patients, respectively. At follow-up, 25% of patients complained from dyspnea and 35% from fatigue, lung diffusion capacity (DLCO) was decreased in 45%, 17% had HRCT abnormalities affecting more than 5% of their lung parenchyma while signs of fibrosis were found in 21%. In multiple linear regression model, number of days in ICU were related to the extent of persisting lesions on HRCT, while intubation was associated with signs of fibrosis at follow-up (P = 0.0005, Fisher's exact test). In contrast, the severity of lung imaging or PFT changes were not predictive of fatigue and dyspnea. Interpretation: Although most hospitalized COVID-19 patients recover, a substantial proportion complains from persisting dyspnea and fatigue. Impairment of DLCO and signs suggestive of fibrosis are common but are not strictly related to long-lasting symptoms.



DIAGNOSTIC AND INTERVENTIONAL IMAGING

Instability of the extensor digitorum tendons in Jaccoud arthropathy assessed by semi-dynamic MRI of the metacarpophalangeal joints

Kirchgesner T, Stoenoiu M, Michoux N, Libouton X, Houssiau F, Vande Berg B

Purpose: The purpose of this study was to test the hypothesis that Jaccoud arthropathy (JA) in patients with systemic lupus erythematosus (SLE) is associated with instability of the extensor digitorum (ED) tendons during flexion of the metacarpophalangeal (MCP) joints by comparing the position of the ED tendons between SLE patients with JA and control subjects on hand MRI obtained with flexed and extended MCP joints. Materials and methods: Thirty-two hands of SLE patients with JA (13 women and 3 men; mean age, 50.0 ± 12.2 [SD] years; age range: 26–68 years) and 24 hands of sex- and age-matched control subjects (20 women and 4 men; mean age, 50.1 ± 13.0 [SD] years; age range: 24–68 years) were included in the study. Axial spin echo T1-weighted MRI images of the second to fifth MCP joints in flexion and in extension were obtained. Two radiologists (R1 and R2) separately measured the amplitude and assessed the direction of the displacement of the ED tendons with respect to the midline at the level of each MCP joint. Statistical analysis included two-way ANOVA with random effects to assess differences in amplitude and Fisher–Freeman–Halton exact test to assess differences in direction with P-values < 0.0083 and < 0.0063 considered as statistically significant respectively. Results: Amplitude of the displacement of the ED tendons was statistically significantly greater in SLE patients with JA than in control subjects in flexion for both readers (median 58°, 95% confidence interval [CI]: 50°–65° vs. 20°, 95% CI: 16°–24°; P < 0.0001 for R1 and 54°, 95% CI: 47°–61° vs. 25°, 95% CI: 22°–28°; P < 0.0001 for R2) and in extension for one reader (17°, 95% CI: 15°–20° vs. 14°, 95% CI: 11°–16°; P = 0.0048 for R1 and 20°, 95% CI: 15°–25° vs. 16°, 95% CI: 12°–18°; P = 0.0292 for R2). Ulnar deviation of the ED tendons was statistically significantly more frequent in SLE patients with JA than in control subjects in flexion and in extension for both readers (P < 0.0001). Conclusion: JA is associated with instability of the ED tendons in patients with SLE best depicted when MCP joints are flexed.

DIAGNOSTIC AND INTERVENTIONAL IMAGING

Contrast-enhanced T1-weighted Dixon water- and fat-only images to assess osteitis and erosions according to RAMRIS in hands of patients with early rheumatoid arthritis

Kirchgesner T, Stoenoiu M, Michoux N, Durez P, Vande Berg B

Purpose: To assess the agreement between readers using contrast-enhanced T1-weighted Dixon water- and fat-only images and OMERACT-recommended sequences for the scoring of osteitis and erosions according to the rheumatoid arthritis (RA) MRI scoring system (RAMRIS) in hands of patients with early RA. Materials and methods: Both hands of 24 patients (16 women, 8 men; mean age, 45.7 ± 14.5 [SD] years; age range: 25–70 years) with early RA were prospectively imaged with fat-saturated T2-weighted sequences, non-Dixon T1-weighted imaging prior to contrast material injection and T1-weighted Dixon imaging after contrast material injection at 1.5 T. There were Two radiologists separately quantified osteitis and erosions according to RAMRIS using contrast-enhanced T1-weighted Dixon water-only and fat-saturated T2-weighted images for osteitis and contrast-enhanced T1-weighted Dixon fat-only and T1-weighted images prior to contrast material injection for erosions. Intraclass correlation coefficients (ICC) were calculated to assess inter-technique, intra-observer and inter-observer agreement. Results: Mean ICC for the agreement between Dixon and non-Dixon images ranged from 0.68 (95%CI: 0.20–0.90) to 0.99 (95%CI: 0.95–1.00) for the scoring of osteitis and from 0.77 (95%CI: 0.38–0.93) to 0.99 (95%CI: 0.95–1.00) for the scoring of erosions. Mean ICC for the agreement between first and second readings ranged from 0.94 (95%CI: 0.81–0.98) to 0.97 (95%CI: 0.91–0.99) for the scoring of osteitis using Dixon and 0.91 (95%CI: 0.72–0.97) to 0.98 (95%CI: 0.92–0.99) using non-Dixon images and from 0.80 (95%CI: 0.45–0.94) to 0.97 (95%CI: 0.91–0.99) for the scoring of erosions using Dixon and 0.72 (95%CI: 0.29–0.91) to 0.98 (95%CI: 0.92–0.99) using non-Dixon images. Conclusion: Contrast-enhanced T1-weighted Dixon water- and fat-only images can serve as an alternative to fat-saturated T2-weighted and T1-weighted MRI sequences for the assessment of osteitis and erosions according to the RAMRIS scoring system in hands of patients with early RA.

MUSCULOSKELETAL RADIOLOGY

Semi-quantitative CT scoring of nailed shaft fractures during normal healing and in non-unions: comparison with radiographic scoring

Perlepe V, Michoux N, Kirchgesner T, Lecouvet F, Vande Berg B

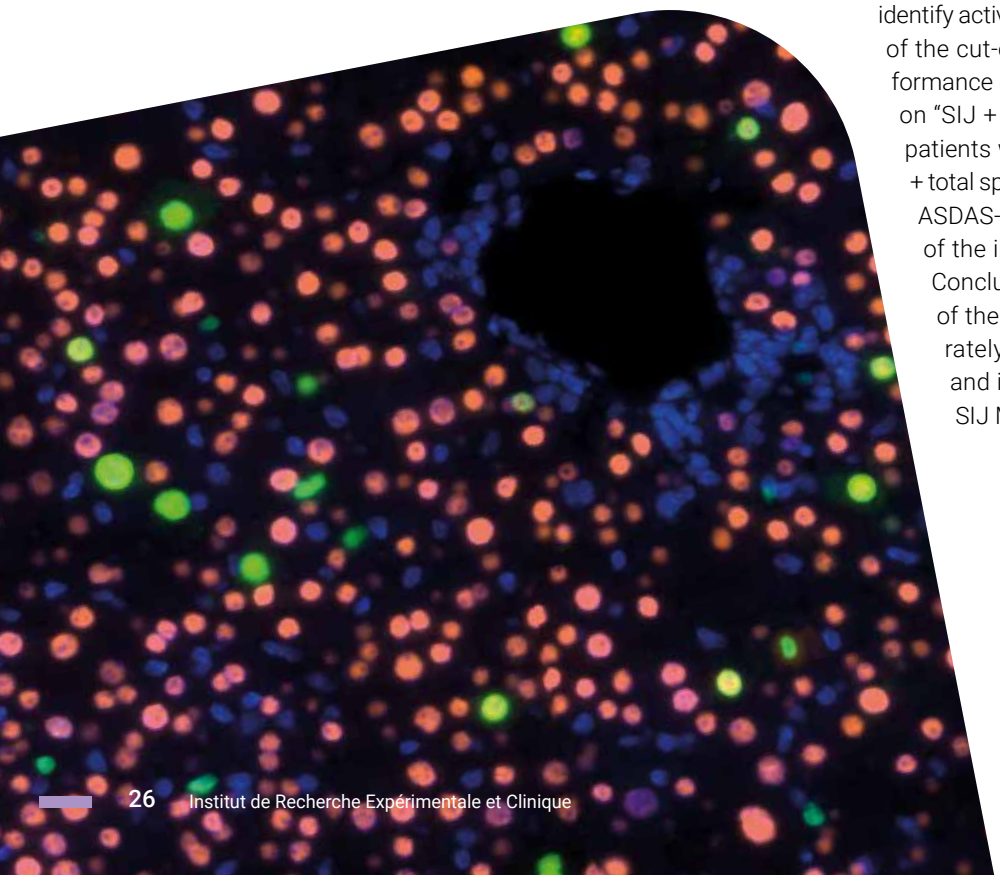
Purpose: To compare tomographic (TUS) with radiographic (RUS) union scores in nailed shaft fractures during normal healing and in non-unions. Methods: Two radiologists blinded to fracture age separately determined RUS and TUS in nailed femoral or tibial shaft fractures by analyzing the radiographic and CT examinations obtained in 47 patients during normal healing (early fracture group; 24 study participants, 17 men,19 tibias, mean fracture-CT delay 109 ± 57 days [42–204 days]) and in surgically proven non-united fractures (late fracture group, 23 patients, 14 men, 12 tibias, mean fracture-CT delay 565 ± 519 days[180–1983 days]). In both study groups, we determined the inter- and intra-observer agreement of RUS and TUS and compared TUS with RUS. Results: Intra- and inter-observer agreement of RUS and TUS was very good in the early fracture group and good in the late fracture group for both readers. TUS correlated with RUS substantially in the early fracture group and only weakly in the late fracture group. TUS was statistically significantly lower than RUS in study participants with RUS ≥ 8 or 9 for R2 only and ≥ 10 for both readers in the early fracture group and in patients with RUS ≥ 8, 9 or 10 in the late fracture group for both readers. Conclusion: RUS and TUS of nailed shaft fractures during normal healing or in non-unions are both feasible and reproducible. They yield similar values in fractures with no or limited callus. TUS yields lower values than RUS in fractures with callus.

DIAGNOSTIC AND INTERVENTIONAL IMAGING

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

Plier M, Nzeusseu Toukap A, Michoux N, Stoenoiu MS, Kirchgesner T, Durez P, Lauwerys B, Lecouvet FE

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.



MUSCULOSKELETAL RADIOLOGY

Comparison between 3-point Dixon- and CHESS-based OMERACT-recommended MRI protocols in hands of patients with suspicion of early rheumatoid arthritis

Kirchgesner T, Stoenoiu M, Michoux N, Durez P, Vande Berg B

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 1.5 T 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 ($p \leq 0.042$). 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). Conclusions: Dixon sequences yield more effective fat suppression and more reproducible RAMRIS scoring than CHESS sequences in hands with suspicion of early RA.

WHOLE-BODY MRI IN ONCOLOGY

Comparison of 68ga-prostate specific membrane antigen (Psma) positron emission tomography computed tomography (pet-ct) and whole-body magnetic resonance imaging (wb-mri) with diffusion sequences (dwi) in the staging of advanced prostate cancer

Van Damme J, Tombal B, Collette L, Van Nieuwenhove S, Pasoglou V, Gérard T, Jamar F, Lhommel R, Lecouvet FE

Background: Prostate specific membrane antigen (PSMA) positron emission tomography computed tomography (PET-CT) and whole-body magnetic resonance imaging (WB-MRI) outper-form standard imaging technology for the detection of metastasis in prostate cancer (PCa). There are few direct comparisons between both modalities. This paper compares the diagnostic accuracy of PSMA PET-CT and WB-MRI for the detection of metastasis in PCa. One hundred thirty-four patients with newly diagnosed PCa (n = 81) or biochemical recurrence after curative treatment (n = 53) with high-risk features prospectively underwent PSMA PET-CT and WB-MRI. The diagnostic accuracy of both techniques for lymph node, skeletal and visceral metastases was compared against a best valuable comparator (BVC). Overall, no significant difference was detected between PSMA PET-CT and WB-MRI to identify metastatic patients when considering lymph nodes, skeletal and visceral metastases together (AUC = 0.96 (0.92–0.99) vs. 0.90 (0.85–0.95); p = 0.09). PSMA PET-CT, however, outperformed WB-MRI in the subgroup of patients with newly diagnosed PCa for the detection of lymph node metastases (AUC = 0.96 (0.92–0.99) vs. 0.86 (0.79–0.92); p = 0.0096). In conclusion, PSMA PET-CT outperforms WB-MRI for the detection of nodal metastases in primary staging of PCa.

RADIOMICS IN IMAGING CLINICAL TRIALS

Incorporating radiomics into clinical trials: expert consensus endorsed by the European Society of Radiology on considerations for data-driven compared to biologically driven quantitative biomarkers

Fournier L, Costaridou L, Bidaut L, Michoux N, Lecouvet FE, de Geus-Oei L-F, Boellaard R, Oprea-Lager DE, Obuchowski NA, Caroli A, Kunz WG, Oei EH, O'Connor JPB, Mayerhoefer ME, Franca M, Alberich-Bayarri A, Deroose CM, Loewe C, Manniesing R, Caramella C, Lopci E, Lassau N, Persson A, Achten R, Rosendahl K, Clement O, Kotter E, Golay X, Smits M, Dewey M, Sullivan DC, van der Lugt A, deSouza NM

Existing quantitative imaging biomarkers (QIBs) are associated with known biological tissue characteristics and follow a well-understood path of technical, biological and clinical validation before incorporation into clinical trials. In radiomics, novel data-driven processes extract numerous visually imperceptible statistical features from the imaging data with no a priori assumptions on their correlation with biological processes. The selection of relevant features (radiomic signature) and incorporation into clinical trials therefore requires additional considerations to ensure meaningful imaging endpoints. Also, the number of radiomic features tested means that power calculations would result in sample sizes impossible to achieve within clinical trials. This article examines how the process of standardising and validating data-driven imaging biomarkers differs from those based on biological associations. Radiomic signatures are best developed initially on datasets that represent diversity of acquisition protocols as well as

diversity of disease and of normal findings, rather than within clinical trials with standardised and optimised protocols as this would risk the selection of radiomic features being linked to the imaging process rather than the pathology. Normalisation through discretisation and feature harmonisation are essential pre-processing steps. Biological correlation may be performed after the technical and clinical validity of a radiomic signature is established, but is not mandatory. Feature selection may be part of discovery within a radiomics-specific trial or represent exploratory endpoints within an established trial; a previously validated radiomic signature may even be used as a primary/secondary endpoint, particularly if associations are demonstrated with specific biological processes and pathways being targeted within clinical trials.

WHOLE-BODY DIFFUSION -WEIGHTED MRI

Repeatability and reproducibility of ADC measurements: a prospective multicenter whole-body-MRI study

Michoux N, Ceranka JW, Vandemeulebroucke J, Peeters F, Lu P, Absil J, Triqueneaux P, Liu Y, Collette L, Willekens I, Brussaard C, Debeir O, Hahn S, Raeymaekers H, de Mey J, Metens T, Lecouvet FE

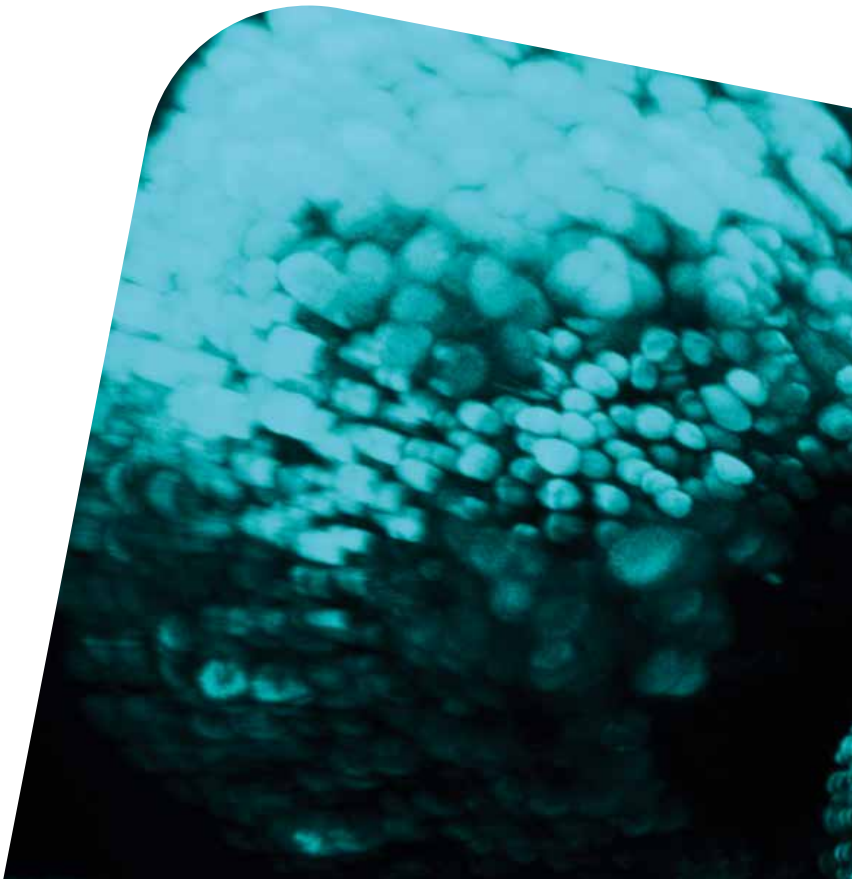
Multicenter oncology trials increasingly include MRI examinations with apparent diffusion coefficient (ADC) quantification for lesion characterization and follow-up. However, the repeatability and reproducibility (R&R) limits above which a true change in ADC can be considered relevant are poorly defined. This study assessed these limits in a standardized whole-body (WB)-MRI protocol. Methods: A prospective, multicenter study was performed at three centers equipped with the same 3.0-T scanners to test a WB-MRI protocol including diffusion-weighted imaging (DWI). Eight healthy volunteers per center were enrolled to undergo test and retest examinations in the same center and a third examination in another center. ADC variability was assessed in multiple organs by two readers using two-way mixed ANOVA, Bland-Altman plots, coefficient of variation (CoV), and the upper limit of the 95% CI on repeatability (RC) and reproducibility (RDC) coefficients. Results: CoV of ADC was not influenced by other factors (center, reader) than the organ. Based on the upper limit of the 95% CI on RC and RDC (from both readers), a change in ADC in an individual patient must be superior to 12% (cerebrum white matter), 16% (paraspinal muscle), 22% (renal cortex), 26% (central and peripheral zones of the prostate), 29% (renal medulla), 35% (liver), 45% (spleen), 50% (posterior iliac crest), 66% (L5 vertebra), 68% (femur), and 94% (acetabulum) to be significant. Conclusions: This study proposes R&R limits above which ADC changes can be considered as a reliable quantitative endpoint to assess disease or treatment-related changes in the tissue microstructure in the setting of multicenter WB-MRI trials.

MUSCULOSKELETAL RADIOLOGY

3D Whole-Body MRI of the Musculoskeletal System

Pasoglou V, Van Nieuwenhove S, Peeters F, Duchêne G, Kirchgesner T, Lecouvet FE

With its outstanding soft tissue contrast, spatial resolution, and multiplanar capacities, magnetic resonance imaging (MRI) has become a widely used technique. Whole-body MRI (WB-MRI) has been introduced among diagnostic methods for the staging and follow-up assessment in oncologic patients, and international guidelines recommend its use. In nononcologic applications, WB-MRI is as a promising imaging tool in inflammatory diseases, such as seronegative arthritis and inflammatory myopathies. Technological advances have facilitated the introduction of three-dimensional (3D) almost isotropic sequences in MRI examinations covering the whole body. The possibility to reformat 3D images in any plane with equal or almost equal resolution offers comprehensive understanding of the anatomy, easier disease detection and characterization, and finally contributes to correct treatment planning. This article illustrates the basic principles, advantages, and limitations of the 3D approach in WB-MRI examinations and provides a short review of the literature.



REFERENCES (selection)

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85118551890&doi=10.1016%2fj.ekir.2021.08.013&partnerID=40&md5=d58146068c2f8a2ea74bc73d83312fa7

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85115920169&doi=10.52628%2f87.2.09&partnerID=40&md5=3a0020ac08d7462734563539984de4c8

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85081239116&doi=10.1007%2fs13760-020-01306-5&partnerID=40&md5=aa2845653a306b73a554a4d-25f675e47

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85103726086&doi=10.1016%2fj.neuchi.2021.03.001&partnerID=40&md5=25d-f1570aa09f9696485eb21ff555196

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85111909225&doi=10.1080%2f01658107.2021.1958870&partnerID=40&md5=ea780e-8f4271a7005cb891e1453d6656

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85103714264&doi=10.1016%2fj.rmed.2021.106383&partnerID=40&md-5=9912253cf32fbbdf4221b0ad59b19e65

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85106613304&doi=10.1016%2fj.diii.2021.03.005&partnerID=40&md5=11a8a18ae40deb4be7d-674bf45587199

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85100994306&doi=10.1016%2fj.diii.2021.01.011&partnerID=40&md5=7069aef112b2dbf3919caf1f675901c5

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85101971732&doi=10.1016%2fj.ejrad.2021.109618&partnerID=40&md5=bdcc81079f0b-43836306bc18ba807ac7

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85089697952&doi=10.1016%2fj.diii.2020.07.001&partnerID=40&md5=40e88dcb5e0d719858ce7c90929ef7a4

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85096167115&doi=10.1016%2fj.ejrad.2020.109412&partnerID=40&md5=8f528b-cadaa240ee24d44565ab4bc3fc

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85117258688&doi=10.3390%2fcancers13215286&partnerID=40&md5=3f040118bcdc48daa24234a0f10f7a34

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85099741243&doi=10.1007%2fs00330-020-07598-8&partnerID=40&md5=56e2a6ab198942925172a5e-300f54cc7

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85099032937&doi=10.1007%2fs00330-020-07522-0&partnerID=40&md5=138f5f98362e21606f-74cb48e0438343

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85116160126&doi=10.1055%2fs-0041-1730401&partnerID=40&md5=ce569a59d7f5d-4c30630a0e5c86c668b

CLINICAL AND TRANSLATIONAL IMMUNOLOGY

Tissue-specific or systemic dysregulation of the immune system leads to several diseases or disease compli- cations 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, pneumologists, nephrolo- gists, and others according to the affected system. By contrast, understanding mechanisms of disease and finding innovative strategies in order to stratify patients for severity and therapeutic option (and thereby personalize medical de- cisions) 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 and tissue samples from well-charac- terized 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 in- ternational research networks gave rise to significant advances in the field, as described below.

POLE OF RHEUMATOLOGY RESEARCH (RUMA)

Patrick Durez, MD

Frédéric Houssiau, MD, PhD

Gaëlle Tilman, PhD

Farah Tamirou, MD, PhD

Laurent Méric de Bellefon, MD
Maria Stoenoiu, MD, PhD
Adrien Nzeusseu Toukap, MD
Pauline Montigny, PhD Student
Clément Triaille, PhD Student
Emilie Sapart, PhD Student
Charlotte Baert, PhD Student
Joëlle Marchandise, Laboratory assistant
Samantha Genten, Laboratory assistant
Tatiana Sokolova, Clinical Research Coordinator
Isabelle Faille, Clinical Research Coordinator
Séverine Nieuwland, Study Nurse
Aleksandra Avramovska, Study Nurse
Marie M'Zoughui, Trial Coordinator

Research Projects

Our research interests are in line with our clinical expertise in the field of systemic and inflammatory rheumatic disorders, in particular Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) and Systemic Scleroderma (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. Our research unit is chaired by Patrick Durez.

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).

It is now clear that lupus kidney is not simply a passive target of systemic autoimmunity but also hosts pathogenic mechanisms determining renal disease severity. These likely involve both the infiltrating immune and resident renal cell compartments. In collaboration with the Genetics of Autoimmune Diseases & Cancer group at the Duve Institute, we dissect kidney-intrinsic mechanisms in LN, with a view to identifying early markers of poor long-term renal outcome and novel therapeutic targets.

Recently, we set out to assess for cellular senescence in LN. Cellular senescence, triggered by stimuli such as chronic inflammation, leads to cell cycle arrest through the accumulation of cyclin dependent kinase inhibitors such as p16INK4a (CDKN2A). Senescent cells acquire a pro-inflammatory, pro-fibrotic senescence-associated secretory phenotype (SASP), important for their clearance by immune cells. In a series of 40 baseline LN biopsies, we showed that p16INK4a was associated with renal impairment not only at baseline, but also 5 years later1: a novel finding. Intriguingly, p16INK4a-positive cells showed a tight spatial co-localization with CD8+ T cells and tissue fibrosis (2). CD8+ T lymphocytes, historically under-studied in the LN kidney, are emerging as relevant players. Their presence may be attributed to the recognition of renal (neo)antigens, with collateral damage to tissue rendering their activation pathogenic. In accordance, we identified an oligoclonal T cell receptor (TCR) repertoire in CD8+ T cells isolated from baseline LN biopsies, supporting local, antigen-driven expansion. We hypothesize that cellular senescence may contribute to LN pathogenesis via (a) Direct (cis) effects on renal tissue due to damaging effects of the SASP and/or functional incapacitation of kidney cells; (b) Indirect (trans) effects on recruitment, local expansion and activation of immune cells including CD8+ T cells, which may in turn have a feed-back effect. This would represent a novel mechanism of disease-amplification between the immune and non-immune compartments that we are now investigating.

The very long-term consequences of absence of remission in LN remain understudied. In 2021, we studied a selected cohort of 128 patients with biopsy-proven class III, IV or V incident LN followed for a median period of 134 months (minimum 25) (3). Remission was defined as a urine protein to creatinine (uP:C) ratio <0.5 g/g and a serum creatinine value <120% of baseline. Renal relapse was defined as the reappearance of a uP:C >1 g/g, leading to a repeat kidney biopsy and treatment change. Poor long-term renal outcome was defined as the presence of chronic kidney disease (CKD). Twenty per cent of patients never achieved renal remission. Their baseline characteristics did not differ from those who did. Absence of renal remission was associated with a threefold higher risk of CKD (48% vs 16%) and a 10-fold higher risk of end-stage renal disease (20% vs 2%). Patients achieving early remission had significantly higher estimated glomerular filtration rate (eGFR) at last follow-up compared with late remitters. Accordingly, patients with CKD at last follow-up had statistically longer time to remission. Among patients who achieved remission, 32% relapsed, with a negative impact on renal outcome, that is, lower eGFR values and higher proportion of CKD (33% vs 8%). Early remission should be achieved to better preserve long-term renal function.

Also, prognosis of lupus nephritis among African-descents patients living in Europe has been understudied. In 2021, we conducted a retrospective study performed in two European university hospitals, we compared the prognosis of African-descent and Caucasian lupus nephritis patients (4). Remission and relapse were defined as in the previous study. Observance was retrospectively assessed through medical files and/or hydroxychloroquine dosages. Fifty- two African-descent patients and 85 Caucasian patients were included in this analysis. Class III and isolated class V were more common among African-descent patients. They suffered from earlier renal flares, CKD was more common and time to CKD was shorter after a flare. There was no significant difference in non-adherence to treatment between the two groups. African-descent patients have worse renal outcomes, especially the subgroup experiencing a renal flare.

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 susceptibil- ity 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

Our RA UCLouvain clinic include arround 2000 patients and we have developed a prospective cohort of 600 early RA From these patients, we collect a full spectrum of clinical, imaging and laboratory data. We are active in many clinical trials in RA in order to devel- op and validate targeting therapies. Our large recruitment of RA patients allow us to analyze the predictive factors for severity and therapy responses. Using synovial biop- sies (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 re- cruitment of patients in sponsored and national / inter- national academic clinical trials (in particular the Cap48 cohort, including young patients with new-onset arthritis, and WelBio) provides us with additional clinical, biologi- cal and imaging data in order to develop novel patients' stratification algorithms (5-7). Our expertise in the field led to the european collaboration with all the expert center in synovial tissue analysis (RA 3TR initiative). We are active to generate single cell RNASeq data from RA synovial biopsies with a main interest in patients with early and naïve RA.

Pathogenesis of systemic sclerosis

Systemic sclerosis (SSc) is a rare chronic autoimmune connective tissue disorder and considered an orphan disease. SSc has a multifactorial aetiology, and develops in patients with a **susceptible genetic background,** upon exposure to likely specific, but at present largely unknown, **environmental triggers.**

Unravelling of the environmental exposure associated risk factors towards the initiation and perpetuation of autoimmunity has a high economic and societal value: ideally, this allows for introduction of preventive measures reducing disease incidence and subsequent societal costs as well as suffering for the patient. In addition, such insights will also provide inroads for pathobiology and gene-environment interactions that can identify new therapeutic targets.

The research hypothesis states that environmental exposure to silica or solvents is associated with SSc in genetically predisposed individuals. Therefore, the exposure-associated SSc patient model is the ideal starting point to investigate this relationship.

The scientific objective of this project is to firmly establish the association between occupational exposure to respirable silica particles as well as organic solvents and SSc in Belgium, to examine clinical phenotypes of SS associated with occupational exposure, to explore the HLA genotypes associated with exposure-associated SS and to investigate objective markers of exposure to silica in SS patients.

Another research area will quantify the exposure of patients to environmental and occupational agents **(exposome)** by modelling (exposure matrix/environment) or analytical measurement. This research intends also to map the immune profiles **(immunome)** and determine their links with exposome and autoimmunity.

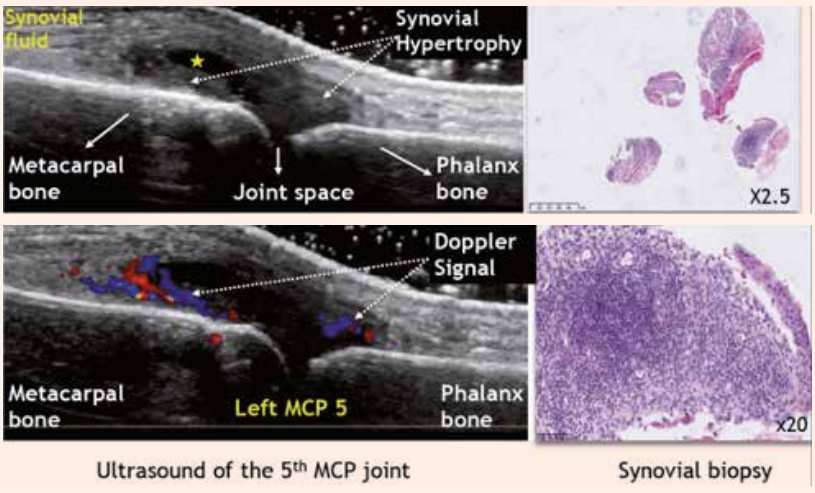


Figure 1: Ultrasound-guided synovial biopsies deliver material for a better stratification of RA patients based on the identification of specific molecular profiles in the tissue.

REFERENCES (selected)

Rituximab versus tocilizumab in anti-TNF inadequate re- sponder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-la- bel, phase 4 randomised controlled trial.

Humby F, **Durez P**, Buch MH, Lewis MJ, Rizvi H, Rivellese F, Nerviani A, Giorli G, Mahto A, Montecucco C, Lauwerys B, Ng N, Ho P, Bombardieri M, Romão VC, Verschueren P, Kelly S, Sainaghi PP, Gendi N, Dasgupta B, Cauli A, Reynolds P, Cañete JD, Moots R, Taylor PC, Edwards CJ, Isaacs J, Sasieni P, Choy E, Pitzalis C; R4RA collaborative group.Humby F, et al. Among authors: **Durez P.** Lancet. 2021 Jan 23;397(10271):305-317.

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis.

Furie R, Rovin BH, **Houssiau F**, Malvar A, Teng YKO, Contreras G, Amoura Z, Yu X, Mok CC, Santiago MB, Saxena A, Green Y, Ji B, Kleoudis C, Burriss SW, Barnett C, Roth DA.Furie R, et al. Among authors: **Houssiau F**. N Engl J Med. 2020 Sep 17;383(12):1117-1128.

Parodis I, T**amirou F**, **Houssiau FA**. Prediction of prognosis and renal outcome in lupus nephritis. **Lupus Sci Med** 2020; 18: e000389.

De Groof A, **Ducreux J**, Aleva F, Long AJ, Ferster A, van der Ven A, van de Veerdonk F, **Houssiau FA**, **Lauwerys BR**. STAT3 phosphorylation mediates the stimulatory effects of inter- feron alpha on B cell differentiation and activation in SLE. **Rheumatology (Oxford)**. 2020 Mar 1;59(3):668-677.

De Groof A, **Ducreux J**, Vidal-Bralo L, Tyteca D, Galant C, Marot L, Coulie PG, Van den Eynde BJ, Rodriguez-Martinez L, Santos MJ, Suarez A, Carreira P, Marchini M, Gonzàlez A, **Houssiau FA**, **Lauwerys BR**. Toll-like receptor 3 increases an- tigen-presenting cell responses to a pro-apoptotic stimulus, yet does not contribute to systemic lupus erythematosus genetic susceptibility. **Clin Exp Rheumatol**. 2020 Jan 20. [Epub ahead of print]

Houssiau FA, Thanou A, Mazur M, Ramiterre E, Gomez Mora DA, Misterska-Skora M, Perich-Campos RA, Smakotina SA, Cerpa Cruz S, Louzir B, Croughs T, Tee ML. IFN-a kinoid in systemic lupus erythematosus: results from a phase IIb, ran- domised, placebo-controlled study. **Ann Rheum Dis** 2020; 79: 347-55.

Triaille C, **Lauwerys BR**. Synovial tissue : turning the page to precision medicine in arthritis. **Front Med (Lausanne)** 2019; [In press]

Meric De Bellefon L, **Lazarou I**. **US-Guided Biopsies: Over- arching Principles**. Front Med (Lausanne). 2019 Jan 22;6:1. Lazarou I, Kelly SG, **Meric de Bellefon L**. Ultrasound-Guided Synovial Biopsies of Wrists, Metacarpophalangeal, Metatar- sophalangeal, Interphalangeal Joints, and Tendon Sheaths. **Front Med (Lausanne)**. 2019 Jan 21;6:2.

Galant C, Marchandise J, Stoenoiu MS, Ducreux J, De Groof A, Pirenne S, Van den Eynde B, Houssiau FA, Lauwerys BR. Overexpression of ubiquitin-specific peptidase 15 in system- ic sclerosis fibroblasts increases response to transforming growth factor **Rheumatology (Oxford**). 2019; 58: 708-18.

Brunner HI et al. Maintenance of antibody response to diphte- ria/tetanus vaccine in patients aged 2-5 years with polyarticu- lar-course juvenile idiopathic arthritis receiving subcutaneous abatacept. **Pediatri Rheumatol Online J.** 2020; 18 : 19.

Ruiz-Limon P et al. Molecular characterization of monocyte subsets reveals specific and distinctive molecular signatures associated with cardiovascular disease in rheumatoid arthri- tis. **Front Immunol.** 2019 ; 10 : 111.

Brogan PA, et al. Rapid and sustained long-term efficacy and safety of canakinumab in patients with cryopyrin-associat- ed periodic syndrome ages five years and younger. **Arthritis Rheumatol.** 2019 ; 71 : 1955-63.

Lazarou I et al. Inflammatory arthritides pathotypes. **Rev Med Suisse**. 2019 ; 15 : 522-7.

Distler O et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. **N Engl J Med** 2019 ; 380 : 2518-28. Sobanski V et al. Phenotypes determined by cluster analysis and their survival in the prospective European scleroderma trials and research cohort of patients with systemic sclerosis.

Arthritis Rheumatol. 2019 ; 71: 1553-70.

Elhai M et al. Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice : a prospective cohort study. **Ann Rheum Dis** 2019 ; 78 : 979-87.

Barakat E et al. The « birth of death » : MRI step-by-step re- veals the early appearance of a bone marrow infarct. **Acta Radiol Open** 2019 ; 8 : 2058460119834691.

Fanouriakis A et al. 2019 update of the EULAR recommenda- tions for the management of systemic lupus erythematosus. **Ann Rheum Dis** 2019 ; 78 : 736-45.

Meyer A et al. Idiopathic inflammatory myopathies : state of the art on clinical practice guidelines. **RMD Open** 2019 ; 4 : e000784.

Acosta-Herrera M et al. Genome-wide meta analysis reveals shared new loci in systemic seropositive rheumatic diseases. **Ann Rheum Dis** 2019 ; 78 : 311-9.

Mackay M, et al. Establishing Surrogate Kidney End Points for Lupus Nephritis Clinical Trials: Development and Val- idation of a Novel Approach to Predict Future Kidney Outcomes. **Arthritis Rheumatol.** 2019 Mar;71(3):411-419.

Costedoat-Chalumeau N et al. A prospective international study on adherence to treatment in 305 patients with flar- ing SLE : assessment by drug levels and self-administered questionnaires. **Clin Pharmacol Ther** 2019 ; 106 : 374-82.

Ciregia F et al. Glycosylation deficiency of lipopolysaccha- ride-binding protein and corticosteroid-binding globulin associated with activity and response to treatment for rheumatoid arthritis. J **Transl Med** 2020 ; 18 : 8.

Rivellese F, et al. B cell synovitis and clinical phenotypes in rheumatoid arthritis : relationship to disease stages and drug exposure. **Arthritis Rheumatol** 2019 ; [Epub ahead of print]

Ahmad HA, et al. Baseline objective inflammation by mag- netic resonance imaging as a predictor of therapeutic ben- efit in early, poor prognosis rheumatoid arthritis. **Arthritis Care Res (Hoboken)** 2019 ; [Epub ahead of print]

Fleischmann RM et al. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. **Ann Rheum Dis** 2019 ; 78 : 1454 -62.

Fleischmann R et al. Upadacitinib versus placebo or adal- imumab in patients with rheumatoid arthritis and an inadequate response to methotrexate : results of a phase III, double-blind, randomized controlled trial. **Arthritis Rheu- matol** 2019 ; 71 : 1788-1800.

Legrand J et al. Early clinical response and long-term radiographic progression in recent-onset rheumatoid ar- thritis: clinical remission within six months remains the treatment target. Joint **Bone Spine** 2019 ; 86 v: 594-9.

Mathew AJ, et al. The OMERACT MRI in Enthesitis Initiative: Definitions of Key Pathologies, Suggested MRI Sequences and Novel Heel Enthesitis Scoring System (HEMRIS). **J Rheumatol.** 2019; 46: 1232-8.

Krabbe S, et al. Development and Validation of an OMER- ACT MRI Whole-Body Score for Inflammation in Peripheral Joints and Entheses in Inflammatory Arthritis (MRI-WIPE). **J Rheumatol**. 2019; 46: 1215-21.

Wong PC et al. Musculoskeletal ultrasound in systemic lupus erythematosus: systematic literature review by the lupus task force of the OMERACT ultrasound working group. **J Rheumatol** 2019; 46: 1379-87.

Should we use glucocorticoids in early rheumatoid arthritis? Results at 5 years from the early RA UCLouvain Brussels cohort.

Sapart E, Sokolova T, de Montjoye S, Dierckx S, Nzeusseu A, Avramovska A, Durez P.

Rheumatology (Oxford). 2021 Dec 1;60(12):5576-5582.

Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry.

Machado P, Lawson-Tovey S, Strangfeld A, Mateus E, Hyrich K, Gossec L, Carmona L, Rodrigues A, Raffeiner B, Duarte C, Hachulla E, Veillard E, Strakova E, Burmester G, Yardımcı G, Gomez-Puerta J, Zepa J, Kearsley-Fleet L, Trefond L, Cunha M, Mosca M, Cornalba M, Soubrier M, Roux N, Brocq O, Durez P, Conway R, Goulenok T, Bijlsma J, McInnes I, Mariette X.

Ann Rheum Dis. 2021 Dec 31:annrheumdis-2021-221490.

MRI of Hands with Early Rheumatoid Arthritis: Usefulness of Three-Point Dixon Sequences to Quantitatively Assess Disease Activity.

Kirchgesner T, Stoenoiu M, Durez P, Michoux N, Vande berg B.

Journal of the Belgian Society of Radiology DOI: 10.5334/jbsr.2692.

Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid arthritis: results through 3 years from the SELECT-COMPARE study.

Fleischmann R, Mysler E, Bessette L, Peterfy C, Durez P, Tanaka Y , Swierkot J, Khan N, Bu X, Li Y, SonI.

RMD Open 2022 Feb;8(1):e002012.

Anti-TNF Induced Sarcoidosis-Like Disease in Rheumatoid Arthritis Patients: Review Cases from the RA UCLouvain Brussels Cohort.

Theunssens X. Bricman L. Dierckx S, Sapart E, Sokolova T, Avramovska A, Durez P.

Rheumatol Ther. 2022 Feb 8. doi: 10.1007/s40744-022-00424-1.

EULAR points to consider for minimal reporting requirements in synovial tissue research in rheumatology.

Najm A, Costantino F, Alivernini S, Alunno A, Bianchi E, Bignall J, Boyce B, Canete J, Carubbi F, Durez P, Fonseca J, Just S, Largo R, Manzo A, Maybury M, Naredo E, Orr C, Pitzalis C, Rivellese F, Romão V, van Rompay J, Tas S, Veale D, D'Agostino M-A, Filer A.

Ann Rheum Dis 2022;0:1–7. doi:10.1136/annrheumdis-2021-221875

Identification of poor prognostic joint locations in an early rheumatoid arthritis cohort at risk of rapidly progressing disease: a post-hoc analysis of the Phase III AGREE study.

Durez P, Westhovens R, Baeke F, Elbez Y, Robert S, Ahmad HA.BMC Rheumatol. 2022 Apr 14;6(1):24.

The safety and efficacy of ABX464 (50 and 100 mg q.d.) in patients with moderate-to-severe Rheumatoid Arthritis and inadequate response to methotrexate and/or anti-TNFα therapy: a placebo-controlled phase II study

Claire Daien1, Marek Krogulec2, Paul Gineste3, Jean-Marc Steens4, Laurence Desroys du Roure3, Sophie Biguenet3, Didier Scherrer5, Julien Santo 5, Hartmut Ehrlich3, Patrick Durez. Ann Rheum Dis 2022 May.

LOUVAIN CENTRE FOR TOXICOLOGY AND APPLIEDPHARMACOLOGY - LTAP

François Huaux, PhD

Leïla Belkhir, PhD
Jean-François Geuens, tech
Vincent Haufroid, PhD
Léa Hiéronimus, PhD student
Perinne Hoet, PhD
Saloua Ibouraadaten, tech
Riccardo Leinardi, PhD student
Dominique Lison, PhD
Chiara Longo Sanchez-Calero, PhD student
Sarah Nauwelaerts, PhD student
Laeticia Perez, PhD student
Amandine Pochet, Tech
Francine Uwambayinema, tech
Sybille Van Den Brûle, PhD
Yousof Yakoub, tech

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.

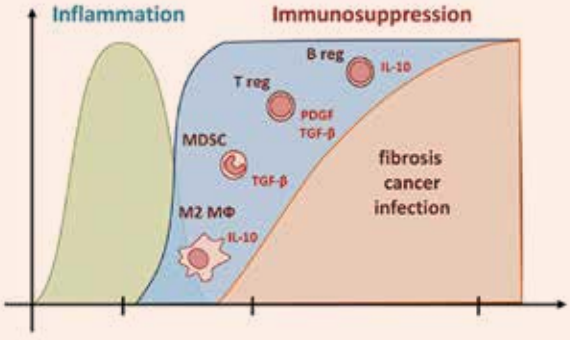


Figure 1: ***Pathological functions of persistent immunosuppressive cells and mediators during long-term responses to particles.*** Unresolved Immunosuppression (in blue) represents an alternative event during the responses to particles. According to this new pathological pathway, fibrogenesis, and carcinogenesis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

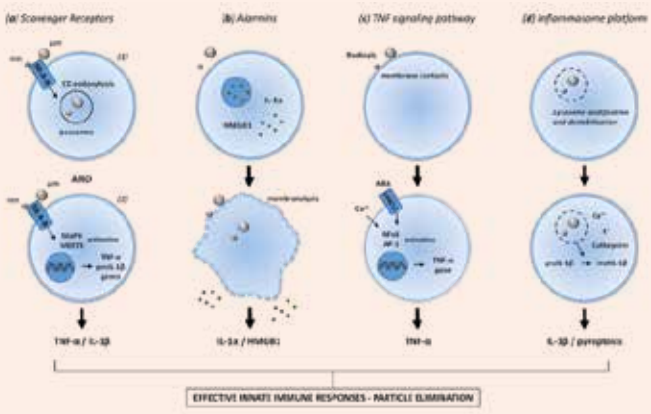


Figure 2: ***Early sensing and alerting processes are combined and mutually linked in response to inhaled particles.*** (a1) Micrometric (µm) and nanometric (nm) particles are internalized by phagocytes through the scavenger receptors (SR) A and B and clathrin-dependent (CD) endocytosis. (a2) Particle 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.

Huaux F. Innate immunity to inhaled particles: A new paradigm of collective recognition. Current Opinion in Toxicology Volume 10, August 2018, Pages 84-90.

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.

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

Charles Pilette, MD, PhD

Sophie Gohy, MD, PhD

Antoine Froidure, MD, PhD

Marie Baeck, MD, PhD

Frank Aboubakar, MD, PhD student
Anne-Sophie Aubriot, PT
Nicolas Audag, PhD student
Philippe Collard, MD, PhD
Caroline Dahlqvist, MD
Céline Decouvreur, PhD student
Charlotte de Fays, PhD student
Naïma Deggouj, MD*
Laurence De Montjoye, MD, PhD
Caroline Detoeuf, MD
Bruno Detry, Techn
Fabrice Duplaquet, MD
Frédéric Duprez, PT, PhD
Philippe Eloy, MD, PhD
Antoine Froidure, MD, PhD
Valérie Hox, MD, PhD
Giuseppe Liistro, MD, PhD
Juliana Macedo, PhD student
Eric Marchand, MD, PhD
Liliane Marot, MD
Natalia Morales, PhD student
Benny Mwenge, MD, PhD
Sebahat Ocak, MD, PhD
Thierry Pieters, MD
Elise Piraux, PhD student
Françoise Pirson, MD
William Poncin, PT, PhD
Gregory Reychler, PT, PhD
Philippe Rombaux, MD, PhD*
Alba Sanchez Montalvo, PhD student
Diana Santos Ribeiro, PhD student
Carine Sohy, MD
Olivier Vandenplas, MD, PhD

*Membres affiliés à l'IREC (Mandat de clinicien chercheur)

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 CPAP compliance should be better assessed. We evaluated the main motivations for CPAP use among patients who had accepted CPAP and have been using it for many years. We found that the main motivation for use was sleep comfort and this motivation increased with CPAP duration. However, the fear of cardiovascular complications related to OSA and partner distress as main motivation for using CPAP decreased with years. 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. Sulthiam, a drug that attenuates CO2 fluctuations and thus respiratory drive, has demonstrated a consistent reduction among patients in the apnea and hypopnea index. A phase III study is currently ongoing. 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. In a new study, we observed assess the specific effectiveness

of a tongue elevation muscle protocol in reducing OSA severity. We hypothesised that a 6 weeks tongue strength and endurance training program would reduce AHI in patients with OSA. However, Our data suggest that 6 weeks of isolated tongue muscle elevation task has no effect on OSA severity (1). 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. Patients with neuromuscular diseases (NMDs) are followed by our multidisciplinary team. These patients are often at risk for the development of respiratory failure and deglutition disorders leading to severe pulmonary infections. Dysphagia is common in these patients but its management differs by country and clinical setting. The purpose of this study was to describe current practices in the management of dysphagia in NMDs across Europe. An online survey of sixteen questions was developed, including basic information on facilities, existence of a management protocol, availability of dedicated therapists, tools used during screening, assessment, treatment stages, and treatment strategies. The survey was rolled out to European healthcare facilities providing care for NMDs. A total of 140 facilities across 25 European countries completed the survey. Our survey highlighted the absence of a defined protocol concerning the management of dysphagia in most of the surveyed healthcare facilities. Standardized training strategies and guidelines are necessary in the future to familiarize clinicians with each stage of the management of dysphagia (2).

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). This year, we compared in a systematic review the effect between tele-pulmonary rehabilitation and classical supervised pulmonary rehabilitation. This review demonstrated that the telerehabilitation is safe and well accepted by the patients, and could be considered as one option of classical pulmonary rehabilitation to improve the functional exercise capacity, quality of life, anxiety and depression, and the impact of COPD on personal's life (3). 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. We determined the efficacy of the surgical facemask and the double-trunk mask on top of the low-flow oxygen nasal cannula on arterial partial pressure of oxygen (PaO2) in hypoxemic COVID-19 patients. This study showed that the addition of the surgical facemask or the double-trunk mask above the nasal cannula improves arterial oxygenation and reduces oxygen consumption (4).

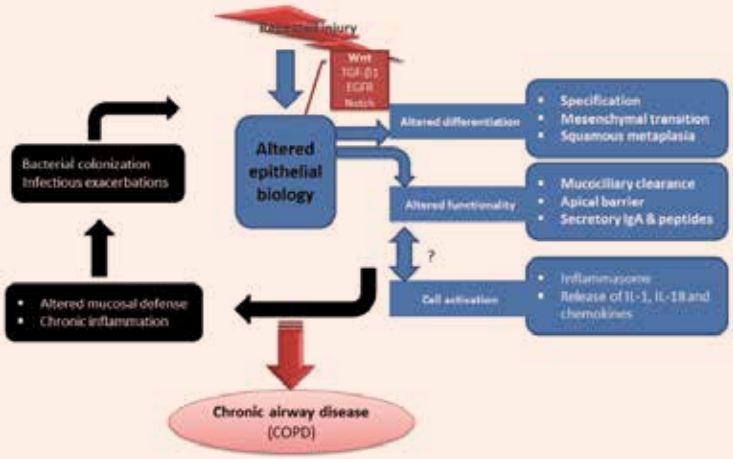


Figure 1. Hypothesis of airway epithelial cell dysregulation in COPD. The epithelium, repeatedly activated by cigarette smoke may become persistently dysregulated through aberrant signalling, with altered differentiation and functionality. This leads to impaired front-line defense against pathogens,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

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. A first focus was the airway 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 (5). 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 bronchial epithelium (Figure 1). Different interactions (e.g., with airway microbiome) probably condition distinct changes in pIgR expression observed in airway disorders such as asthma (6), COPD, cystic fibrosis, or during acute lung injury/ARDS. A second focus is on airway inflammatory and specific IgE responses in asthma following exposure to occupational agents (7). More recently, we have implemented in our pole, in collaboration with F. Huaux (LTAP), a murine model of pulmonary fibrosis that mimics features observed in human IPF, following repeated instillation of bleomycin. This model enabled to study the role of the IgA system and epithelial pIgR in vivo, using PIGR and IGA KO mice, and the determinants of lung epithelial changes. Also more recently chronic rhinosinusitis (CRS) has been modelled in two mouse models representing both subtypes of disease (8), in which the involvement of the pIgR/IgA axis is studied (9). Moreover, repair mechanisms of the olfactory neuro-epithelium during CRS or post-trauma/viral are also explored (10). In the skin, patients with allergic contact dermatitis (11) or chronic urticaria (12) 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 of the former is dominated by Th2-biased T cells and includes IL-4 producing γδ T cells, generation a foundation of further investigations with other contact allergens.

Novel biological targets in lung cancer:

The FAK pathway in SCLC. Small cell lung cancer (SCLC) is the most aggressive subtype of lung cancer, with a five-year overall survival below 5%.

In previous works, we found that Focal Adhesion Kinase (FAK), a non-receptor tyrosine kinase regulating cell proliferation, survival, migration, and invasion, was amplified, commonly expressed in SCLC tumors (Fig. 3), and constitutively phosphorylated in SCLC cell lines (13). 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. 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 (14). While FAK shRNA transduction decreased total and phospho-FAK (Tyr397) expression, it did not affect proliferation, DNA synthesis, or progression through cell cycle. However, restoration of FAK-targeting (FAT) domain (attached to focal adhesion complex where it inhibits pro-proliferative proteins such as Rac-1) by FRNK transduction inhibited proliferation, DNA synthesis, and induced apoptosis. Moreover, while FAK shRNA transduction increased active Rac1 levels, FRNK re-expression in cells previously transduced with FAK shRNA decreased it. From this work, we concluded that FAK is central in SCLC biology and that targeting its kinase domain may have a therapeutic potential, while targeting its FAT domain should be avoided to prevent Rac1-mediated pro-tumoral activity. Currently, we attempt to further investigate the role of FAK and address its potential as a targeted therapy in SCLC by pursuing the following specific aims. 1/ To evaluate the antitumoral potential of FAK inhibition in a transgenic 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. Understanding the role of FAK in SCLC may provide greater insight into the molecular steps leading to SCLC progression and, ultimately, may justify the development of FAK-targeted therapeutic strategies to reduce mortality from SCLC.

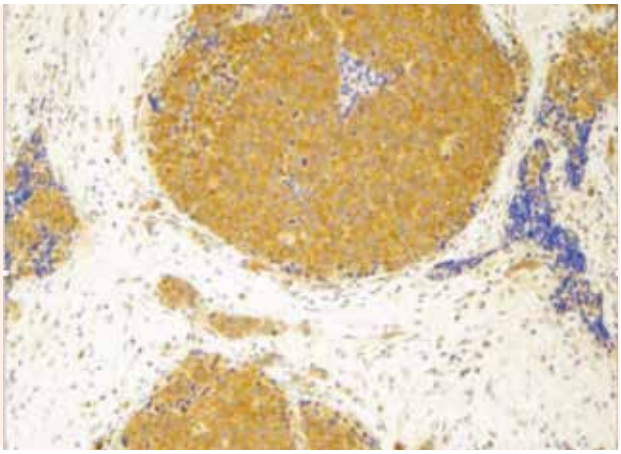


Figure 2. ***Total FAK expression in a small-cell lung cancer tissue.*** Two tissue microarrays consisting of SCLC tissues coming from 85 patients were incubated with an antibody against total FAK (A-17). In this figure is displayed a representative image of SCLC tumor with moderate total FAK expression.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

PUBLICATIONS 2022 (SELECTION)

PNEU

1. Poncin, W., Correvon, N., Tam, J., Borel, J. C., Berger, M., Liistro, G., Mwenge, B., Heinzer, R., & Contal, O. (2022, Nov). The effect of tongue elevation muscle training in patients with obstructive sleep apnea: A randomised controlled trial. J Oral Rehabil, 49(11), 1049-1059. https://doi.org/10.1111/joor.13369

2. Audag, N., Toussaint, M., Liistro, G., Vandervelde, L., Cugy, E., & Reychler, G. (2022, Oct). European Survey: Dysphagia Management in Patients with Neuromuscular Diseases. Dysphagia, 37(5), 1279-1287. https://doi.org/10.1007/s00455-021-10392-3

3. Reychler, G., Piraux, E., Beaumont, M., Caty, G., & Liistro, G. (2022, Sep 17). Telerehabilitation as a Form of Pulmonary Rehabilitation in Chronic Lung Disease: A Systematic Review. Healthcare (Basel), 10(9). https://doi.org/10.3390/healthcare10091795

4. Poncin, W., Baudet, L., Braem, F., Reychler, G., Duprez, F., Liistro, G., Belkhir, L., Yombi, J. C., & De Greef, J. (2022, Apr). Systems on Top of Nasal Cannula Improve Oxygen Delivery in Patients with COVID-19: a Randomized Controlled Trial. J Gen Intern Med, 37(5), 1226-1232. https://doi.org/10.1007/s11606-022-07419-2

5. de Fays, Carlier FM, Gohy ST, Pilette C. Secretory immunoglobulin A immunity in chronic obstructive respiratory diseases. Cells 2022; 11(8):1324 (Review). IF (2021): 7.666

6. Pilette C, Canonica GW, Chaudhuri R, Chupp G, Lee FEH, Lee JK, Almonacid C, Welte T, Alfonso-Cristancho R, Jakes RW, Maxwell A, Price RG, Howarth P. REALITI-A study: Real-world oral corticosteroid-sparing effect of mepolizumab in severe asthma. J Allergy Clin Immunol: In Practice 2022; 10(10):2646-2656.

7. Lemiere C, Lavoie G, Doyen V, Vandenplas O. Irritant-Induced Asthma. J Allergy Clinical Immunol: In Pract 2022; 2022;10:2799-2806. doi: 10.1016/j.jaip.2022.06.045

8. Khaleva E, Knibb R, DunnGalvin A, Vazquez-Ortiz M, Comberiati P, Alviani C, Garriga-Baraut T, Gowland MH, Gore C, Angier E, Blumchen K, Duca B, Hox V, Jensen B, Mortz CG, Pite H, Pfaar O, Santos AF, Sanchez-Garcia S, Timmermans F, Roberts G. Perceptions of adolescents and young adults with allergy and/or asthma and their parents on EAACI guideline recommendations about transitional care: A European survey. Allergy. 2022 Apr;77(4):1094-1104.

9. Sánchez Montalvo A, Gohy S, Rombaux P, Pilette C, Hox V. The Role of IgA in Chronic Upper Airway Disease: Friend or Foe? Front Allergy. 2022 Mar 9;3:852546.

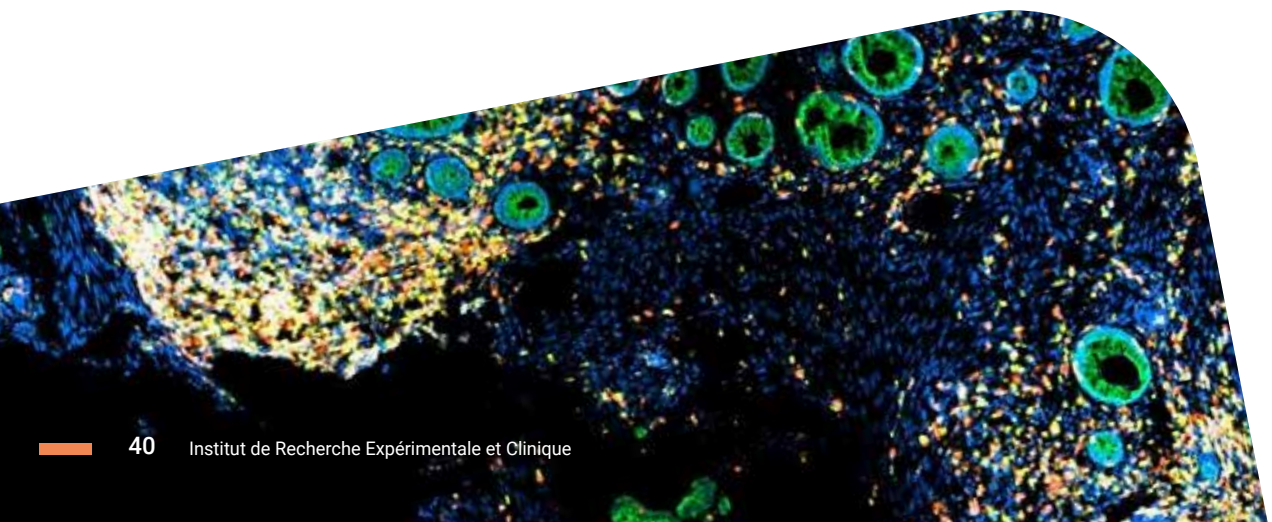
10. Van Regemorter V, Rombaux P, Dricot L, Kupers R, Grégoire A, Hox V, Huart C. Functional Imaging in Olfactory Disorders. Curr Otorhinolaryngol Rep. 2022 Oct 19:1-6.

11. Herman A, Aerts O, Jacobs MC, Scheers C, Gilissen L, Goossens A, Baeck M. Evolution of methylisothiazolinone sensitization: A Belgian multicentric study from 2014 to 2019. Contact Dermatitis. 2021 Dec;85(6):643-649.

12. de Montjoye L, Darrigade AS, Giménez-Arnau A, Herman A, Dumoutier L, Baeck M. Correlations between disease activity, autoimmunity and biological parameters in patients with chronic spontaneous urticaria. Eur Ann Allergy Clin Immunol. 2021 Mar;53(2):55-66.

13. Aboubakar Nana F, Delphine Hoton D, Ambroise J, Lecocq M, Vanderputten M, Sibille Y, Vanaudenaerde B, Pilette C, Bouzin C, Ocak S. Increased Expression and Activation of FAK in Small-Cell Lung Cancer Compared to Non-Small-Cell Lung Cancer. Cancers (Basel) 2019; 11(10):1526.

14. Aboubakar Nana F, Lecocq M, Ladjemi MZ, Detry B, Dupasquier S, Feron O, Massion PP, Sibille Y, Pilette C, Ocak S. Therapeutic Potential of Focal Adhesion Kinase Inhibition in Small Cell Lung Cancer. Mol Cancer Ther. 2019;18(1):17-27. IF: 5.201.



ACUTE MEDICINE

The "acute medicine theme" brings together 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. Therefore, some acute medicine themes are shared with IREC poles (CARD, PNEU, NEFR, FATH) in projects combining fundamental and translational research.

The research is primarily focused on the following topics: (1) sepsis and septic shock; (2) thromboembolic disease; (3) cardiovascular and hemodynamic failure; (4) acute lung injury; (5) peri-operative management; (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).

Due to the COVID19 pandemics, still ongoing during the first months of 2022, many research papers published in 2022 were devoted to severe coronavirus disease, with various scopes, such as oxygenation devices, endothelial function, health care organization, ventilator-associated pneumonia, renal complications, coagulation, renin-angiotensin system, and toxicity of anesthetic agents. Other research works related to sepsis and antibiotics treatment, thromboprophylaxis and management of thrombo-embolic disease, post resuscitation care and acute poisoning.

Montiel Virginie, MD, PhD

Wittebole Xavier MD, PhD

Maximilien Gourdin, MD, PhD

Gerard Ludovic MD, PhD

Detaille Thierry MD, PhD

Lessire Sarah MD, PhD

Pole Contact Person

MONTIEL Virginie
virginie.montiel@saintluc.uclouvain.be

List of Researchers

Bulpa Pierre
Delloye Emilie
Detaille Thierry
Dincq Anne-Sophie
Dubois Philippe
Evrard Patrick
Genbrugge Cornelia
Gourdin Maximilien
Gregoire Charles
Hantson Philippe
Khan David
Lessire Sarah
Gerard Ludovic
Mesland Jean-Baptiste
Michaux Isabelle
Montiel Virginie
Pendeville Philippe
Putz Laurie
Thoma Max
Verschuren Franck
Watremez Christine
Werion Alexis
Wittebole Xavier

COVID-19 associated research

Years 2020 to 2022 were marked by a pandemic of SARS-CoV2 infection, responsible of severe pneumonia in many cases. This pandemic represented a huge burden on our health systems, a challenge for the teams involved in the treatment of the patients, but also an opportunity for our research team to better understand the mechanisms underlying the disease, the development of complications related to COVID-19 or to its treatment, as well as to improve ventilation and oxygen administration techniques.

V Montiel authored a publication focused on the oxidative-stress induced endothelial dysfunction in COVID-19 patients. In this publication, V Montiel and her team showed that endothelial oxidative stress with ensuing decreased NO bioavailability appeared as a likely pathogenic factor of the endothelial dysfunction observed in severe COVID-19 patients. L Gerard performed a comprehensive work on the role of angiotensin-converting enzyme 2, a key enzyme in the renin-angiotensin system, which is also the entry receptor for SARS-CoV2, in COVID-related and unrelated ARDS. It was shown that ACE2 was upregulated both in the serum and in the lung tissue of both COVID-19 related and -unrelated ARDS, which suggested that this pathological trait was part of a generic response of the lung to acute lung injury rather than a specific feature of COVID-19.

COVID-19 patients frequently developed complications, associated with poor outcomes. Among those, venous thromboembolism is a frequent and severe complication in COVID patients, whose diagnostic is still challenging. I Michaux et P Bulpa participated to an observational study that showed that combining serial fibrin monomer and D-dimer plasma levels measurements could identify thrombotic complications in critically ill patients. Another dreaded complications among ventilated patients with severe COVID-19 is ventilator associated pneumonia. J-B Mesland showed that the use of corticosteroid therapy in the treatment of severe COVID-19 was associated with an increase of Ventilator-associated lower respiratory tract infections. Besides, anesthetic agents frequently used at high doses and for prolonged periods for COVID-19 patients, Ketamine and sevoflurane, have been shown by our teams to be associated with complications, such as liver cholestasis and nephrogenic diabetes insipidus.

Finally, innovative techniques to improve and to better understand oxygen administration, such as double-trunk mask or high flow nasal cannulas, were also investigated by our teams.

Improvement in the understanding of sepis and antibiotic treatment

SEPSIS is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Our service developed a field of clinical and fundamental research aiming at the improvement of the understanding of sepsis as well as its treatment by various approaches.

X Wittebole co-authored a study that investigated the safety and tolerability of adrecizumab, a humanized monoclonal adrenomedullin antibody, in septic shock patients with high adrenomedullin. Adrenomedullin is a circulating peptide whose elevated concentrations in septic shock patients are correlated with poor outcomes. In the present study, adrecizumab was well tolerated and associated with a greater improvement of SOFA Score, indicating less organ dysfunction.

In the fight against bacterial infections, antibiotics are precious weapons, but the spread of resistance raise concerns about our ability to treat multi-drug resistant infections. Dr Wittebole co-authored two publications who investigated pharmacokinetics and pharmacodynamics of temocillin, an antibiotic active against many multi-resistant Gram negative bacteria.

Thromboprophylaxis and management of thrombo-embolic disease

Thrombosis physiopathology, management, as well as prophylaxis, treatment and monitoring were studied by our teams.

S Lessire and Bulpa P co-authored a publication related to the management of direct oral anti-coagulants for catheter ablation. S Lessire, P Bulpa, G Horlait, and I Michaux conducted a trial investigating the monitoring of unfractionated heparin in the intensive care unit using a point of care monitoring system. They showed that the results obtained with the point of care device were poorly consistent with those obtained with robust, “gold-standard” methods.

L Gerard and X Wittebole co-authored a publication comparing intravenous and subcutaneous administration of low molecular weight heparin in critically ill patients, in terms of pharmacokinetic profiles. They showed that prolonged iv administration of LMWH leaded to a significantly higher peak anti-Xa activity, without affecting trough value or the area under the curve.

F Verschuren participated to a large trial investigating the recovery of right ventricular function after intermediate-risk pulmonary embolism.

Cardiopulmonary resuscitation and the role of temperature targeted management post resuscitation.

One of the most discussed questions regarding post-resuscitation care after cardiac arrest is the question of temperature control, with conflicting results from the recent litterature.

Due to her extensive expertise in the field of post-resuscitation care, C Genbrugge was one of the authors of the new guidelines from the European Resuscitation Council and European Society of Intensive Care Medicine for temperature control in adults who remain comatose after cardiac arrest. The guidelines recommend to actively prevent fever for at least 72 hours after cardiac arrest. There was insufficient evidence to recommend for or against temperature control at 32 or 36° after cardiac arrest.

Managing acute life-threatening poisoning

The intensive care unit is responsible for treating individual intoxications and evaluating potential new treatments or purification techniques in cases of rare and life-threatening poisonings. Ph. Hantson confirmed his expertise in the management of severe poisoning, such as lipid emulsion for trazodone intoxication or in the specific management of ethylene glycol poisoning.

REFERENCES 2022 (published)

Virginie Montiel, Irina Lobysheva, **Ludovic Gérard**, Marjorie Vermeersch, David Perez-Morga, Thomas Castelein, **Jean-Baptiste Mesland, Philippe Hantson**, Christine Collienne, Damien Gruson, Marie-Astrid van Dievoet, Alexandre Persu, Christophe Beauloye, Mélanie Dechamps, Leïla Belkhir, Annie Robert, Marc Derive, Pierre-François Laterre, A.H.J Danser, **Xavier Wittebole** and Jean-Luc Balligand. Oxidative stress-induced endothelial dysfunction and decreased vascular nitric oxide in COVID-19 patients. eBioMedicine 10.1016/j.ebiom.2022.103893. (IF 2022: 11.2)

Mesland JB, Carlier E, François B, Serck N, **Gerard L**, Briat C, Piagnerelli M, Laterre PF, On Behalf Of The Covcorvap Collaboration Group. Early Corticosteroid Therapy May Increase Ventilator-Associated Lower Respiratory Tract Infection in Critically Ill Patients with COVID-19: A Multicenter Retrospective Cohort Study. Microorganisms. 2022 May 8; 10(5):984. doi: 10.3390/microorganisms10050984. (I.F. 2021: 4.926)

Dupuis C, Robert A, **Gerard L**, Morelle J, Laterre PF, Hantson P. Nephrogenic Diabetes Insipidus following an Off-Label Administration of Sevoflurane for Prolonged Sedation in a COVID-19 Patient and Possible Influence on Aquaporin-2 Renal Expression. Case Rep Anesthesiol. 2022 Mar 11; 2022:3312306. doi: 10.1155/2022/3312306. (I.F. 2021: 0.451)

Mesland JB, Collienne C, Laterre PF, **Hantson P.** Immobilization-Related Hypercalcemia in a COVID-19 Patient With Prolonged Intensive Care Unit Stay. Am J Phys Med Rehabil. 2022 Jan 1; 101(1):61-63. doi: 10.1097/PHM.0000000000001907. (I.F. 2021: 3.412)

Duprez F, de Terwangne C, Bellemans V, Poncin W, Reychler G, Sorgente A, Cuvelier G, Mashayekhi S, Wittebole X. Duprez F, et al. Among authors: **Wittebole x**. High-flow nasal cannula therapy, factors affecting effective inspired oxygen fraction: an experimental adult bench model. J Clin Monit Comput. 2022 Oct; 36(5):1441-1448. doi: 10.1007/s10877-021-00784-z. (I.F. 2021: 1.977)

Ngougni Pokem P, Matzneller P, Vervaeke S, **Wittebole X**, Goeman L, Coessens M, Cottone E, Capron A, Wulkersdorfer B, Wallemacq P, Mouton JW, Muller AE, Zeitlinger M, Laterre PF, Tulkens PM, Van Bambeke F. Binding of temocillin to plasma proteins in vitro and in vivo: the importance of plasma protein levels in different populations and of co-medications. J Antimicrob Chemother. 2022 Sep 30; 77(10):2742-2753.

Hardy M, Douxfils J, **Dincq AS**, Sennesael AL, Xhaet O, Mullier F, **Lessire S**. Uninterrupted DOACs Approach for Catheter Ablation of Atrial Fibrillation: Do DOACs Levels Matter? Front Cardiovasc Med. 2022 Mar 29;9:864899.

De Schryver N, Serck N, Eeckhoudt S, Laterre PF, **Wittebole X, Gérard L.** Pharmacokinetic profiles of intravenous versus subcutaneous administration of low molecular weight heparin for thromboprophylaxis in critically ill patients: A randomized controlled trial. J of Crit Care. 2022 Aug; 70:154029. doi: 10.1016/j.jcrc.2022.154029. (I.F. 2021: 4.298)

Lardinois B, Hardy M, **Michaux I**, Horlait G, Rotens T, Jacqmin H, **Lessire S, Bulpa P**, Dive A, Mullier F. Monitoring of Unfractionated Heparin Therapy in the Intensive Care Unit Using a Point-of-Care aPTT: A Comparative, Longitudinal Observational Study with Laboratory-Based aPTT and Anti-Xa Activity Measurement. J Clin Med. 2022 Feb 28;11(5):1338.

Mavromanoli AC, Barco S, Ageno W, Bouvaist H, Brodmann M, Cuccia C, Couturaud F, Dellas C, Dimopoulos K, Duerschmied D, Empen K, Faggiano P, Ferrari E, Galiè N, Galvani M, Ghuysen A, Giannakoulas G, Huisman MV, Jiménez D, Kozak M, Lang IM, Meneveau N, Münzel T, Palazzini M, Petris AO, Piovaccari G, Salvi A, Schellong S, Schmidt KH, **Verschuren F,** Schmidtmann I, Toenges G, Klok FA, Konstantinides SV; PEITHO-2 Investigators. Recovery of right ventricular function after intermediate-risk pulmonary embolism: results from the multicentre Pulmonary Embolism International Trial (PEITHO)-2. Clin Res Cardiol. 2022 Dec 21.

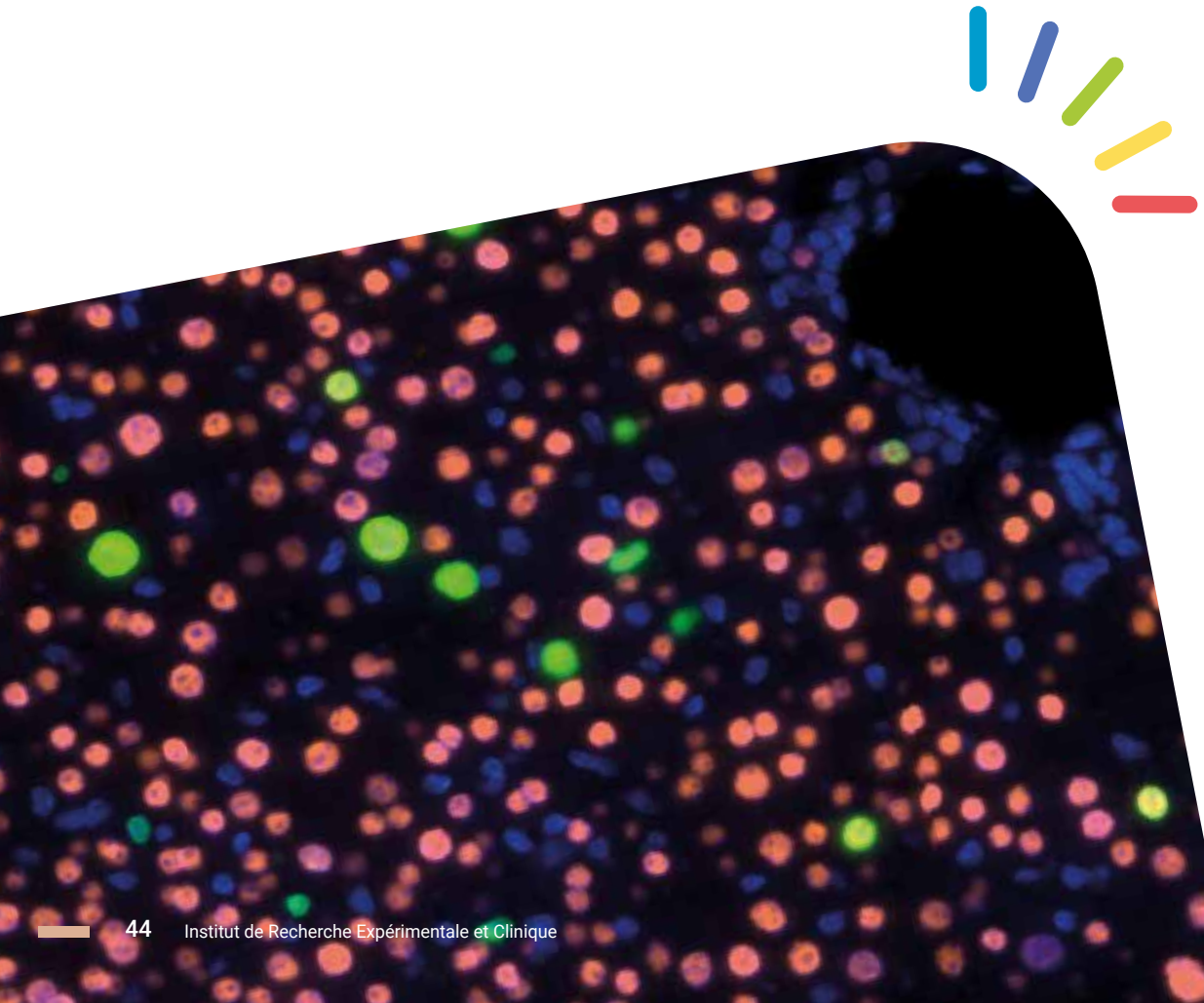
Nolan JP, Sandroni C, Andersen LW, Böttiger BW, Cariou A, Cronberg T, Friberg H, **Genbrugge C**, Lilja G, Morley PT, Nikolaou N, Olasveengen TM, Skrifvars MB, Taccone FS, Soar J. ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Resuscitation. 2022 Mar;172:229-236. doi: 10.1016/j.resuscitation.2022.01.009. Epub 2022 Feb 4. PMID: 35131119.

Delmez Q, Haufroid V, Gohy S, Laterre PF, **Hantson P.** Elevation of alkaline phosphatase and long-term drug therapy for cystic fibrosis. Eur J Clin Pharmacol. 2022 Jan 15; doi: 10.1007/s00228-021-03272-0. (I.F. 2021: 2.953)

de Landsheere F, Saint-Marcoux F, Haufroid V, Dulaurent S, Dewulf JP, Boland L, Laterre PF, **Hantson P.** Unexplained Metabolic Acidosis: Alcoholic Ketoacidosis or Propylene Glycol Toxicity. J Med Toxicol. 2022 Jan 18. doi: 10.1007/s13181-022-00876-5. (I.F. 2021: 2.628)

Nendumba G, Boland L, Haufroid V, Laterre PF, **Hantson P.** Intravenous Lipid Emulsion in a Case of Trazodone Overdose. Prim Care Companion CNS Disord. 2022 Mar 8; 24(2):21cr02994. doi: 10.4088/PCC.21cr02994. (I.F. 2021: 0.92)

Van de Wyngaert C, Dewulf JP, Collienne C, Laterre PF, **Hantson P.** Carnitine Deficiency after Long-Term Continuous Renal Replacement Therapy. Case Rep Crit Care. 2022 Aug 17; 2022:4142539. doi: 10.1155/2022/4142539. (I.F. 2021: 0.94)



REGENERATIVE MEDICINE

REPRODUCTIVE PHYSIOPATHOLOGY (REPR)

Prof. Christiani A. Amorim, DVM, PhD

Prof. Christine Wyns, MD, PhD

Prof. Frédéric Debiève, MD, PhD

Pole Contact Person

Christiani ANDRADE AMORIM
christiani.amorim@uclouvain.be

Researchers:

Jonathan Poels, PhD
Christophe Depoix, PhD

Post-Doc

Janice Vilela, DVM, PhD

PhD

Arthur Colson
Arezoo Dadashzadeh
Sven De Windt
Maria Grazia Giudice
Marc Kanbar
Dhoha Kourta
Yongqian Li
Saeid Moghassemi
Maureen Peers de Niewburgh
Maria João de Sousa
Hanne Vlieghe
Jie Yang
Nour Rahnama

Research Projects

DEVELOPMENT OF AN ENGINEERED OVARY

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

E. Ouni, C. A. Amorim

The ovary is among the most dynamic tissues in the human body, undergoing repeated cycles of growth and involution throughout a woman's life. It achieves this plasticity mainly thanks to its extracellular matrix (ECM) components. We investigated quantitative spatiotemporal changes in collagen, elastin, EMILIN-1, fibrillin-1 and glycopsaminoglycans (GAGs) from prepuberty to menopause, before conducting a closer analysis of the ECM surrounding follicles from primordial to secondary stages in both prepubertal and reproductive-age tissue. Our results revealed ECM deposition and remodeling in an age- and follicle stage-related manner. More precisely, our findings pointed to a more elastic ECM around reproductive-age follicles compared to the less compliant perifollicular ECM of prepubertal tissue (1). 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.

Origin and differentiation of human theca cells

H. Vlieghe, C. A. Amorim

Theca cells play a pivotal role in follicle development and the production of female steroids. Indeed, follicles cannot go further than the secondary stage without them. Despite their importance, the origin of these cells in the human ovary remains elusive. The goal of this study was to investigate the GDF9-HH-GLI pathway in human ovaries and assess whether GLI1, 2, and 3 and PTCH1 are specific markers for precursor theca cells, as has been demonstrated in mice. To this end, we analyzed the expression of proteins and genes involved in the GDF9-HH-GLI pathway in fetal, prepubertal, reproductive-age, and postmenopausal human ovaries (2).

Developing a 3D biomimetic matrix

A. Dadashzadeh, S. Moghassemi, C. A. Amorim

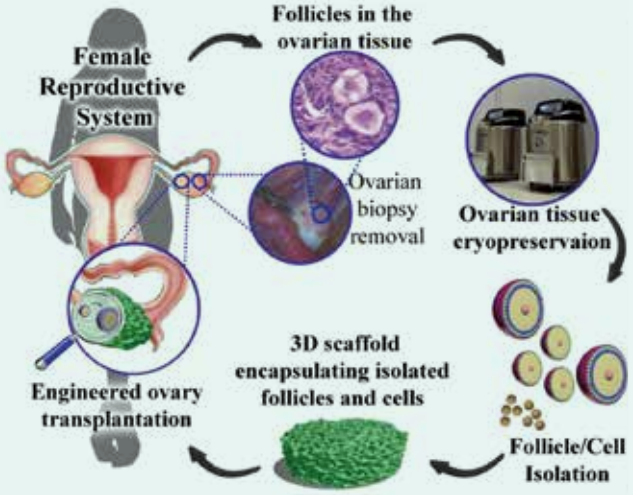
To graft isolated follicles, we must encapsulate them in a matrix with a proper balance between rigidity and elasticity to maintain follicle 3D structure, which is vital for its survival while allowing its growth (3). Using our recently acquired knowledge, we are developing PEGylated fibrin hydrogels to match human ovarian ECM biomechanical properties. This matrix has been shown to enhance the survival and proliferation of ovarian cells and lower the degradation rate compared to fibrin (4). Moreover, we have been also testing other biomaterials with tunable mechanical properties, such as silk-based hydrogels (5).

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

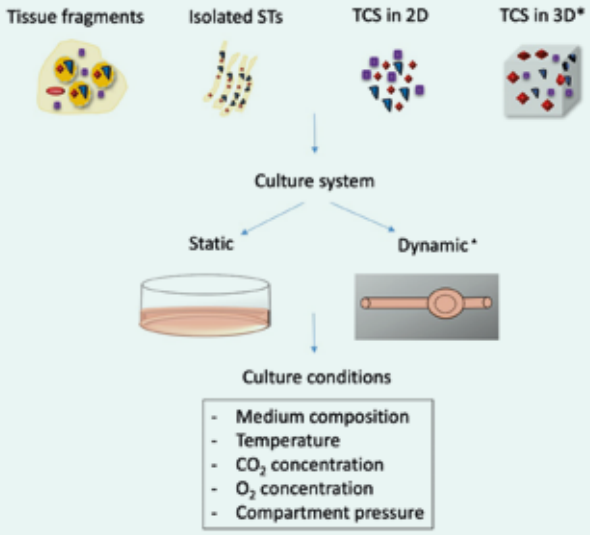
D. Kourta, S. De Windt, J. Poels, MG. Giudice, M. Kanbar, C. Wyns

We aim to elaborate bioengineered testicular scaffolds to incorporate sorted (excluding cancer cells) and propagated

human testicular cells with a view to obtain testicular organoids (TOs) and increasing knowledge on the SSC niche in vitro as well as achieving in vivo differentiation of SSCs after TOs transplantation (6). We therefore developed solid and soluble scaffolds from porcine decellularized ITT. Better results were observed with soluble scaffolds (hydrogels) as they allowed neo-formation of proper seminiferous tubule-like structures with functional Sertoli and Leydig cells during culture. When transplanted in vivo into nude mice, TOs obtained with hydrogels had a higher spermatogonial survival compared to TOs formed with testicular cells suspension alone (6). Experiments using human ITT to generate hydrogel based -TOs are currently ongoing.



A schematic illustration of the fertility preservation strategy using ovarian tissue cryopreservation and ovarian tissue engineering. Before chemo- or radiotherapy, the ovarian tissue is removed and cryopreserved. Once the patient is cured, the tissue fragments are thawed, and their follicles and cells are isolated and seeded/encapsulated in a 3D bioengineered scaffold. Finally, the construct is orthotopically transplanted (3).



Different available options for germ cell in vitro maturation from intact or disaggregated testicular tissue. *: with or without scaffold – including testicular organoids; ▲: Microfluidic, shaking/rotating culture or shaken bioreactors; ST: seminiferous tubule; TCS: testicular cell suspension (6).

new therapy for lung lesions and fetal growth restriction in a premature lamb model

M. Peers de Nieuwburgh, F. Debiève, A. W. Flake (CHOP, Philadelphia, USA).

The Center for Fetal Research at The Children's Hospital of Philadelphia (CHOP) recently developed an Artificial Womb (EXTEND) to provide up to 4 weeks of physiologic support for extreme preterm lambs. The device consists of a closed fluid environment called "biobag" in which the preterm lamb is incubated while immersed in synthetic amniotic fluid and oxygenated via its umbilical cord with a pumpless arteriovenous circuit. This project aims to evaluate the lung lesions in preterm lambs incubated in the EXTEND device. In parallel, the effects of the EXTEND incubation on fetal growth will be assessed in a preclinical model of FGR in lamb.

EQUIPMENTS

- **Inverted microscope with fluorescence**
- **Live cell imaging microscope**
- **Normoxia and hypoxia incubators for cell culture**
- **Microfluidic systems**
- **3D bioprinter**

REFERENCES 2021

1. E. Ouni, A. Peaucelle, K. T. Haas, **O. Van Kerk, M. M. Dolmans, C. A. Amorim**, A blueprint of the topology and mechanics of the human ovary for next-generation bioengineering and diagnosis. *Nat. Commun.* 12, 5603 (2021).
2. P. Asiabi, C. David, **A. Camboni**, E. Marbaix, **M. M. Dolmans**, **C. A. Amorim**, New insights into the GDF9-Hedgehog-GLI signaling pathway in human ovaries: from fetus to postmenopause. *J. Assist. Reprod. Genet.* **38**, 1387-1403 (2021).
3. **A. Dadashzadeh, S. Moghassemi**, A. Shavandi, **C. A. Amorim**, A review on biomaterials for ovarian tissue engineering. *Acta Biomater.* **2021S1742-7061**, 00552-3 (2021).
4. **A. Dadashzadeh, S. Moghassemi, C. A. Amorim**, Evaluation of PEGylated fibrin as a three-dimensional biodegradable scaffold for ovarian tissue engineering. *Mater. Today Chem.* **22**, 100626 (2021).
5. H. Jafari, **A. Dadashzadeh, S. Moghassemi**, P. Zahedi, **C. A. Amorim**, A. Shavandi, Ovarian cell encapsulation in an enzymatically crosslinked silk-based hydrogel with tunable mechanical properties. *Gels.* 7, 138 (2021).
6. **M. Kanbar, M. Vermeulen, C. Wyns**, Organoids as tools to investigate the molecular mechanisms of male infertility and its treatments. *Reproduction.* **161**, R103–R112 (2021).

Marie-Madeleine Dolmans
MD, PhD

Christiani Andrade Amorim
VMD, PhD

Christine Wyns
MD, PhD

Pole Contact Person

Marie-Madeleine Dolmans
marie-madeleine.dolmans@uclouvain.be
Tel. 32 (0) 2.764.52.47

Research Projects

Improving ovarian tissue transplantation using adipose tissue-derived stem cells

L. Cacciottola, M-M. Dolmans

In recent decades, anticancer treatments have become increasingly effective, yielding significantly improved survival rates in cancer patients. Nevertheless, young women of reproductive age are at high risk of experiencing chemo/radiotherapy-induced premature ovarian insufficiency and subsequent infertility (1). Among various fertility preservation options, ovarian tissue cryopreservation and subsequent ovarian tissue transplantation have proved both feasible and capable of restoring fertility in young patients.

As ovarian tissue is exposed to ischemic and oxidative stress damage upon grafting, the ovarian follicle pool suffers massive follicle death, losing between 50% and 90% of follicles. Various approaches have been applied to address this issue in experimental models, including administration of proangiogenic growth factors, hormones and antioxidants, with controversial results (2). Our team developed a strategy to optimize the peritoneal grafting site using adipose tissue-derived stem cells, known for their angiogenic potential. Indeed, they were proven to mitigate follicle loss by reducing the hypoxia-related response in early-stage follicles and enhancing availability of proangiogenic growth factors through their secretome for the entire post-transplantation period (3).

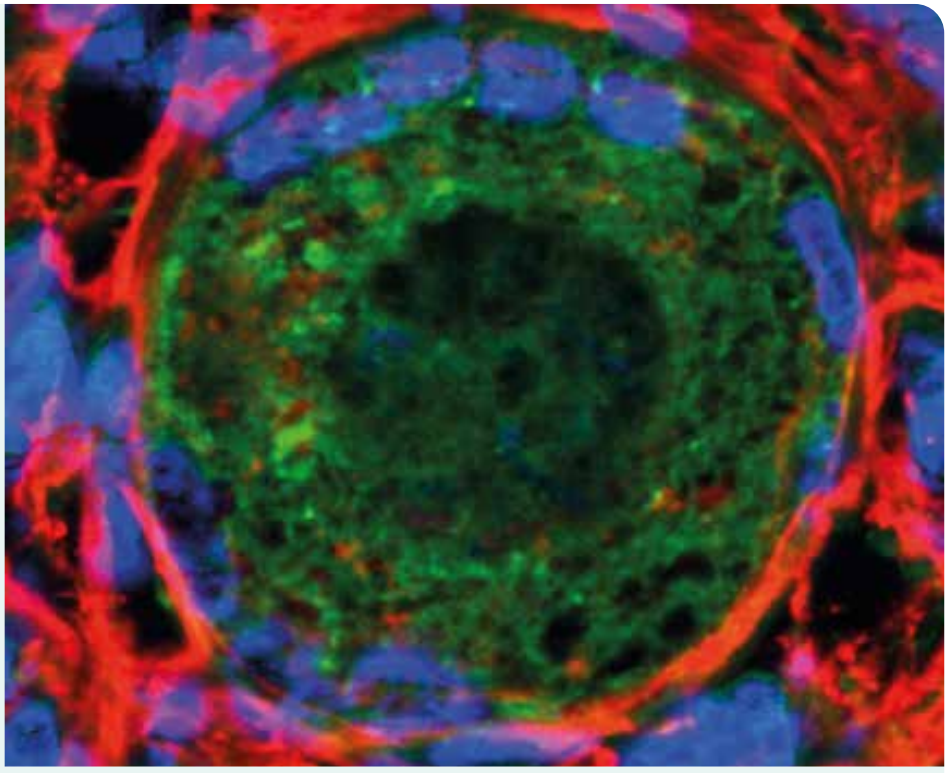


Figure1. FOXO1

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

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

Fertility preservation research in women is increasingly taking advantage of bioengineering techniques to develop new biomimetic materials and solutions to safeguard ovarian cell function and the microenvironment in vitro and in vivo. However, available data on the human ovary are limited. We previously used proteomics before turning to quantitative image analysis to provide a readout of its characteristics. The ovary is among the most dynamic tissues in the human body, undergoing repeated cycles of growth and involution throughout a woman's life. It achieves this plasticity mainly thanks to its extracellular matrix (ECM) components. We investigated quantitative spatiotemporal changes in collagen, elastin, EMILIN-1, fibrillin-1 and 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 (5). Our results revealed ECM deposition and remodeling in an age- and follicle stage-related manner. More precisely, our findings pointed to a more elastic ECM around reproductive-age follicles compared to the less compliant perifollicular ECM of prepubertal tissue. This work may offer a novel molecular basis to develop biomimetic scaffolds tailored to each follicle stage and age, bringing us one step closer to constructing an artificial ovary, or even discovering new mechanisms associating fertility preservation with ECM remodeling.

Developing a 3D matrix for the engineered ovary

A. Dadashzadeh, M.C. Chiti, M.M. Dolmans, C.A. Amorim

To graft isolated follicles, we must encapsulate them in a matrix with a proper balance between rigidity and elasticity to maintain follicle 3D structure, which is vital for its survival while allowing its growth. Recently, we have performed an in-depth study of the human ovarian ECM in order to develop a 3D matrix with similar biomechanical properties. Using our recently acquired knowledge, we are developing PEGylated fibrin hydrogels to match human ovarian ECM biomechanical properties. This matrix has been shown to enhance the survival and proliferation of ovarian cells and lower the degradation rate compared to fibrin (6).

REFERENCES

1. Cacciottola L, Donnez J, Dolmans MM. Ovarian tissue and oocyte cryopreservation prior to iatro-genic premature ovarian insufficiency. **Best Pract Res Clin Obstet Gynaecol**. S1521-6934;00165-6, 2021.
2. Cacciottola L, Donnez J, Dolmans MM. Ovarian tissue damage after grafting: systematic review of strategies to improve follicle outcomes. **Reprod Biomed Online**. 26:S1472-6483;00303-5, 2021.
3. Cacciottola L, Nguyen TYT, Amorim CA, Donnez J, Dolmans MM. Modulating hypoxia and oxidative stress in human xenografts using adipose tissue-derived stem cells. **Fertil Steril Science**. 2:141-152, 2021.
4. Asiabi P, David C, Camboni A, Marbaix E, Dolmans MM, Amorim CA. New insights into the GDF9-Hedgehog-GLI signalling pathway in human ovaries: from fetus to postmenopause. **J Assist Reprod Genet**, 38:1387-1403, 2021.
5. Ouni E, Peaucelle A, Haas KT, Van Kerk O, Dolmans MM, Tuuri T, Otala M, Amorim CA. A blueprint of the topology and mechanics of the human ovary for next-generation bioengineering and diagnosis. **Nat Commun**, 12:5603, 2021.
6. Dadashzadeh A, Moghassemi S, Amorim CA. Evaluation of PEGylated fibrin as a three-dimensional bio-degradable scaffold for ovarian tissue engineering. **Mater Today Chem**, 22:100626, 2021.
7. Kanbar M, Vermeulen M, Wyns C. Organoids as tools to investigate the molecular mechanisms of male infertility and its treatments. **Reproduction** (Cambridge, England), 161(5), R103–R112, 2021.
8. Vermeulen M,. Development of an artificial testis free from neoplastic cells and transplantable to the patient, thesis, **Université Catholique de Louvain** (2020).

VASCULARIZED COMPOSITE TISSUEENGINEERING RESEARCH GROUP (VCE)

Benoît Lengelé, MD, PhD, FRCS, Director

Greet Kerckhofs, PhD

Christophe Beauloye, MD, PhD

David Vancraeynest, MD, PhD

Olivier Cornu, MD, PhD

Thomas Schubert, MD, PhD

Sandrine Horman, PhD

Luc Bertrand, PhD

Chantal Dessy, PhD

Catherine Behets, MD, PhD, MORF Director

Pierre Gianello, MD, PhD, CHEX Director

Pole Contact Person

Benoît Lengelé
Benoit.lengele@uclouvain.be

Researchers:

Guillaume Rougier
Vincent Foulon ***(student)***
Maud Coyette

Post-Doc

Delia Hoffmann

PhD

Louis Maistriaux
Julie Manon
Robin Evrard
Camille Pestiaux
David De Azevedo Coutinho Pereira
Lisa Leyssens

Technicians

Lies Fievé
Walid El Aazmani
Pierre Schneidewind

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.

Vascularized and decellularized bone xenografts: a new model for bioengineered transplantable bone shafts

Guillaume Rougier, Louis Maistriaux, Julie Manon, Robin Evrard, Raphael Olszewski, Fabien Szmytka, Nicolas Thurieau, Jean Boisson, Natacha Kadlub, Pierre Gianello, Catherine Behets, Benoit Lengele

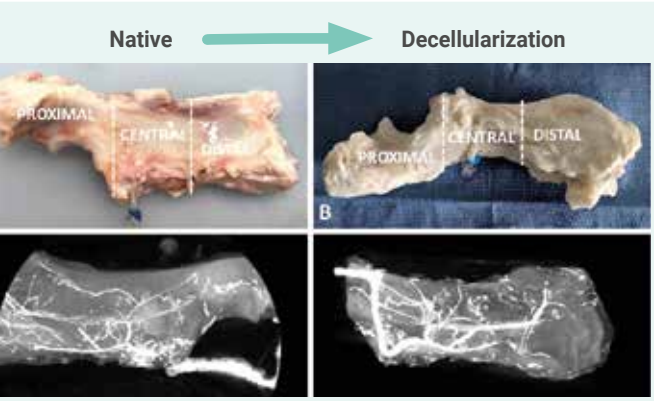
BACKGROUND: Durable reconstruction of critical bone defects still remains a surgical challenge despite the many bone autologous and substitute options available. In this study, we investigate, as a new alternative, the possibility to create a living bone allograft, based on the perfusion/decellularization/recellularization (PDR) technique, applied to the original model of porcine vascularized bone grafts.

MATERIAL AND METHODS: Eleven porcine bone forelimbs including the radius and the ulna were harvested with their vasculature based on the interosseous artery and decellularized following a sequential detergent perfusion protocol. Cellular clearance, vasculature and ECM preservation, biomechanical properties, cytocompatibility and in vitro osteoinductive potential for later in vivo reimplantation were extensively studied in both native and decellularized grafts.

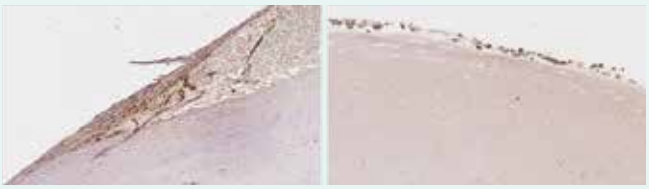
RESULTS: Decellularization was successful for all grafts with an excellent preservation of the 3D morphology and ECM microarchitecture. DNA and ECM proteins measurements revealed the complete cellular clearance and preservation of major proteins. Density acquisitions revealed a slight decrease of density whereas biomechanical testing was unmodified. CBCT confirmed the preservation of the vascular network throughout the whole graft. The noncytotoxicity was shown by the very low amount of residual SDS present in the ECM and also confirmed by the high live/dead ratio of fibroblasts seeded on periosteum and bone ECM grafts after 3, 7 and 16 days of culture. Moreover, proliferation tests showed a significant increase of seeded cells population at the same stages. Finally, the differentiation study confirmed the potential of the ECM grafts to promote osteogenic differentiation with osteoidlike deposition occurring in both groups of AMSCs cultured on bone ECM in proliferative or osteogenic differentiation mediums.

TOP: Macroscopic and angiographic aspects of native and decellularized pig ulna. Bottom: Immunohistochemistry highlighting osteocalcin in cultures of AMSCs on decellularized bone matrix.

CONCLUSION: Fully vascularized decellularized bone transplants can be obtained by perfusion/decellularization, with preservation of the ECM architecture and of their vascular network while promoting cells' growth and differentiation. These decellularized bone shafts xenografts thus present a true potential for future in vivo reimplantation. Thereby, they may offer new perspectives for large bone defects repair and bone tissue engineering.



Bone regeneration - AMSCs Osteocalcin IHC



Differentiation medium – D22 *Proliferation medium – D22*

Periosteum and Fascia lata: Are they so different?

Julie Manon, Robin Evrard, Louis Maistriaux, Ugo Heller, Jean Boisson, Natacha Kadlub, Thomas Schubert, Benoît Lengelé, Catherine Behets, Olivier Cornu

Human fascia lata (HFL) is largely used in reconstructive surgery in other indications than fracture repair. The goal of this study is to compare microscopic, molecular and mechanical properties of HFL and periosteum (HP) in a bone tissue engineering perspective.

Cadaveric HP and HFL (n=4) morphology was characterized with histology and immunohistochemistry (IHC). The extra-cellular matrix (ECM) ultrastructure was assessed by scanning electron microscopy (S.E.M.). DNA, collagen, elastin, glycosaminoglycans (GAGs) and MHC-1 contents were quantified. HP (n=6) and HFL (n=11) were submitted to stretch tests.

Histology and IHC highlighted similarities (type I collagen fibers, 2 layers organization) but also differences (fiber thickness and compaction) between both tissues, as confirmed with S.E.M. The content of collagen was statistically higher in HFL than HP (735 vs 160.2µg/mg dry weight respectively, $p<0.0001$). On the contrary, DNA content was lower in HFL than HP (404.75 vs 1102.2µg/mg dry weight, respectively, $p=0.0032$) and HFL is statistically less immunogenic ($p=0.0033$). HFL supported a significantly higher tension stress than HP.

In summary, HP and HFL present morphological differences despite similar molecular ECM components. HFL stronger stretching resistance can specifically be explained by its higher content of collagen. However, HFL contains much lesser numerous cells and is less immunogenic than HP, which is very rich in periosteal stem cells. Consequently, HFL can be suitable to replace HP architecture to confer a guide for bone consolidation but osteogenicity remains absent. This study could pave the way toward a bio-engineered periosteum built from HFL.

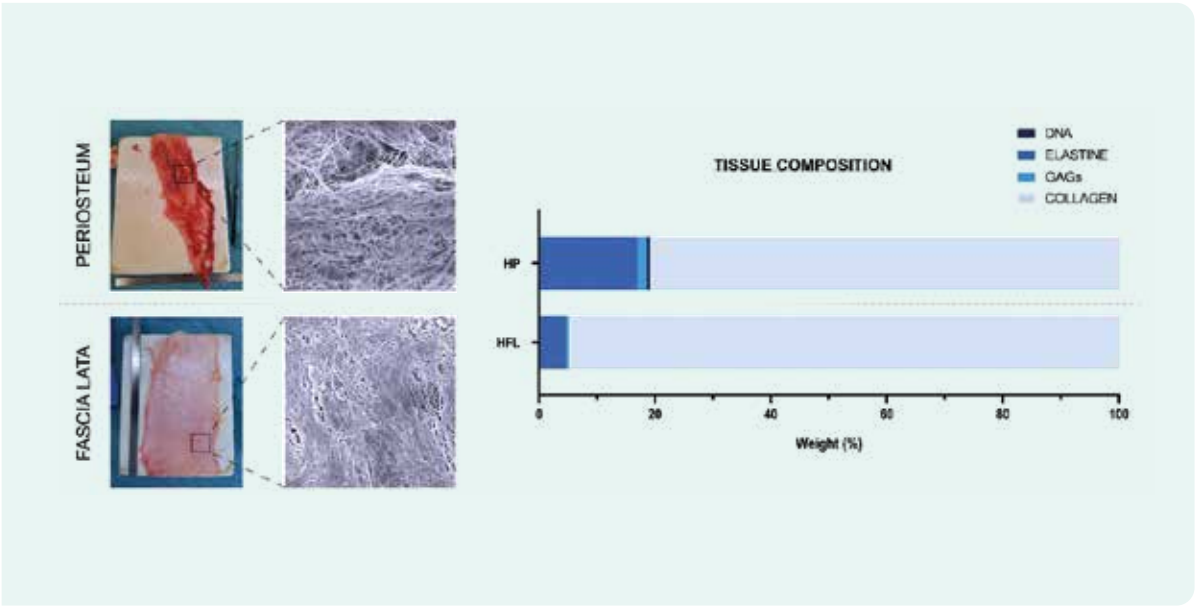
Creation of bioengineered vascularized spleen matrix as an endocrine cell support

Louis Maistriaux, Pierre Gianello, Benoît Lengelé

Diabetes is currently treated by insulin injection. Its best cure, pancreas transplantation, is limited by donor shortage and side effects of immunosuppressive treatment. We hypothesized to overcome these limits using tissue engineering to create a decellularized spleen matrix (DSM) which would be recellularized with pancreatic cells in order to regenerate a functional and biocompatible transplant.

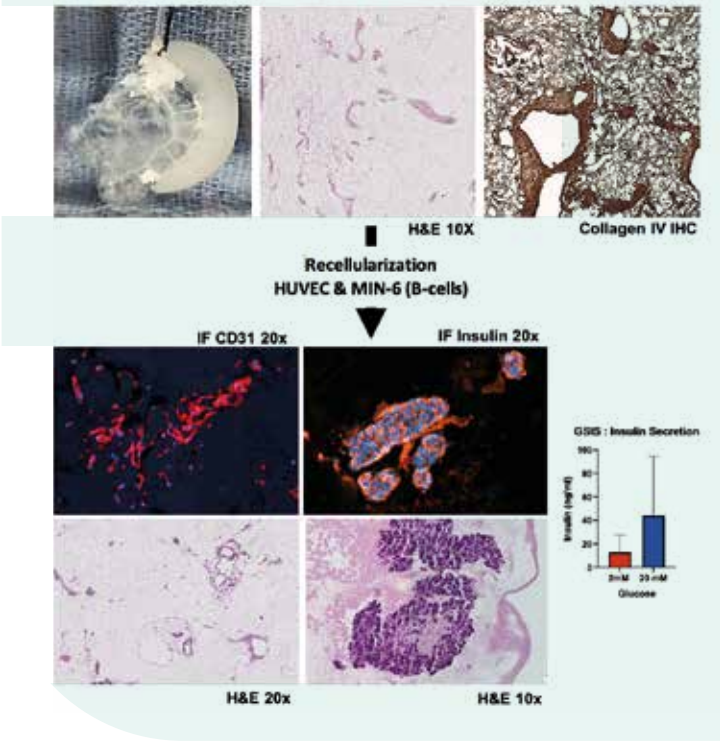
Rat spleen grafts were decellularized with detergent perfusion in their pedicle. DSM was characterized by DNA, collagen, elastin, GAG and residual SDS quantification, as well as histology and immunohistochemistry. PrestoBlue Cell Viability Assay evaluated cytotoxicity in 12 days static culture of MIN-6 cells seeded on DSM patches. Biocompatibility was analyzed after subcutaneous implantation of DSM or native tissue in rats (?). Infiltration of CD68 and CD3 cells was assessed by IHC at 14 & 30 days. Finally, whole DSM were recellularized with HUVECs and MIN-6 cells and cultured in a perfusion bioreactor for 5 days. MIN-6 function was evaluated with Glucose-stimulated insulin secretion test.

Spleen decellularization with 3D architecture preservation was attested by its white aspect, 99% reduction of DNA amount and histology. IHC and protein assays confirmed preservation of collagens I, IV, fibronectin and laminin. The low amount of SDS residues (<1%) and the unchanged cell viability assessed the non-toxicity of the DSM. Biocompatibility was confirmed by a lesser infiltration of CD68 cells in DSM than in native tissue. DSM cultured in bioreactor allowed HUVECs engraftment to the vascular wall and formation of MIN-6 cells clusters into the DSM while preserving their insulin release during a perfused GSIS.



In conclusion, DSM can be obtained by perfusion decellularization while retaining its macro- and microarchitecture, ECM components with a good biocompatibility and without cytotoxicity. Moreover, DSM could be a potential vascularized scaffold for pancreatic regeneration.

Top: Macroscopic, histological and immunohistochemical (Collagen I) aspects of decellularized spleen. Bottom: Recellularization of spleen matrix with HUVEC (left) and MIN-6 (right) and insulin secretion tested with 2mM and 20mM glucose.

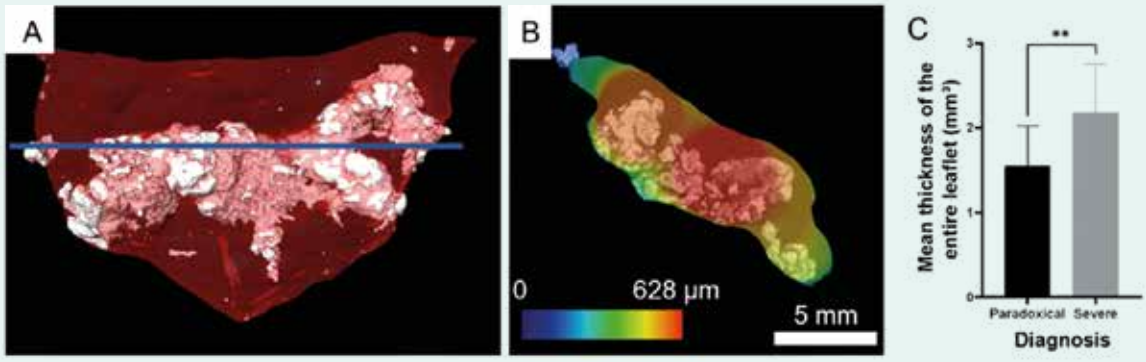


X-ray microfocus computed tomography (microCT)- and contrast-enhanced microCT (CECT)-based characterization of heart valves

Camille Pestiaux, Greet Kerckhofs, Christophe Beauloye, Benoît Lengelé

Ex vivo microCT is known to provide a good visualization of mineralized tissues. This imaging technique was applied without contrast enhancement to obtain a quantitative characterization of calcified aortic valves from human patients. The work was initiated in the frame of a master thesis at the Polytechnical School of Louvain-la-Neuve and demonstrated the added value of ex vivo microCT at much higher spatial resolution compared to in vivo imaging (Fig. 1). The samples were scanned and analysis is ongoing with the goal to submit the results in an international journal in 2022.

MicroCT analysis of fresh human aortic valves explanted for heart valve replacement. A: 3D rendering with soft tissues in red and calcifications in white; B: ortho slice at the level of the blue line in (A), superimposed with the thickness analysis of the leaflet; C: bar graph showing the significant difference of the mean thickness of the leaflet between paradoxical and severe stenosis; **: p-value < 0.01



Reconstruction of Nipple-Areola Complex by tissue engineering approach

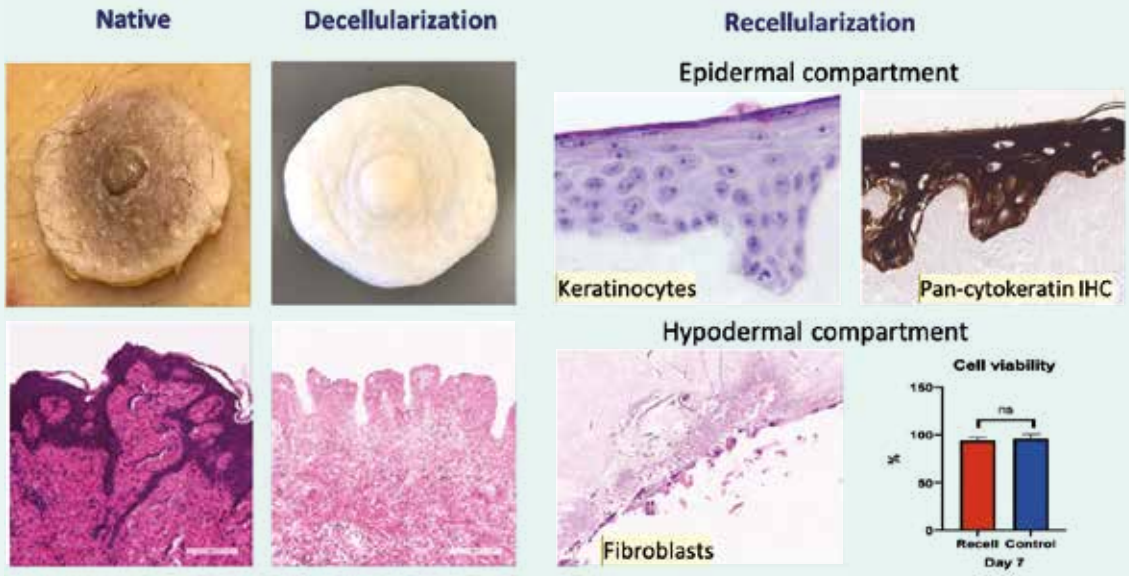
Louis Maistriaux, Vincent Foulon, Maud Coyette, Catherine Behets, Pierre Gianello, Yves Poumay, Benoît Lengelé

Nipple-Areola Complex (NAC) reconstruction remains a challenge in case of mastectomy since it does not reach the same optimal result as breast reconstruction. Tissue engineering could allow to preserve NAC specific 3D morphology by decellularization and re-epithelialization, followed by implantation during surgical breast reconstruction.

Cadaveric NAC were decellularized with detergent solutions (sodium dodecylsulfate – SDS). Cell clearance and extracellular matrix preservation were assessed by histology, immunohistochemistry and quantification of DNA, matrix proteins and growth factors, as well as residual SDS. Cytocompatibility was analyzed by seeding of fibroblasts and keratinocytes on hypodermic and epidermic sides, respectively (« Reconstructed Human Epidermis » technique - RHE).

Decellularized NAC appears white and keeps its particular 3D morphology. Decellularization is attested by DNA concentration <50ng/mg and absence of cells in histological sections. Histology also highlights preservation of microarchitecture, particularly with collagen I and IV, fibronectin and laminin immunohistochemistry. Collagen content is increased, whereas that of glycosaminoglycans, elastin and growth factors is decreased. Residual SDS content is very low. In vitro, fibroblast viability is similar to control cells. With RHE technique, a stratified keratinized epidermis is observed after 7 days of culture with aerial interface.

In summary, decellularized NACs keep their specific microarchitecture and their matrix proteins as well as their cell growth potential and ability to regenerate epidermis



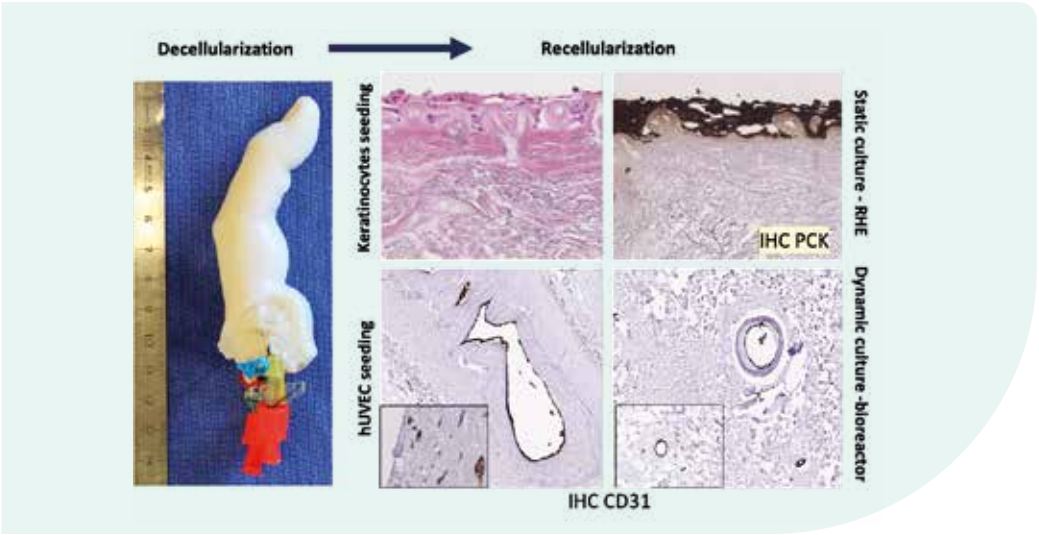
Left: Macroscopic and histological aspect of native and decellularized nipple-areolar complex (NAC). Right: Histological aspect of recellularized NAC matrix with keratinocytes on epidermal side (top) and fibroblasts on hypodermal side (bottom).

Vascularized Composite Tissue Engineering of the Human Hand: A Finger Subunit Approach

Project team: Louis Maistriaux, Donovan Debluts, Jérôme Duisit, Benoit Herman, Emmanuel Coche, Giuseppe Orlando, Yves Poumay, Pierre Gianello, Benoît Lengelé

Life-long immunosuppression risks and frequent chronic rejection are the main factors limiting a wider clinical adoption of hand transplantation. Perfusion-Decellularization-Recellularization strategy (PDR) allows to create acellular vascularized extracellular matrix (ECM) and had as aim, to recellularize with patient's cells to create immunocompatible, functional and transplantable grafts. As low tissular volume and non-vital tissue, the finger subunit seems to be an ideal model for vascular composite allotransplantation (VCA) experimental research and for an earlier clinical application due to the few comorbidities in case of explanation of a bioengineered finger. In the present study, we applied the PDR to human fingers and whole hands and evaluated their cell clearance, ECM preservation and cell compatibility after static or perfusion seeding. In a clinical perspective, decellularized graft vasculature was challenged in vivo by temporary revascularization on a porcine vascular shunt. PDR successfully created ECM scaffold from fresh human deceased donors demonstrating complete cell and immunogenic clearance associated to an efficient scaffold recellularization on static samples and then in a finger perfusion bioreactor, after selective seeding of keratinocytes, fibroblasts, and endothelial cells in the appropriate tissue compartments. Maintenance of extrinsic finger function, graft sterility and vascular integrity by a robust vascular patency and oxygen saturation following in vivo reperfusion were also emphasized. As a matter of fact, this vascularized composite tissue engineering (VCE) technology could be considered as a further potential alternative to VCA for the repair of disabling hand tissue defects.

Recellularization of decellularized finger matrix with keratinocytes and HUVEC. Pan-cytokeratin is highlighted in seeded keratinocytes. CD31 is expressed by seeded HUVEC.



REFERENCES 2022

Manon, Julie ; Evrard, Robin ; Maistriaux, Louis ; Fievé, Lies ; Heller, Ugo ; Magnin, Delphine ; Boisson, Jean ; Kadlub, Natacha ; Schubert, Thomas ; Lengelé, Benoît ; Behets Wydemans, Catherine ; Cornu, Olivier. Periosteum and fascia lata: Are they so different?. In: Frontiers in bioengineering and biotechnology, Vol. 10, p. 944828 [1-16] (2022). doi:10.3389/fbioe.2022.944828.

Maes, Arne ; Pestiaux, Camille ; Marino, Alice ; Balcaen, Tim ; Leyssens, Lisa ; Vangrunderbeeck, Sarah ; Pyka, Grzegorz ; De Borggraeve, Wim M. ; Bertrand, Luc ; Beauloye, Christophe ; Horman, Sandrine ; Wevers, Martine ; Kerckhofs, Greet. Cryogenic contrast-enhanced microCT enables nondestructive 3D quantitative histopathology of soft biological tissues. In: Nature Communications, Vol. 13, no.1, p. - (2022). doi:10.1038/s41467-022-34048-4.

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 Pole of Pediatrics (PEDI), the Pole of Hepato-Gastroenterology (GAEN), and the team of Pierre Gianello at the Pole of experimental surgery (CHEX) focus on the mechanisms of action of hormones, their therapeutic use in human diseases, the causes and consequences of obesity, diabetes mellitus and other metabolic dieases 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 re-spect to luctuating microenvironmental conditions (e.g., hypoxia, uneven bioavailability of nutrients, exposure to therapy and acidosis), tumor progression to metastasis, cancer-host cells relationships and resistance to treat-ments. Most research programs include translational aspects, with the aim of identifying new anticancer ap-proaches 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 atro-phy and to develop new biomarkers for its diagnosis.

The central role of metabolism in human diseases, in-cluding cancer, and the ever-growing prevalence of obe-sity 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 (IREC) and Patrice Cani from the Louvain Drug Research 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.

Thematic Group Contact Person

Jean-Christophe Jonas, MD, PhD
jean-christophe.jonas@uclouvain.be

POLE OF ENDOCRINOLOGY, DIABETES AND NUTRITION (EDIN)

Jean-Christophe Jonas, MD, PhD

Sonia Brichard, MD, PhD

Patrick Gilon, PhD

Jean-Paul Thissen, MD, PhD

Damien Gruson, Pharm D., EuSpLM, PhD

Etienne Delgrange, MD, PhD.

Orsalia Alexopoulou, MD, PhD

Pole Contact Person

Jean-Christophe Jonas, MD, PhD
jean-christophe.jonas@uclouvain.be

Clinical Researchers:
C Burlacu, V Cardone, E Delgrange, Z Denamur, R Furnica, M Hermans, C Jonas, A Loumaye, D Maiter, V Preumont, P Rousseau

Post-Docs :
M Abou-Samra, A de Souza, HY Chae, E Gatineau, R Versèle, A Dereli

PhD Students:
F Butaye, SM Constantinescu, N Dubuisson, Y Hajj Hassan, F Khattab, I Massart, Y Murdasov, L Orioli, L Ruiz, C Selvais, B Singh, M Parambath

Technicians:
M de Barsy, F Belhaj Aïssa, C Despontin, D Dias Fernandes, F Knockaert, P Lause, L Noël

POLE OF PEDIATRICS (PEDI)

Etienne Sokal, MD, PhD
Head of the Unit

Philippe Lysy, MD, PhD

Mustapha Najimi, PhD

Isabelle Scheers, MD, PhD

Françoise Smets, MD, PhD

Xavier Stéphenne, MD, PhD

Dimitri Van der Linden, MD, PhD

Members:

Ananya Ajith, PhD student, *Grégory De Bodt*, MD, PhD student, *Jonathan Evraerts,* Research assistant, *Antoine Harvengt,* MD, PhD student, *Giulia Jannone*, MD, PhD student, *Olivier Polle, MD,* PhD student, *Joachim Ravau,* Research assistant, *Marie-Astrid Van Dievoet,* MD, PhD student, *Ilse van Elewijck,* Personal assistant, *Brieuc Van Nieuwenhuyse,* MD, PhD student, *Julia Versavau*, CRA, *Sandrine Lambert*, CRA *Manel Jallouli*, CRA, *Sophie Welsch*, PhD student

Pole Contact Person

Etienne Sokal, MD, PhD
etienne.sokal@uclouvain.be

POLE OF EXPERIMENTAL SURGERY (CHEX)

Pierre Gianello, MD, PhD

Post-Doc:
N Mourad

PhD Student:
M Ramirez

Technicians:
M Vergauwen, D Xhema, G Beaurin

Pole Contact Person

Pierre Gianello, MD, PhD
pierre.gianello@uclouvain.be

POLE OF HEPATO-GASTROENTEROLOGY (GAEN)

Isabelle Leclercq, MD, PhD

Peter Stärkel, MD, PhD

Nicolas Lanthier, MD, PhD

Ivan Borbath, MD, PhD

Yves Horsmans, MD, PhD

Alexandra Dili, MD, PhD

Researchers and Technicians

Post-doctoral Researchers :
Gérladine Dahlqvist, MD PhD, *Rita Manco,* MSc PhD *Justine Lallement* MSc PhD

PhD student :
Maxime Nachit, MD, *Luca Maccioni, Justine Gillard, Camille Pichon, Sebastian Bott, Maxime De Rudder, Arthur de Schaetzen, Laurent Coubeau* (MD), *Ami Toulehohoun, Guillaume Henin* (MD), *Sandra Calvo-Blanco, Yifan Hu,*

Technicians :
Natacha Feza Bingi, Mathilde Beka, Simon Ravau, Corinne Picalausa

Pole Contact Person

Isabelle Leclercq, MD, PhD
isabelle.leclercq@uclouvain.be

POLE OF PHARMACOLOGY AND THERAPEUTICS (FATH)

Cyril Corbet, PhD

Olivier Feron, PhD

Pierre Sonveaux, PhD

Post-Docs:

E Bastien, N Trempolec, T de Miranda Capeloa, Z Benyahia, M Liberelle, M Vara Messler

PhD:

J Santiago, C Vander Linden, E Dierge, M Blackman, L Zampieri, A Colson, J Van de Velde, C Brustenga, P Savoyen, M Shahin, J Rondeau, B Matthieu, E Richiardone, V Van den Bossche, F Derouane, J Vignau

Technicians:

E Vandenhooft, C Guilbaud, L Petit, A Canevat, T Vazeille, L Hamelin, M Bedin

Pole Contact Person

Olivier Feron, PhD
olivier.feron@uclouvain.be
https://uclouvain.be/fr/instituts-recherche/irec/fath

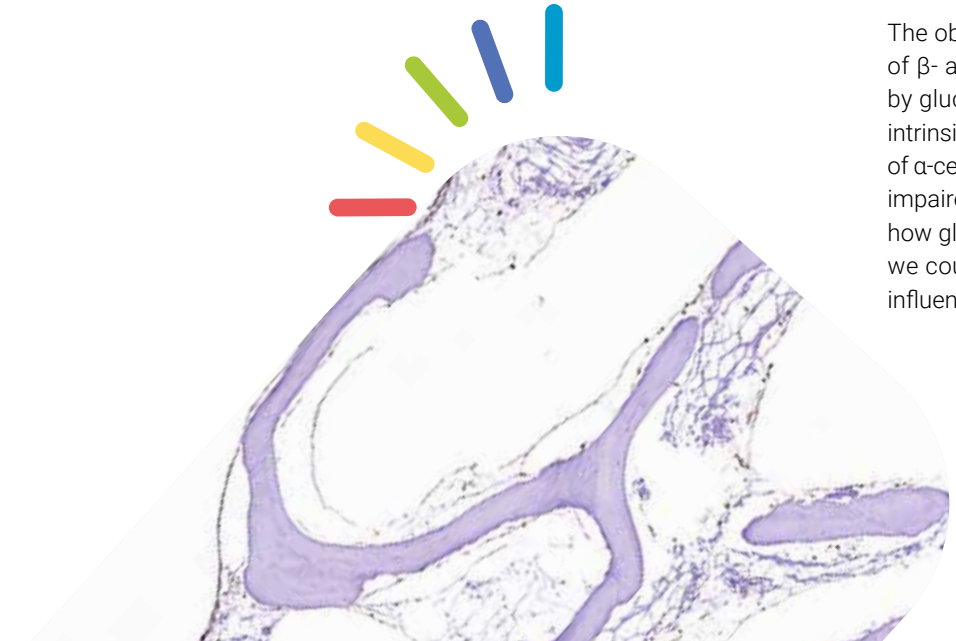
Research Projects

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.



Role 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, 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).

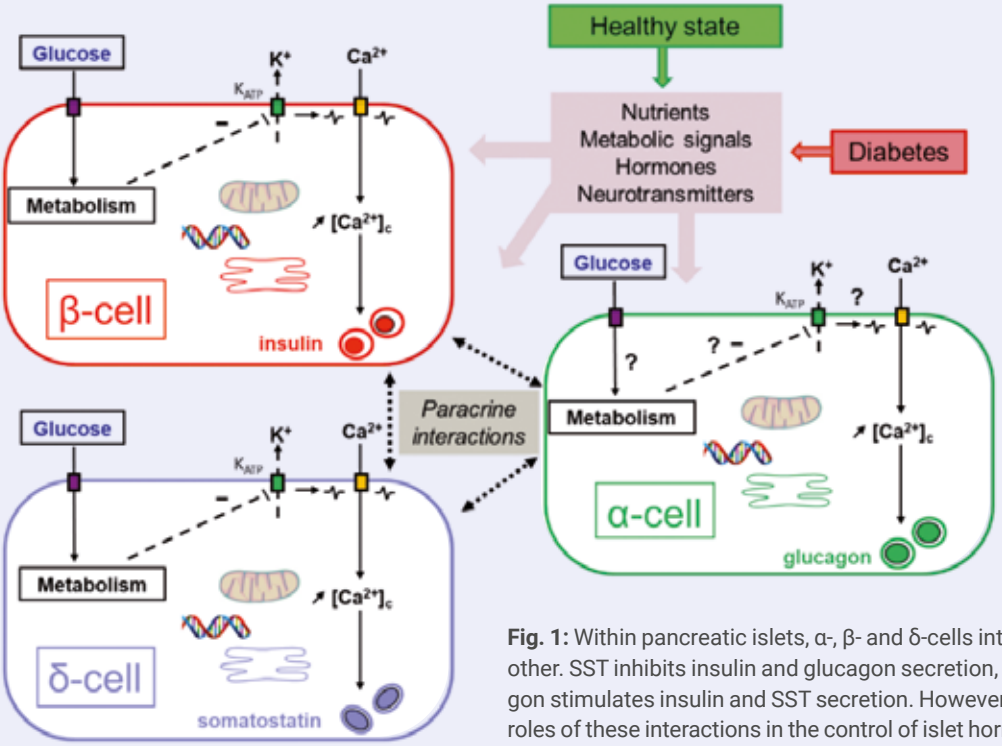


Fig. 1: Within pancreatic islets, α-, β- and δ-cells interact with each other. SST inhibits insulin and glucagon secretion, whereas glucagon stimulates insulin and SST secretion. However, the respective roles of these interactions in the control of islet hormone secretion by nutrients is only partly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

Control of the subcellular redox state in pancreatic β-cells

Y Hajj Hassan, JC Jonas

We use protein-based fluorescent redox probes target-ed 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 (Fig. 2).

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

HY Chae, P Gilon, Y Hajj Hassan, JC Jonas, 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 and test the effect of antidiabetic drugs to improve their treatment.

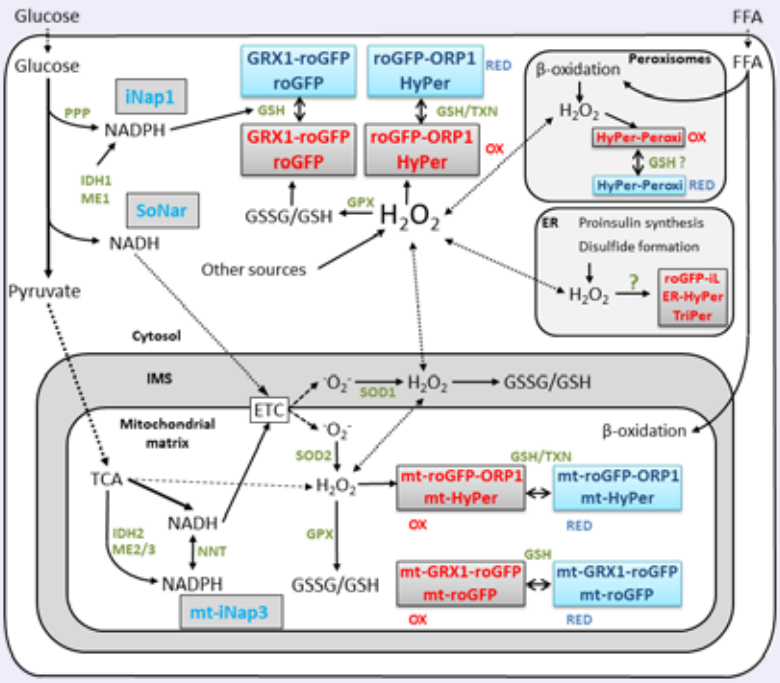


Fig. 2: Compartmentalized redox reactions and the genetically encoded probes used to measure the impact of nutrient metabolism on β-cell subcellular redox state. Schematic representation of the pathways by which nutrients affect NADH, NADPH, and GSH. Enzymes are shown in green, oxidized (OX) probes in red font, and reduced (RED) probes in blue font. Probes measuring NADPH and the NADH/NAD+ ratio are in light 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.

Prolonged culture of human pancreatic islets under glucotoxic conditions changes their acute beta cell calcium and insulin secretion glucose response curves from sigmoid to bell-shaped

M Tariq, AH de Souza, M Bensellam, H Chae, AF Close, JP Deglasse, LRB Santos, A Buemi, NI Mourad, P Gilon, JC Jonas

Over the last 10 years, we investigated how prolonged culture at normal, intermediate and high glucose con-cen-trations affect glucose-induced insulin secretion and up-stream coupling events in human pancreatic islets isolated from non-diabetic and type 2 diabetic cadaveric donors. Our results confirm the large increase in glucose sensitiv-ity of glucotoxicity exposed islets and reveal a bell-shaped acute glucose response curve for changes in $[Ca^{2+}]_c$ and insulin secretion, with maximal stimulation at 5 or 10 mmol/l glucose and rapid inhibition above that con-centration. This novel glucotoxic alteration may contribute to beta cell dysfunction in type 2 diabetes independently from a detectable increase in beta cell apoptosis (Fig. 3).

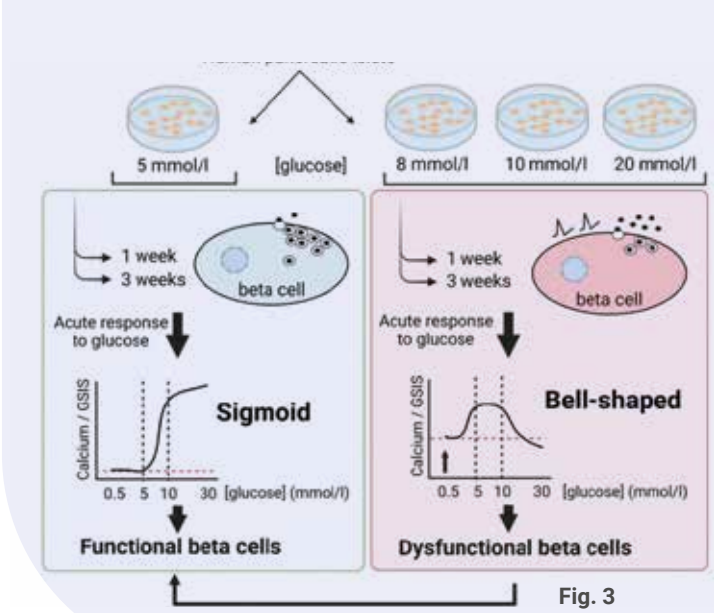


Fig. 3

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

Porcine islets have notoriously low insulin secretion levels in response to glucose stimulation. While this is somehow expected in the case of immature islets iso-lated from fetal and neonatal pigs, disappointingly low secretory responses are frequently reported in studies using in vitro-maturated fetal and neonatal islets and even fully-differentiated adult islets. This project aims to improve the secretory function of porcine islets by means of beta-cell specific expression of a modified glucagon-like peptide 1 (GLP-1) and of a constitutively activated type 3 muscarinic receptor (M3R) to amplify glucose-stimulated insulin secretion (GSIS)."

PATHOGENESIS OF LIVER DISEASES

The study of metabolic dysfunction-associated fatty liver disease (MAFLD) and its progression to non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis

I Leclercq, N Lanthier, J Gillard, M Nachit, C Pichon, S Bott, G Henin, S Calvo-Blanco, G Dahlqvist, C Picalausa, N Feza-Bingi, M Beka, S Ravau

The study of MAFLD is divided in three main projects.

(1) Bile acids (BA), gut microbiota and NASH.

The alterations of the enterohepatic BA composition and signaling were shown to contribute to the devel-opment of NASH in preclinical models. Experimental modulation of the BA composition restored perturbed activation of BA receptors FXR and TGR5, and prevented NASH and associated metabolic disorders. Changes in the microbiota and its metabolic functions do ot explain the modification in the bile acid pool size and composition. howver, our data support the operation of an up to then unsuspected biotransfor-mation of bile acids within the liver. If verified, this enzymatic step could be manipulated for anti-NASH therapeutic purposes.

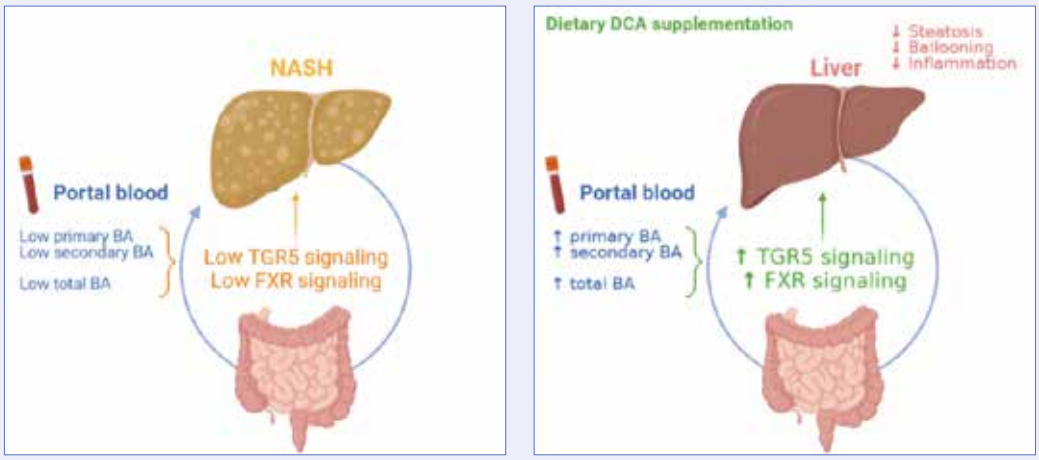


Fig. 4: BA contribute to the development of NASH in mice. In foz/foz mice fed a high fat diet and in C57BL6/J mice fed a western and high fructose diet, the enterohepatic BA composition and signaling are altered compared to their respective controls. Supplementation of the diet with deoxycholic acid (DCA, a secondary BA) restored the BA alterations and prevented NASH.

(2) Crosstalk between muscles and MAFLD.

MAFLD severity was shown to strongly associate with skeletal muscle steatosis in several preclinical models, suggesting myosteatosis as a possible non-invasive marker of NASH. The mechanisms linking liver disease and muscle changes including ammonia metabolism, which is impaired in our preclinical models of NASH, are under investigation.

In humans, our clinical data show that the amount of intramuscular fat assessed on an abdominal CT scan is significantly higher in patients with more severe MAFLD (higher liver elasticity measured by elastometry). On multivariate analysis, myosteatosis is the strongest predictor of high liver elasticity. The study still goes on to better understand muscle changes in relation to MAFLD and if and how physical exercise may interfere with liver disease progression.

we also study the relationship between the changes in the muscle compartment in patients with end-stage liver disease with the prognosis for the patient and whether liver transplantation reverses muscle alteratiosn and alters the prognostic relationship.

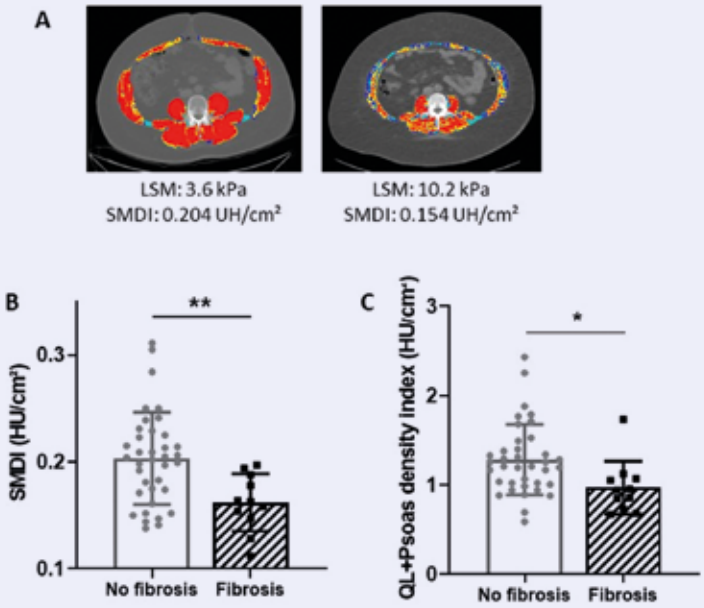


Fig. 5: Analysis of body composition by CT scan according to liver disease severity assessed by elastometry (LSM). (A) Comparison of two patients with MAFLD and obesity: on the left, normal muscle density (muscles in red) and absence of fibrosis at liver elasticity; on the right, low muscle density (muscles in red, yellow and blue) associated with high liver elasticity (fibrosis).(B) Skeletal muscle density index (SMDI) is presented for all abdominal muscles or specifically for the quadratus lumborum and the psoas (C). It is significantly lower for patients with severe MAFLD (with fibrosis) compared to patients with mild MAFLD (without fibrosis).

(3) Cardiovascular diseases (CVD) and MAFLD.

Our analyses of the cardiovascular system in foz/foz mice with NASH indicate the development of adverse cardiac remodeling, the presence of endothelial dysfunction and a reduced bioavailability of nitric oxide. We are now investigating possible as a mechanistic links between CVD and MAFLD.

Alterations of the gut-brain-liver axis in alcohol use disorder (AUD): contribution to liver disease progression

P Stärkel, N Lanthier, L Maccioni, A Toulehohoun, Y Hu

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

We show that changes in the gut microbiome and mycobiome are involved in the development of ALD. In particular, specific bacteria, fungi and products released by those microbes could play an important role in initiating and/ or perpetuating ALD. 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. We revealed that gut T resident memory cells undergo apoptosis driven by lysosomal alterations leading to immune dysfunction and exhaustion especially in alcohol use disorder patients with progressive forms of ALD. We are currently setting up an ex vivo model based on enteroids derived from small intestinal stem cells of AUD patients to study interactions of immune and intestinal epithelial cells in response to alcohol, bacterial products and metabolites.

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

I Leclercq, R Manco, N Lanthier, M De Rudder,N Feza-Bingi

We demonstrated that in chronic liver disease proliferative cholangiocytes – also called Ductular Reaction cells (DR) – proliferate and differentiate into bona fide hepatocytes. We are now working on deciphering the niche around the DR and unravelling the molecular mechanisms that drive this DR-to-hepatocytes differentiation.

Promoting optimal regeneration after extended hepatectomy

I Leclercq, A Dili, R Manco, L Coubeau, M De Rudder, A de Schaetzen,

Liver resection is the only curative treatment for liver tumors. We previously demonstrated that hypoxia after an extended hepatectomy protects against the "Small For Size Syndrome" (SFSS), a complication of big liver resection, and increases survival in rats. We now show, in mouse, that hypoxia after a SFSS-setting hepatectomy induces an early proliferation of liver sinusoidal endothelial cells (LSEC), increasing their density in the regenerating liver. Moreover, hypoxia ensured a proper lobular perfusion and avoid sinusoidal leakiness. Altogether, the function of the liver remnant was increased compared to mice in normoxia, even though hepatocyte proliferation was reduced. Using a transgenic mouse model tracking the native LSEC, we are now investigating the implication of an endothelial progenitor cell, capable of reconstructing the vascular network and their potential influence on liver function, zonation and hepatocyte proliferation. Clinical studies are ongoing to define early biomarkers for post operative liver failure and procedures to control the function in a small for size liver.

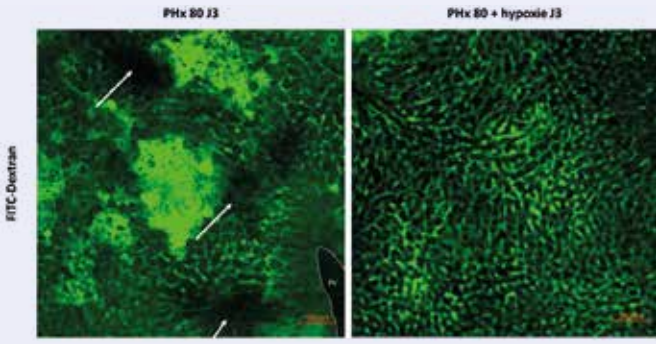


Fig. 5: Hypoxia prevents the appearance of unperfused areas and vascular leaks in the remaining liver parenchyma after small for size hepatectomy . Representative images of liver remnants perfused with FITC-Dextran (green) through the inferior vena cava in normoxia (left panel) and hypoxia (right panel). Arrows highlight non-perfused areas and bright green areas represent sinusoidal leaks of FITC-Dextran.

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

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

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

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 muscle diseases and disorders

S.M. Brichard, M. Abou-Samra, R. Versèle, C. Selvais, N. Dubuisson, and L. Noel

The team of S. Brichard is mainly involved in the study of hormone called Adiponectin (ApN), known to exert powerful and beneficial pleiotropic effects on a variety of tissues and organs, with a particular focus on muscle. They recently demonstrated that activation of ApN receptor is potent to delay and/or counteract the progression of a severe degenerative muscle disease, Duchenne muscular dystrophy (DMD). Adiponectin receptor agonists are now also tested in metabolically challenged and aged-diseased muscles. A very recent publication from their group shows that ApN mimics could greatly protect against the severe metabolic and degenerative effects of caloric excess in obese middle-aged mice, thereby promoting 'healthy ageing' (Fig.6.).

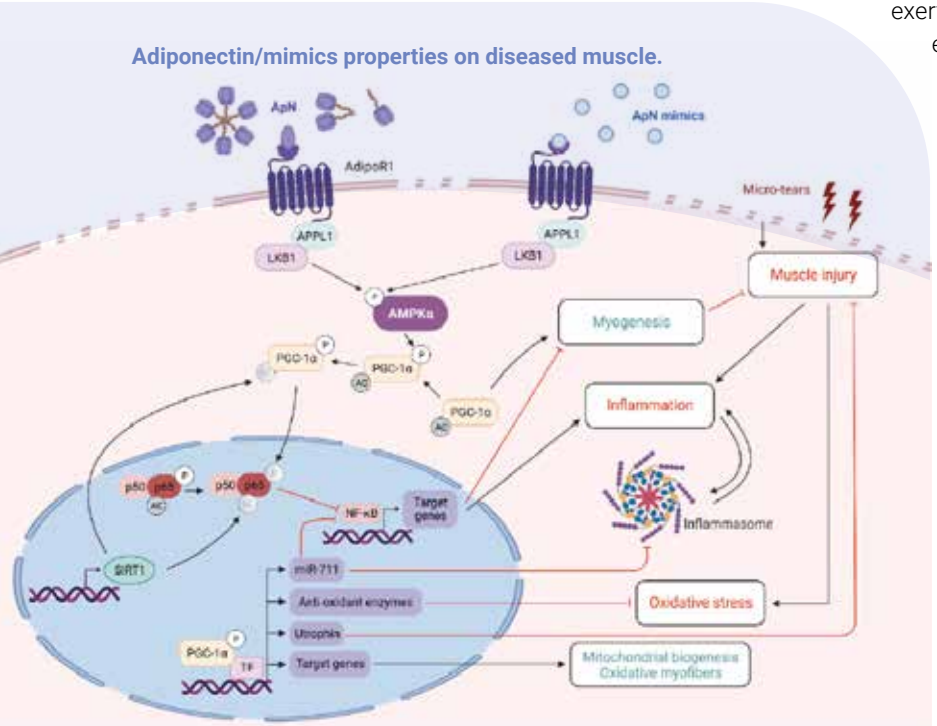


Fig. 6: Signal transduction mediating Adiponectin (ApN) and ApN mimics protection on the dystrophic skeletal muscle: binding to AdipoR1 activates the AMPK/SIRT1/PGC-1α pathway. Briefly, ApN (mimic) leads to AMPK phosphorylation/activation. P-AMPK then phosphorylates PGC-1α and indirectly increases the 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 inflammasome, inflammation and oxidative stress. In addition, activation of the AMPK pathway leads to an improved myogenic program, a better oxidative capacity and more resistant fiber phenotype. All these processes help rescue the dystrophic phenotype. Additionally, in aged mice, ApN mimic, through improved mitochondria function and enhanced AMP-mediated autophagy, reverses myosteatosis, sarcopenia and increases endurance. Pointed-head black arrows indicate activation or induction, while blunted-head red arrows indicate inhibition. Dashed and blurred circle represents removal of the indicated residue. Boxes with processes in green represent net beneficial effects of ApN (mimic), while boxes with processes in red represent deleterious factors inhibited by ApN (mimic).

CANCER AND METABOLISM

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

JP Thissen, A Loumaye, I Massart, 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. Focus is now oriented toward the role of inflammation in the development of cachexia.

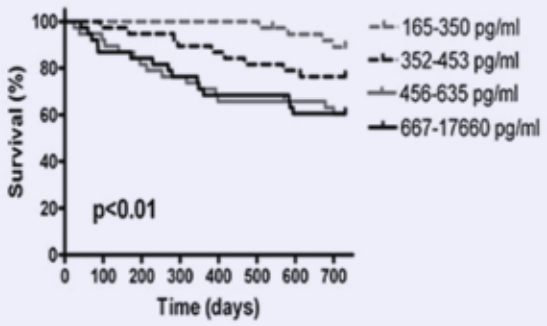


Fig. 7: Kaplan–Meier survival curves according to plasma Activin A levels [quartiles and cut-off statistically determinated (408 pg/mL)] in colorectal or lung cancer patients (n=152).

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

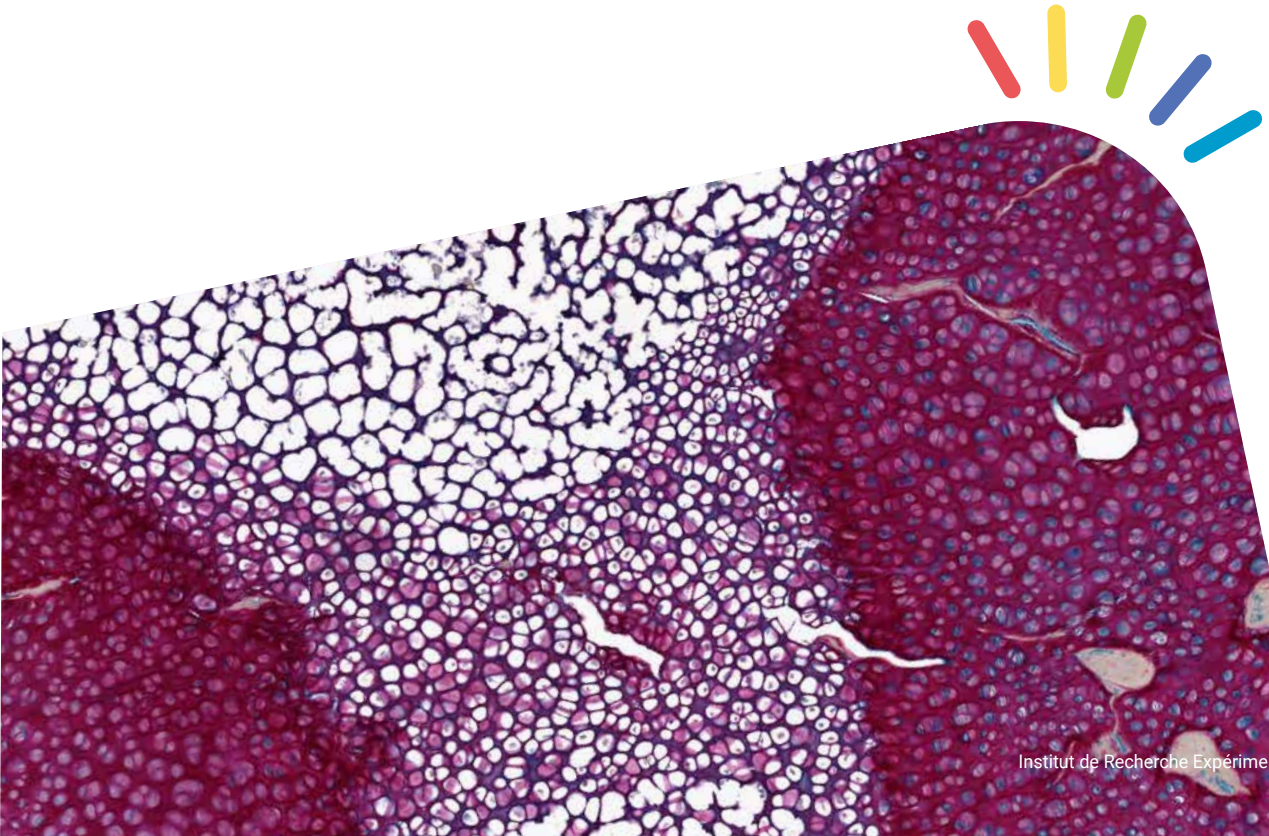
O. Feron

The main research topic in the group of O. Feron consists of the study of different aspects of the tumor (lipid) metabolism impacting on, or influenced by the tumor microenvironment. In particular, hypoxia and acidosis parameters are integrated in all the studies by using a variety of 3D tumor models. Recent research axes of the O. Feron lab include the interplay between circadian rhythm, nutrition and cancer progression, and the search for the most promising combination of metabolism-targeting drugs with either chemotherapy or second generation immune checkpoint inhibitors.

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, among which MitoQ is a promising agent to prevent cancer recurrence and metastasis.



EXPERIMENTAL SURGERY AND TRANSPLANTATION (CHEX)

The Laboratory of Experimental Surgery and Transplantation (CHEX) offers all the facilities and infrastructures for the development of research projects using experimental surgical models based on both small and large animal models, as well as projects using non-transplantable human organ allografts. Different projects are currently underway in our unit on the field of allograft organ preservation and function improvement, new strategies to treat diabetes, new strategies to improve bone grafts and its acceptance. Some of these projects are described below:

Improved secretory function of transgenic InsGLP-1Ser8M3R porcine islets

N Mourad

Porcine islets have notoriously low insulin secretion levels in response to glucose stimulation. While this is somehow expected in the case of immature islets isolated from fetal and neonatal pigs, disappointingly low secretory responses are frequently reported in studies using in vitro-maturated fetal and neonatal islets and even fully-differentiated adult islets. This project aims to improve the secretory function of porcine islets by means of beta-cell specific expression of a modified glucagon-like peptide 1 (GLP-1) and of a constitutively activated type 3 muscarinic receptor (M3R) to amplify glucose-stimulated insulin secretion (GSIS) and to study pancreatic hormone secretion from such modified islets both in vitro and in vivo in xenotransplantation models for the treatment of type I diabetes.

Enhancing massive bone allografts

R. Evrard

In cases of large bone defect, transplanting bone from a deceased donor can often be the most appropriate solution for the reconstruction. Unfortunately, these massive bone allografts present many post-operative complications. In our research, we have created a perfusion protocol to improve the osseointegration of these grafts and decrease the complication rate. This research is applied to the porcine model and several steps have already been validated. The bone perfusion decellularization treatment has proven to be efficient and reproducible from a cellular and immunological point of view. These grafts have already been tested in vivo on a porcine model. Mechanical and recellularization tests are currently still ongoing.

Reconstruction of critical bone loss by massive allograft and recellularized periosteal membrane

J. Manon

Our objective is to propose a new therapeutic approach for the regeneration of massive bone loss by integrating the concepts of osteoconductive membrane, osteogenic stem cells, osteoinductive growth factors, mechanical stability and vascularisation. The creation of a collagenous membrane revitalised by the seeding of periosteal mesenchymal stem cells and transplanted in a single surgery would provide the biological conditions for the allograft to integrate. The central point that remains to be investigated is the capacity for (neo)vascularisation. A preclinical porcine model will also evaluate the improvement of consolidation and colonisation of the allograft. This model will be representative of what surgeons face in the patient and, if successful, will open up new clinical treatment options.

Hypothermic oxygenated machine perfusion can be used as a platform to delivery therapies to mitigate the impact of ischemia and reperfusion injury and improve liver allograft function.

E Bonaccorsi Riani

Liver transplantation is affected by organ shortage, forcing liver transplant surgeons to use extended criteria donor (ECD) liver allografts. However, such organs are more susceptible to the consequences of ischemia and reperfusion injury IRI. The hypothermic oxygen machine perfusion (HOPE) is a promising technology to improve allograft preservation conditions and increase the use of liver ECD grafts. Using a rat liver transplant model, we tested our hypothesis that HOPE can be used as a platform to deliver graft-directed therapies to improve organ function by administering Fas-associated small interference RNA (FAS-siRNA) in order to mitigate the IRI-induced liver injury.

EQUIPMENTS

- **VIS spectrum bioluminescence and biofluorescence imaging**
- **Seahorse XFe96 and ISCUSflex CMA600 bioanalyses**
- **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**

POLE OF PEDIATRIC RESEARCH (PEDI)

The research pole PEDI, historically dedicated to paediatric research, is focusing on the study of liver, pancreatic endocrine and infectious diseases. The unit works in close collaboration with the Paediatric department, the Paediatric Clinical Investigation Center and is also closely involved in the Liver & Liver stem cell tissue Bank of Cliniques Universitaires Saint-Luc.

Thanks to liver cell and stem cell tissue bank, PEDI has accumulated significant knowledge during these last two decades on handling liver cell types, which ensures significant high level national and international collaborations. For instance, it is recognized worldwide for its expertise in isolating and transplanting isolated hepatocytes (more than 220 different liver cell isolations, and more than 15 transplanted patients). The hepato-PEDI team has also combined expertise in cell/tissular stem cell biology, isolation and banking as well as in liver disease mechanisms, a significant know-how in pre-clinically developing and clinically translating stem cell based regenerative medicine. Indeed, our team has identified a proprietary progenitor cell population within the adult human liver (HALPCs) that has been successfully manufactured under good manufacturing practices and granted medicinal products according to the EU regulation on advanced therapies. Those cells were developed as allogeneic products and their safety was demonstrated in three patients with inborn metabolic diseases transplanted at Saint-Luc Hospital. Using this PEDI identified stem/progenitor cell technology, a spinoff company has been launched "Promethera Biosciences" in 2009 which confirmed its safety and preliminary efficacy in a phase I/II clinical trial in pediatric patients with Crigler–Najjar syndrome and urea cycle diseases. Those cells were the subject of more than 40 international publications, more than 200 citations and the attribution of 7 related patents. After demonstrating their ability to home to the liver after peripheral infusion, as well as their immunomodulatory and anti-fibrotic properties, HALPCs were evaluated in a phase IIa clinical study in adult patients with acute-on-chronic liver failure (ACLF) or with acute decompensation at risk of developing ACLF. This trial revealed the ability of HALPCs to ameliorate survival rate, systemic inflammation, and liver functions. Currently, those cells are evaluated in a phase IIb study involving 130 patients.

The diabetes axis team of the PEDI lab studies type 1 diabetes and atypical forms of diabetes in children and adolescents to determine new clinical and biological markers that may improve the understanding of the pathophysiology of diabetes as well as the related clinical approach. In 2022, two clinical research studies were completed. The first one, DIATAG, demonstrated the importance of combining clinical parameters and glycemic data in the glycemic follow-up of the patients with de novo type 1 diabetes to optimize the personalization of the therapeutic management. The second study, DIABGRAFT, investigated the incidence of diabetes in patients with either a renal or a liver transplant and demonstrated the importance of regular blood glucose measurements in transplanted patients during an acute complication (i.e., infection, graft rejection) to target patients at risk of diabetes.

Because of its steadily progression these last 30 years, antimicrobial resistance has become a major global health issue. While development of new antibiotics is necessary but probably not sufficient in the short to mid-term, complementary tools to fight these "superbugs" are dearly needed. Phage therapy by using environmentally-sourced bacteriophages (viruses that specifically and exclusively infect and destroy bacteria) as bactericidal therapeutic agents, is one of the therapeutic strategies that PEDI is currently developing. The translational research conducted at PEDI is willing to develop appropriate 3D culture models to deeply monitor the mechanisms of phage-bacterium-host-drug interactions that could influence its outcome towards success or failure via also selecting the ideal phage candidate according to its specific environment-dependent properties.

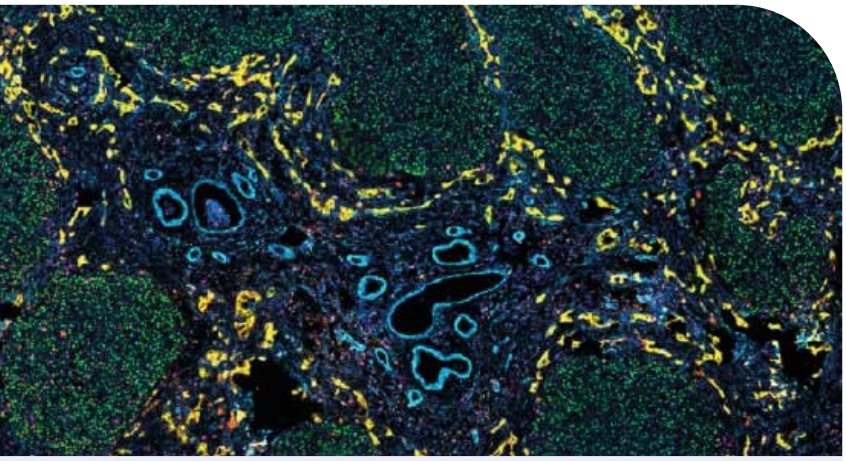


Fig 1: Multiple immunofluorescence staining of a biliary atresia liver fragment obtained at the time of liver transplantation, evidencing important ductular reaction and established biliary cirrhosis. The staining identifies hepatocytes (HNF4-α; green), cholangiocytes (CK-19; yellow), myofibroblasts (α-SMA; light blue), cells containing DNA-damage foci (γH2AX; orange) and proliferative cells (Ki67; pink). The section was counterstained with Hoechst to evidence all cellular nuclei (dark blue). Scale bar: 500 µm.

LIVER REGENERATIVE MEDICINE

Inhibition of disease related liver tissue senescence: a potential mechanism of action of Human Adult Derived Liver Stem/progenitor Cells (HALPCs) in liver regenerative medicine

G. Jannone, M. Najimi & E. Sokal

Cholestatic liver diseases – and especially biliary atresia (BA) – remain the first cause of liver transplantation in the pediatric population, generating a need for alternative therapies (1). Premature senescence has emerged as an important feature of adult chronic hepatobiliary diseases since this phenomenon was associated to disease severity and prognosis (2, 3). Numerous preclinical studies were conducted in this context and demonstrated that liver disease improves when senescence decreases (4-6). A few studies also suggested the presence of liver senescence in BA, but the possibility of using anti-senescence therapies was never explored in pediatric biliary cirrhosis (7, 8). In this context, we are currently deeply investigating liver premature senescence in cholestatic liver diseases,

and particularly in BA and Alagille syndrome. In order to do so we developed multiple techniques, including an optimized senescence-associated beta-galactosidase activity protocol, and performed the first digital spatial profiling whole transcriptome analysis on BA livers. We also developed the bile duct ligation preclinical model of biliary cirrhosis and senescence in two-months-old rats to test anti-senescence therapies that would be translated for clinical applications. The senotherapies that we selected for our experiments are our in-house medicinal signaling cells – human adult liver-derived progenitor cells (HALPCs) – and the well-described combination of senolytics dasatinib and quercetin.

Study of the effect of HALPCs on the epigenetic dysregulation of Kupffer cells and T regulatory cells throughout chronic liver diseases

A. Ajith, E. Sokal, & M. Najimi

The liver in its normal state is an immunotolerant organ, and liver homeostasis is maintained by different resident and infiltrating immune cell types. Two important types of immune cells involved in liver homeostasis and pathogenesis are Kupffer cells (KCs) and T-regulatory cells (Tregs). KCs are the resident macrophages of the liver, and they act as the first line of defense against pathogens and liver damage. While Tregs is a subtype of T cells with immunosuppressive function. During liver fibrosis, KCs promote the infiltration and activation of other immune cells leading to inflammation. At the same time, they also activate Tregs as a counterweight mechanism. In the tumor microenvironment, anti-inflammatory KCs and Tregs together promote tumorigenesis by suppressing cytotoxic T cells and NK cells. MicroRNAs (miRNA/miR) are small non-coding RNAs that control cell development, proliferation, differentiation, metabolism, and apoptosis by regulating gene expression at the post-transcriptional level. The dysregulation of miRNA expression in liver tissue is well described in the literature. However, the expression and role of miRNAs in inflammatory cells of chronic liver disease are still largely unknown. In this project, we aim to understand the role of KCs and Tregs by analyzing the dysregulated miRNA profiles during the progression of chronic liver diseases to hepatocellular carcinoma. The second objective is to use this information in a therapeutic aspect by using HALPCs. Due to their high proliferative capacity, immunomodulatory and anti-fibrotic effects, HALPCs have already been used for advanced human clinical development for metabolic liver diseases and liver inflammatory diseases like acute-on-chronic liver failure. Investigating the effect of HALPC transplantation on the modulation of miRNA profiles of Tregs and KCs during the progression of chronic liver diseases to cancer will give interesting insight for the study.

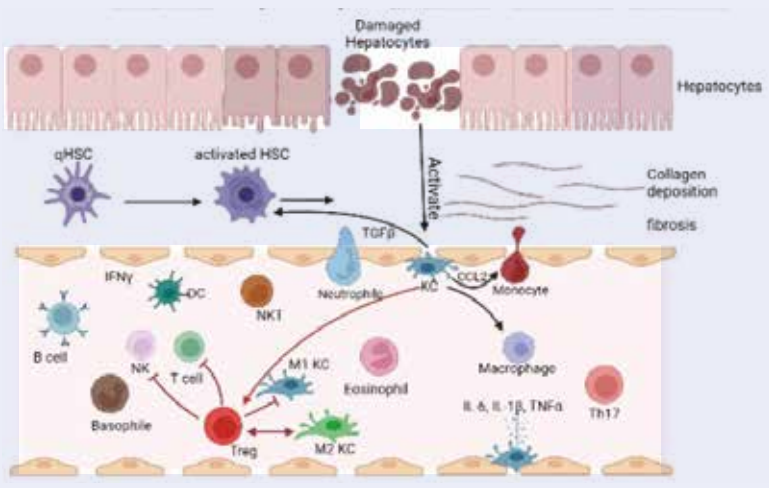


Fig 2: During chronic liver disease progression to hepatocellular carcinoma, the immune microenvironment of the liver changes from a balanced immune response-to an inflammatory response-to an immune tolerant microenvironment.

Multi-target RNA transfection-based bioengineering of liver derived MSCs as killer cargo of hepatocellular dysplasia and carcinoma cells

G. de Bodt, M. Najimi & E. Sokal

Conflicting reports exists regarding the role of mesenchymal stem cells (MSCs) in oncogenesis and their potential place as cell therapy tools in cancer. On one hand, they can display prominent anti-tumoral effects in various in vitro and in vivo models, inhibiting the growth of tumor cells, improving their chemo-sensibility, or hampering their migration potential. On the other hand, MSCs demonstrate the exact opposite properties in other models and are naturally recruited towards tumoral sites in vivo, leading some to believe that they could be precursor to cancer associated fibroblasts. Our laboratory has reproducibly obtained a population of mesenchymal-like stem cells form the liver of healthy human adult donors. These HALPCs are being investigated in a phase IIB human clinical trial in Acute-On-Chronic Liver Failure. Using a 3D co-culture multi-cellular spheroid model, we are currently investigating the interactions between HALPCs and human Hepatocellular Carcinoma (HCC) cells, the resident tumor from HALPCs' organ of origin. This will help us to better understand MSCs' stance during carcinogenesis and to explore HALPCs' potential as a cell therapy tool against HCC.

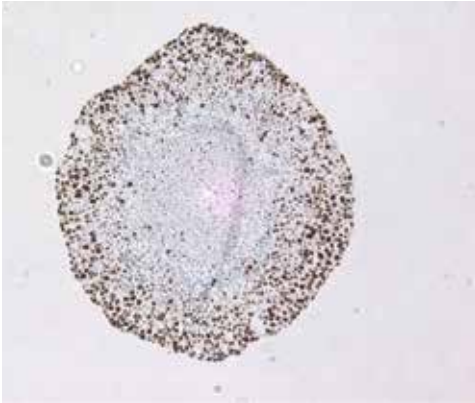


Fig 3: Ki67 immunostaining in HuH7 cell spheroid

DIABETES

Deep characterization and identification of new biomarkers of partial remission in pediatric patients with new-onset type 1 diabetes

O. Pollé, P. Lysy

Prevention therapies aiming to prevent loss of β-cell mass in children with type 1 diabetes (T1D) did not reach their primary endpoint as reliable markers of both β-cell function and patient stratification currently lack. Using a cross-sectional multilevel approach (i.e., continuous glucose monitoring [CGM], pancreas MRI, and plasma proteome), our research team focused on a better characterization and prediction of T1D heterogeneity and partial remission (PR). In children with new-onset T1D from the **DIA**betes **TAG**ging trial (NCT04007809), CGM results challenged the binary definition of PR, and identified new minimal-invasive and clinically meaningful markers of β-cell function (1–3). Furthermore, both MRI and CGM studies provided additional evidence for more aggressive disease in children with prepubertal T1D onset (e.g., increased pancreas atrophy (4) and higher levels of dysglycemia (1)). Going further into the stratification of patients at diagnosis, both MRI and plasma proteomic studies identified short-term predictive markers of glucose homeostasis and PR. Some of our protein candidates were validated using targeted proteomic (PRM) in the raw plasma.

Drug-induced diabetes

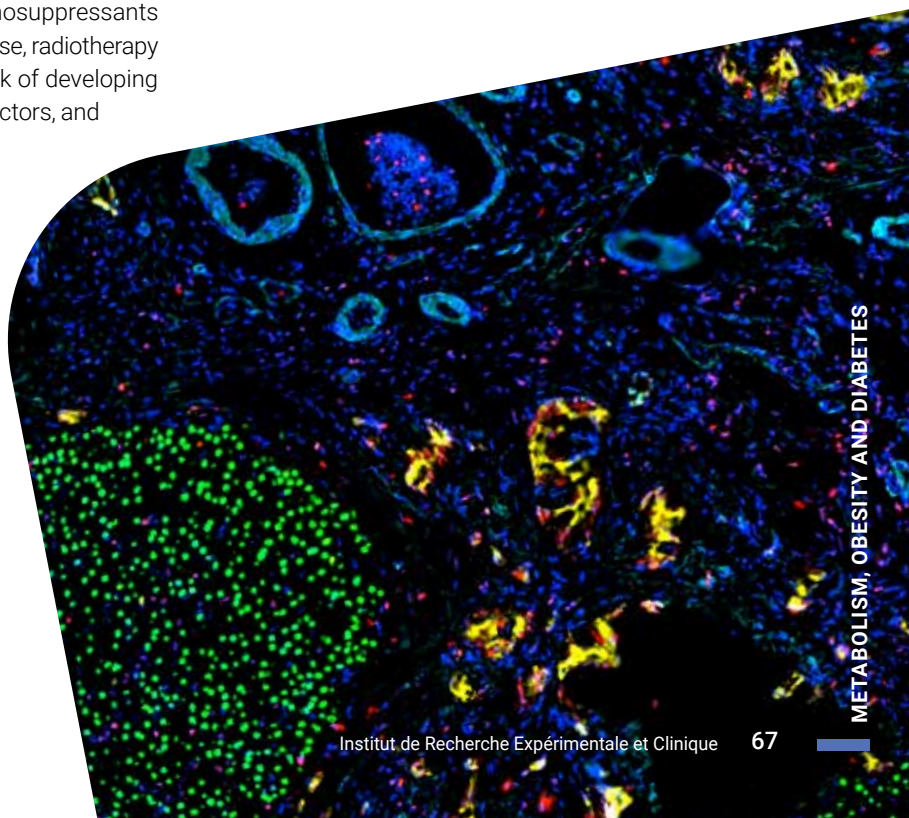
S. Welsch, P. Lysy

Part of our objectives in PEDI-lab was to study the atypical side of diabetes, whether it is represented in a cohort of patients with a diagnosis attributed to type 1 diabetes (T1D) or 2 (T2D) or present secondary to a pathology. Diabetes secondary to a pathology are, for their part, often under-studied and under-diagnosed. Indeed, despite all the elements suggesting that immunosuppressants such as glucocorticoids (GC), asparaginase, radiotherapy and anti-rejection drugs increase the risk of developing diabetes, its incidence, associated risk factors, and the predictive biological markers remain unknown. In addition, it is particularly important to study the risk of diabetes in this context because its occurrence is associated with an unfavourable prognosis and an increase in cardiovascular events. Therefore, there is a need to identify in clinical practice children with cancer and paediatric transplant recipients at risk of developing diabetes.

Longitudinal study of the GLUcagon REsponse to hypoglycemia in children and adolescents with new-onset type 1 DIAbetes (GLUREDIA study): characteristics and predictive biomarkers

A. Harvengt & P. Lysy

The natural course of type 1 diabetes is marked by a progressive destruction of insulin-producing cells, responsible for the decrease in blood glucose levels. However, it appears that other hormones are lacking or are abnormally secreted, such as counter-regulation hormones, whose role is to increase blood glucose to avoid hypoglycemia. One of the consequences of this disruption of the counter regulation mechanism (CRR) is the increased risk for patients to experience severe hypoglycemia with unconsciousness, which has a significant impact on quality of life. The exact mechanism that explains CRR dysfunction is still misunderstood and we are therefore unable to predict which patient is at risk for severe hypoglycemia. Faced with this situation, the GLUREDIA study will study the mechanisms of glucose regulation in patients recently diagnosed with type 1 diabetes for 18 months, during tests of hypoglycemia. The clear objective of this study is to describe the temporal evolution of the mechanisms of glycemic regulation during the first 18 months after the diagnosis of type 1 diabetes. These investigations will help us to identify patients at risk of developing severe hypoglycemia, and the precise moment when this risk appears, to adapt the therapeutic management of patients and prevent these acute events. In addition, studying the evolution of the mechanisms of glycemic regulation will allow us to better understand the mechanisms of the development of type 1 diabetes.



INFECTIOUS DISEASES

Phage therapy through case-based translational research and gut-on-a-chip model

B. Van Nieuwenhuyse, D. Van der Linden

This project encompasses the study of various aspects of phages and phage therapy through the lens of both translational and experimental research.

Translational research (Fig. 4) investigates determinants of phage therapy's success or failure in patients treated by phage therapy for various indications in Saint-Luc. This includes i) the detection of immune humoral reaction against administered phages (PIN), ii) the development of Bacterial Phage Resistance (BPR) during treatment and its potentially associated Phage-Induced Virulence Tradeoffs (PIVT), and iii) the synergistic properties, or lack thereof, of phage-antibiotic combinations.

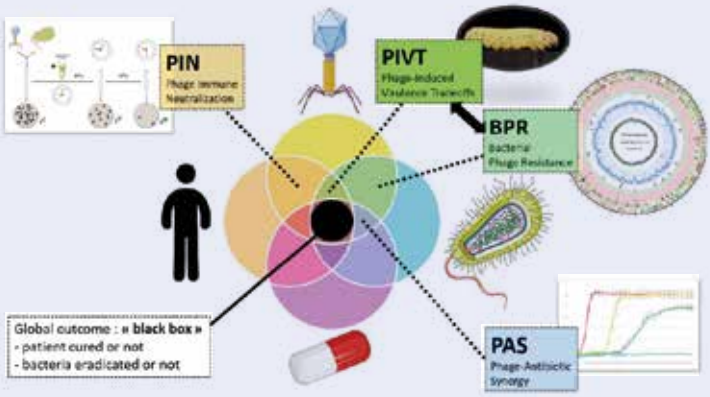


Fig. 4: Translational research investigates potentially clinically-relevant mechanisms at different intersections in the patient-bacterium-phage-antibiotic consortium.

Experimental research focuses on the study of phage-bacteria dynamics in the mucus-rich digestive environment, using a dynamic 3D flux culture model of the "organ-on-chip" family: the gut-on-a-chip (Fig. 5 – schematic longitudinal cut). It consists of a 3D tubular culture of a pseudo-intestinal segment secreting a mucus lining in which bacterial infections are voluntarily implemented and then submitted to various conditions of in-model phage instil Cancer lations under continuous culture medium flux.

CANCER

Childhood liver cancer

I. Scheers

Our team is investigating the oncogenetics of childhood liver diseases (Hepatoblastomas and Hepatic adenomas) with the aim is to develop a decision tree and targeted therapies for the management of those hepatic tumor diseases.

Hepatocellular Adenoma (HCA) are benign liver tumors mainly occurring in women (W/M ratio 8:1) taking oral contraceptives. Observations on our center's pediatric HCA cohort (n=15) and after a systematic literature review (n=277) showed that a vast majority (88%) of HCA occurred in children with underlying genetic disorders or liver vascular anomalies, unrelated to gender. The predisposing disease was largely predictive of the HCA molecular subtype. As such, children with glycogenosis developed inflammatory adenomas (I-HCA), although some tumors additionally showed WNT-pathway activation due to the gain of a somatic mutation in WNT-pathway effector CTNNB1 (BI-HCA). Maturity onset diabetes of the young type 3 (MODY3) patients had HNF1A mutated HCA (H-HCA) and children with porto-systemic shunts developed either H-HCA, B-HCA or a combination of both. Our data further demonstrated that 15% of pediatric HCA transform in HCC. Uni and multivariate data analyses suggest that B-HCA are at significant risk for HCC. Furthermore, transformed HCA invariably re-expressed telomerase (TERT).

IMMUNOLOGY

Hemostasis-cirrhosis study

M.A. van Dievoet & X. Stéphenne

Cirrhotic patients suffer from multiple coagulation disorders leading to so-called rebalanced hemostasis. This is however a fragile balance. Primary hemostasis, particularly platelet function, is a part of this rebalanced equilibrium. Up to this day, platelet function has been rarely investigated in cirrhotic patients. While some studies reported clear platelet dysfunction, others demonstrated elevated platelet activation. By its complex phenotype the platelet plays a diverse and key role in hemostasis: main thrombus component, scaffold for thrombin by exposure of phosphatidyl serine, fibrin generation and finally

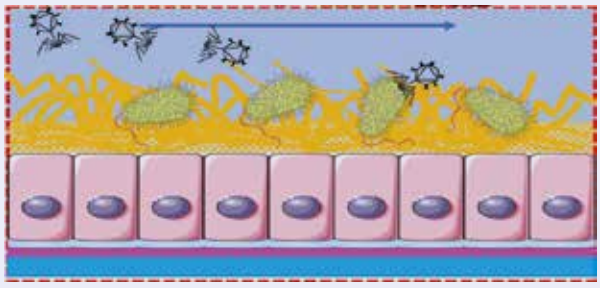


Fig. 5: Schematic longitudinal cut view in the wall of the gut-on-a-chip model, from bottom to top: glass slide covered by extracellular matrix is host to a 3D tubular digestive epithelium secreting a parietal mucus layer purposefully infected by a chosen bacterial species, being then submitted to cognate phages instilled through the culture medium flow.

clot retraction. Recently, the concept of a single group of platelets has been questioned by demonstrating the existence of platelet subpopulations (procoagulant versus proaggregant platelets). Flow cytometry is a powerful tool to unravel the phenotypic state of platelets requiring only a small volume of whole blood. A multi-color flow cytometry protocol is of importance to characterize platelet subpopulations. Maastricht flow chamber, a microfluidic assay, is another innovative tool to study platelet function under flow conditions. Both pediatric and adult patients with decompensated cirrhosis are studied before and after liver transplantation. For every patient an age and sex matched healthy volunteer is included. The whole hemostatic system (primary hemostasis, coagulation cascade and fibrinolysis) is studied, with a special focus on platelets.

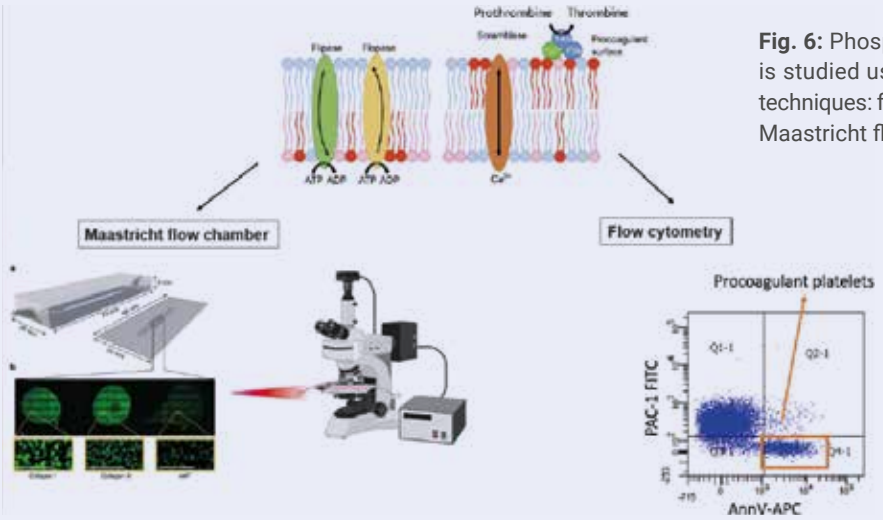


Fig. 6: Phosphatidyl exposure is studied using two different techniques: flow cytometry and Maastricht flow chamber.

REFERENCES 2022-2023

EDIN

Singh B, Khattab F, **Gilon P.** Glucose inhibits glucagon secretion by decreasing $[Ca^{2+}]_c$ and by reducing the efficacy of Ca^{2+} on exocytosis via somatostatin-dependent and independent mechanisms. ***Molecular Metabolism*** 61:101495 (2022)

Fantuzzi F, Toivonen S, Schiavo AA, Chae H, Tariq M, Sawatani T, Pachera N, Cai Y, Vinci C, Virgilio E, Ladriere L, Suleiman M, Marchetti P, Jonas JC, **Gilon P**, Eizirik DL, Igoillo-Esteve M, Cnop M. In depth functional characterization of human induced pluripotent stem cell-derived beta cells *in vitro and in vivo*. ***Front Cell Dev Biol.*** Aug 17;10:967765. (2022)

Tariq M, de Souza AH, Bensellam M, Chae H, Jaffredo M, **Close AF**, **Deglasse JP, Santos LRB, Buemi A, Mourad NI**, Wojtusciszyn A, Raoux M, **Gilon P**, Broca C, **Jonas JC**. Prolonged culture of human pancreatic islets under glucotoxic conditions changes their acute beta-cell calcium and insulin secretion glucose-response curves from sigmoid to bell-shaped. *Diabetologia* **66**: 709-723 (2023)

Ngomba Muakana JA, Thissen JP, Loumaye A, Thoma M, Deswysen Y, Navez B. Distalization of Standard Roux-en-Y Gastric Bypass: Indications, Technique, and Long-Term Results. Obes Surg. doi: 10.1007/s11695-023-06524-3. Online ahead of print (2023)

Gosseaume C, Fournier T, Jéru I, Vignaud ML, Missotte I, Archambeaud F, Debussche X, Droumaguet C, Fève B, Grillot S, Guerci B, Hieronimus S, Horsmans Y, Nobécourt E, Pienkowski C, Poitou C, Thissen JP, Lascols O, Degrelle S, Tsatsaris V, Vigouroux C, Vatier C. Perinatal, metabolic, and reproductive features in PPARG-related lipodystrophy. Eur J Endocrinol. **188**(3):lvad023 (2023)

Etienne Q, Lebrun V, Komuta M, Navez B, **Thissen JP**, Leclercq IA, Lanthier N. Fetuin-A in Activated Liver Macrophages Is a Key Feature of Non-Alcoholic Steatohepatitis. Metabolites **12**(7):625 (2022)

Binet Q, **Loumaye A, Preumont V, Thissen JP, Hermans MP**, Lanthier N. Non-invasive screening, staging and management of metabolic dysfunction-associated fatty liver disease (MAFLD) in type 2 diabetes mellitus patients: what do we know so far ? Acta Gastroenterol Belg. **85**(2):346-357 (2022)

Loumaye A, Lause P, Zhong X, Zimmers TA, Bindels LB, **Thissen JP**. Activin A Causes Muscle Atrophy through MEF2C-Dependent Impaired Myogenesis. Cells **11**(7):1119 (2021)

Rodriguez J, Neyrinck AM, Van Kerckhoven M, Gianfrancesco MA, Renguet E, Bertrand L, Cani PD, Lanthier N, Cnop M, Paquot N, **Thissen JP**, Bindels LB, Delzenne NM. Physical activity enhances the improvement of body mass index and metabolism by inulin: a multicenter randomized placebo-controlled trial performed in obese individuals. BMC Med. **20**(1):110 (2022)

Vande Berg P, Ulaj A, de Broqueville G, de Vos M, Delire B, Hainaut P, **Thissen JP**, Stärkel P, Komuta M, Henry P, Lanthier N. Liver Decompensation after Bariatric Surgery in the Absence of Cirrhosis. Obes Surg. **32**(4):1227-1235 (2022)

Binet Q, **Hermans MP**, Lanthier N. Screening for NAFLD and its severity in type 2 diabetic patients: Value of magnetic resonance imaging and outstanding issues. J Hepatol. **14**:S0168-8278(22)03329-3 (2022)

Burlacu MC, Attanasio R, Hegedüs L, Nagy EV, Papini E, Perros P, Sawadogo K, Bex M, Corvilain B, Daumerie C, Decallonne B, **Gruson D**, Lapauw B, Reyes RM, Petrossians P, Poppe K, Van den Bruel A, Unuane D. Use of thyroid hormones in hypothyroid and euthyroid patients:

PEDI

Pollé, O. G., Delfosse, A., Martin, M., Louis, J., Gies, I., Den Brinker, M., ... & DIATAG Working Group. Glycemic variability patterns strongly correlate with partial remission status in children with

newly diagnosed type 1 diabetes. Diabetes care, 45(10), 2360-2368 (2022)

Polle, O., Delfosse, A., Michoux, N., Peeters, F., Duchene, G., Mouraux, T., ... & **Lysy, P.** RF16| PSUN203 Deep Characterization of Pancreas Volume of New-Onset Type 1 Diabetes Patients Reveals Puberty-Specific Patterns and New Topographic Correlations with Pancreatic Functions. Journal of the Endocrine Society, 6(Supplement_1), A424-A425 (2022)

Boutsen, L., Costenoble, E., **Pollé, O**., Erdem, K., Bugli, C., & **Lysy, P. A.** Influence of the occurrence and duration of partial remission on short-term metabolic control in type 1 diabetes: the DIABHONEY pediatric study. Therapeutic Advances in Endocrinology and Metabolism, 14, 20420188221145550 (2023)

Welsch, S., Sawadogo, K., Brichard, B., De ville de Goyet, M., Van Damme, A., Boulanger, C., & **Lysy, P. A.** Characterization and risk factors of hyperglycaemia during treatment of childhood hematologic malignancies. Diabetic Medicine, 39(2), e14720 (2022)

Welsch, S., Mailleux, V., de Beaulieu, P. L. H., Ranguelov, N., Godefroid, N., Robert, A., ... & Lysy, P. A. Characterization, evolution and risk factors of diabetes and prediabetes in a pediatric cohort of renal and liver transplant recipients. Frontiers in Pediatrics, 11 (2023)

CHEX

N. I. Mourad, D. Xhema, P. Gianello, In vitro assessment of pancreatic hormone secretion from isolated porcine islets. Front Endocrinol (Lausanne) 13, 935060 (2022).

Rougier, G., Maistriaux, L., Fievé, L., Xhema, D., Evrard, R., Manon, J., ... & Lengelé, B. (2023). Decellularized vascularized bone grafts: an in vitro porcine model for bioengineered transplantable bone shafts. Frontiers in Bioengineering and Biotechnology, 10, 2378.

Heller, U., Evrard, R., Lengelé, B., Schubert, T., Kadlub, N., & Boisson, J. (2023). Decellularized vascularized bone grafts as therapeutic solution for bone reconstruction: A mechanical evaluation. Plos one, 18(1), e0280193.

Manon, J., Evrard, R., Maistriaux, L., Fievé, L., Heller, U., Magnin, D., ... & Cornu, O. (2022). Periosteum and fascia lata: Are they so different? Frontiers in bioengineering and biotechnology, 10.

Manon, J., Evrard, R., Fievé, L., Bouzin, C., Magnin, D., Xhema, D., ... & Cornu, O. (2023). A New Osteogenic Membrane to Enhance Bone Healing: At the Crossroads between the Periosteum, the Induced Membrane, and the Diamond Concept. Bioengineering, 10(2), 143.

Bonaccorsi-Riani E, Gillooly AR, Iesari S, Brüggenwirth IMA, Ferguson CM, Komuta M, Xhema D, Daumerie A, Maistriaux L, Leuvenink H, Kupiec-Weglinski J, Porte RJ, Khvorova A, Cave DR, Gianello P, Martins PN. Delivering siRNA Compounds During HOPE to Modulate Organ Function: A Proof-of-concept Study in a Rat Liver Transplant Model. Transplantation. 2022 Aug 1;106(8):1565-1576.

GAEN

Domingues I, Michalowski CB, Marotti V, Zhang W, Van Hul M, Cani PD, **Leclercq IA**, Beloqui A. Exploiting the biological effect exerted by lipid nanocapsules in non-alcoholic fatty liver disease. J Control Release. 2023; 356:542-553.

Nachit M, Montemagno C, Clerc R, Ahmadi M, Briand F, Bacot S, Devoogdt N, Serdjebi C, Ghezzi C, Sulpice T, Broisat A, **Leclercq IA**, Perret P. Molecular imaging of liver inflammation using an anti-VCAM-1 nanobody. Nat Commun. 2023; 14:1062.

Gillard J, **Leclercq IA**. Biological tuners to reshape the bile acid pool for therapeutic purposes in non-alcoholic fatty liver disease. Clin Sci (Lond). 2023 ; 137:65-85.

Selvais CM, Davis-López de Carrizosa MA, **Nachit M**, Versele R, Dubuisson N, Noel L, **Gillard J**, **Leclercq IA,** Brichard SM, Abou-Samra M. AdipoRon enhances healthspan in middle-aged obese mice: striking alleviation of myosteatosis and muscle degenerative markers. J Cachexia Sarcopenia Muscle. 2023; 14:464-478.

Zeng S, Rosati E, ..., Bacher P, **Stärkel P**, Schnabl B. Candida albicans-specific Th17 cell-mediated response contributes to alcohol-associated liver disease. Cell Host Microbe. 2023;31:389-404. Zeng S, Hartmann P, Park M, Duan Y, Lang S, Llorente C, Wang Y, Cabré N, Fouts DE, Bacher P, Jung WH, **Stärkel P**, Schnabl B. Malassezia restricta promotes alcohol-induced liver injury. Hepatol Commun. 2023;7:e0029.

Hsu CL, Lang S, Demir M, Fouts DE, **Stärkel P**, Schnabl B. Any alcohol use in NAFLD patients is associated with significant changes to the intestinal virome. Hepatology. 2023 Jan 13. doi: 10.1097/HEP.0000000000000238

Peeters M, Schenk J, De Somer T, Roskams T, Locus T, Klamer S, Subissi L, Suin V, Delwaide J, **Stärkel P**, De Maeght S, ..., Van Gucht S, Vanwolleghem T; Belgian Association for the Study of the Liver. Viral clade is associated with severity of symptomatic genotype 3 hepatitis E virus infections in Belgium, 2010-2018. J Hepatol. 2023;78:67-77.

Settmacher U, Ali-Deeb A, **Coubeau L**, Cillo U, Line PD, Guba M, Nadalin S, Rauchfuß F. Auxilliary Liver Transplantation According to the RAPID Procedure in Noncirrhotic Patients: Technical Aspects and Early Outcomes. Ann Surg. 2023;277:305-312

Pichon C, Nachit M, Gillard J, Vande Velde G, **Lanthier N, Leclercq IA**. Impact of L-ornithine L-aspartate on non-alcoholic steatohepatitis-associated hyperammonemia and muscle alterations. Front Nutr. 2022; 9:1051157.

Lanthier N, Lebrun V, Molendi-Coste O, van Rooijen N, **Leclercq IA**. Liver Fetuin-A at Initiation of Insulin Resistance. Metabolites. 2022;12(:1023.

Serdjebi C, Bertotti K, Huang P, Wei G, Skelton-Badlani D, **Leclercq IA**, Barbes D, Lepoivre B, Popov YV, Julé Y. Automated whole slide image analysis for a translational quantification of liver fibrosis. Sci Rep. 2022;12:17935.

Maccioni L, Loriot A, Dewulf J, Bommer G, **Horsmans Y, Lanthier N, Leclercq I**, Schnabl B, **Stärkel P**. Duodenal CD8+ T resident memory cell apoptosis contributes to gut barrier dysfunction and microbial translocation in early alcohol-associated liver disease in humans. Aliment Pharmacol Ther. 2022;56:1055-1070.

Etienne Q, Lebrun V, Komuta M, Navez B, **Thissen JP, Leclercq IA, Lanthier N**. Fetuin-A in Activated Liver Macrophages Is a Key Feature of Non-Alcoholic Steatohepatitis. Metabolites. 2022;12:625

Gillard J, Picalausa C, Ullmer C, Adorini L, Staels B, Tailleux A, **Leclercq IA**. Enterohepatic Takeda G-Protein Coupled Receptor 5 Agonism in Metabolic Dysfunction-Associated Fatty Liver Disease and Related Glucose Dysmetabolism. Nutrients. 2022;14:2707.

Binet Q, Hermans MP, **Lanthier N**. Screening for NAFLD and its severity in type 2 diabetic patients: Value of magnetic resonance imaging and outstanding issues. J Hepatol. 2022:S0168-8278(22)03329-3.

Goffaux A, Delorme A, **Dahlqvist G, Lanthier N**. Improving the prognosis before and after liver transplantation: Is muscle a game changer? World J Gastroenterol. 2022;28:5807-5817.

Clerbaux LA, Mayasich SA, Muñoz A, Soares H, Petrillo M, Albertini MC, **Lanthier N**, Grenga L, Amorim MJ. Gut as an Alternative Entry Route for SARS-CoV-2: Current Evidence and Uncertainties of Productive Enteric Infection in COVID-19. J

Clin Med. 2022;11:5691.

Lanthier N, Delzenne N. Targeting the Gut Microbiome to Treat Metabolic Dysfunction-Associated Fatty Liver Disease: Ready for Prime Time? Cells. 2022;11:2718.

Rodriguez J, Neyrinck AM, Van Kerckhoven M, Gianfrancesco MA, Renguet E, Bertrand L, Cani PD, **Lanthier N**, Cnop M, Paquot N, Thissen JP, Bindels LB, Delzenne NM. Physical activity enhances the improvement of body mass index and metabolism by inulin: a multicenter randomized placebo-controlled trial performed in obese individuals. BMC Med. 2022;20:110.

Lanthier N, Spahr L. Letter: the value of quality liver biopsy before initiation of corticosteroids for severe alcoholic hepatitis. Aliment Pharmacol Ther. 2022;55:889-890.

Vande Berg P, Ulaj A, de Broqueville G, de Vos M, Delire B, Hainaut P, Thissen JP, **Stärkel P**, Komuta M, Henry P, **Lanthier N**. Liver Decompensation after Bariatric Surgery in the Absence of Cirrhosis. Obes Surg. 2022;32:1227-1235.

Gao B, Zhu Y, Shen W, **Stärkel P**, Schnabl B. Correlation between Serum Steroid Hormones and Gut Microbiota in Patients with Alcohol-Associated Liver Disease. Metabolites. 2022;12:0.

Gao B, Zeng S, Maccioni L, Shi X, Armando A, Quehenberger O, Zhang X, **Stärkel P**, Schnabl B. Lipidomics for the Prediction of Progressive Liver Disease in Patients with Alcohol Use Disorder. Metabolites. 2022;12:433.

Amadieu C, **Maccioni L**, Leclercq S, Neyrinck AM, Delzenne NM, de Timary P, **Stärkel P.** Liver alterations are not improved by inulin supplementation in alcohol use disorder patients during alcohol withdrawal: A pilot randomized, double-blind, placebo-controlled study. EBioMedicine. 2022;80:104033.

Hsu CL, Zhang X, Jiang L, Lang S, Hartmann P, Pride D, Fouts DE, **Stärkel P**, Schnabl B. Intestinal virome in patients with alcohol use disorder and after abstinence. Hepatol Commun. 2022;6:2058-2069.

Ventura-Cots M,..., Mueller S, **Stärkel P**, Bataller R. Clinical, histological and molecular profiling of different stages of alcohol-related liver disease. Gut. 2022;71:1856-1866.

Amadieu C, Coste V, Neyrinck AM, Thijssen V, Leyrolle Q, Bindels LB, **Piessevaux H, Stärkel P**, de Timary P, Delzenne NM, Leclercq S. Restoring an adequate dietary fiber intake by inulin supplementation: a pilot study showing an impact on gut microbiota and sociability in alcohol use disorder patients. Gut Microbes. 2022;14:2007042

Demir M, Lang S, ..., Kruglov A, Eckmann L, **Stärkel P**, Fouts DE, Schnabl B. The fecal mycobiome in non-alcoholic fatty liver disease. J Hepatol. 2022;76:788-799.

Pairon C, **Dili A**, Bertrand C, D'Hondt L, Fervaille C, Donckier JE. Effective multimodal management of a giant adrenocortical carcinoma. Acta Chir Belg. 2022:1-4.

Coubeau L, Iesari S, Henry P, D'Abadie P, Vanbuggenhout A, Reding R. Insights in living-donor liver transplantation associated with two-stage total hepatectomy: First case in neuroendocrine tumor metastases and functional assessment techniques. Hepatobiliary Pancreat Dis Int. 2022;21:392-395

Gillard J, Clerbaux LA, Nachit M, Sempoux C, Staels B, Bindels LB, Tailleux A, **Leclercq IA**. Bile acids contribute to the development of non-alcoholic steatohepatitis in mice. JHEP Rep. 2021;4:100387. eCollection 2022 Jan.

Salavrakos M, de Timary P, Ruiz Moreno A, Thissen JP, **Lanthier N**. Fructoholism in adults: The importance of personalised care in metabolic dysfunction-associated fatty liver disease. JHEP Rep. 2021;4:100396. eCollection 2022 Jan. 2673-2682 (2021) doi: 10.1016/j.clnu.2021.03.029.

FATH

Lan J, Cadassou O, Corbet C, Riant O, Feron O. Discovery of Mitochondrial Complex I Inhibitors as Anticancer and Radiosensitizer Drugs Based on Compensatory Stimulation of Lactate Release. Cancers (Basel). 2022 Nov 6;14(21):5454.

Deskeuvre M, Lan J, Dierge E, Messens J, Riant O, Corbet C, Feron O, Frédérick R. Targeting cancer cells in acidosis with conjugates between the carnitine palmitoyltransferase 1 inhibitor etomoxir and pH (low) insertion peptides. Int J Pharm. 2022 Aug 25;624:122041.

Cappellesso F, Orban MP, Shirgaonkar N, Berardi E, Serneels J, Neveu MA, Di Molfetta D, Piccapane F, Caroppo R, Debellis L, Ostyn T, Joudiou N, Mignion L, Richiardone E, Jordan BF, Gallez B, Corbet C, Roskams T, DasGupta R, Tejpar S, Di Matteo M, Taverna D, Reshkin SJ, Topal B, Virga F, Mazzone M. Targeting the bicarbonate transporter SLC4A4 overcomes immunosuppression and immunotherapy resistance in pancreatic cancer. Nat Cancer. 2022 Dec;3(12):1464-1483.

Buyse C, Joudiou N, Warscotte A, Richiardone E, Mignion L, Corbet C, Gallez B. Evaluation of Syrosingopine, an MCT Inhibitor, as Potential Modulator of Tumor Metabolism and Extracellular Acidification. Metabolites. 2022 Jun 17;12(6):557.

Capeloa T, Van de Velde JA, d'Hose D, Lipari SG, Derouane F, Hamelin L, Bedin M, Vazeille T, Duhoux FP, Murphy MP, Porporato PE, Gallez B, Sonveaux P. Inhibition of Mitochondrial Redox Signaling with MitoQ Prevents Metastasis of Human Pancreatic Cancer in Mice. Cancers (Basel). 2022 Oct 7;14(19):4918.

d'Hose D, Mathieu B, Mignion L, Hardy M, Ouari O, Jordan BF, Sonveaux P, Gallez B. EPR Investigations to Study the Impact of Mito-Metformin on the Mitochondrial Function of Prostate Cancer Cells. Molecules. 2022 Sep 10;27(18):5872.

Blackman MCNM, Capeloa T, Rondeau JD, Zampieri LX, Benyahia Z, Van de Velde JA, Fransolet M, Daskalopoulos EP, Michiels C, Beauloye C, Sonveaux P. Mitochondrial Protein Cox7b Is a Metabolic Sensor Driving Brain-Specific Metastasis of Human Breast Cancer Cells. Cancers (Basel). 2022 Sep 8;14(18):4371.

Weber DD, Aminzadeh-Gohari S, Thapa M, Redtenbacher AS, Catalano L, Capelôa T, Vazeille T, Emberger M, Felder TK, Feichtinger RG, Koelblinger P, Dallmann G, Sonveaux P, Lang R, Kofler B. Ketogenic diets slow melanoma growth in vivo regardless of tumor genetics and metabolic plasticity. Cancer Metab. 2022 Jul 18;10(1):12.

Macchi C, Moregola A, Greco MF, Svecla M, Bonacina F, Dhup S, Dadhich RK, Audano M, Sonveaux P, Mauro C, Mitro N, Ruscica M, Norata GD. Monocarboxylate transporter 1 deficiency impacts CD8+ T lymphocytes proliferation and recruitment to adipose tissue during obesity. iScience. 2022 May 23;25(6):104435.

Ippolito L, Sonveaux P, Chiarugi P. Unconventional roles of lactate along the tumor and immune landscape. Trends Endocrinol Metab. 2022 Apr;33(4):231-235.

Capeloa T, Krzystyniak J, d'Hose D, Canas Rodriguez A, Payen VL, Zampieri LX, Van de Velde JA, Benyahia Z, Pranzini E, Vazeille T, Fransolet M, Bouzin C, Brusa D, Michiels C, Gallez B, Murphy MP, Porporato PE, Sonveaux P. MitoQ Inhibits Human Breast Cancer Cell Migration, Invasion and Clonogenicity. Cancers (Basel). 2022 Mar 16;14(6):1516.

Capeloa T, Krzystyniak J, Rodriguez AC, Payen VL, Zampieri LX, Pranzini E, Derouane F, Vazeille T, Bouzin C, Duhoux FP, Murphy MP, Porporato PE, Sonveaux P. MitoQ Prevents Human Breast Cancer Recurrence and Lung Metastasis in Mice. Cancers (Basel). 2022 Mar 15;14(6):1488.

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.

Thematic Group Contact Persons

Catherine Behets
catherine.behets@uclouvain.be
Gaëtan Stoquart
gaetan.stoquart@uclouvain.be
Gregory Reychler
gregory.reychler@uclouvain.be

NEUROMUSCULOSKELETAL POLE (NMSK)


Christine Detrembleur
PT, PhD


Olivier Cornu
MD, PhD


Pierre Louis Docquier
MD, PhD


Thierry Lejeune
MD, PhD


Philippe Mahaudens
PT, PhD


Raphael Olszewski
MD, PhD


Laurent Pitance
PT, PhD


Gaëtan Stoquart
MD, PhD


Emmanuel Thienpont
MD, MBA, PhD

Researchers:
Jean-Louis Peters-Dickie, David Renard, Gaelle Schurman

Post-Doc:
Stéphanie Dehem, Gauthier Everard

PhD Students:
Randy Buzisa Mbuku, Timothée Cayrol, Valérie-Anne Chantrain, Louise Declerck, Marine Devis, Ioannis Doumas, Alexandre Englebert, Robin Evrard, Alain Kabakuli, Nicolas Lambricht, Alexandre Luc, Julie Manon, Anhphong Nguyen, Virginie Otlet, Clara Selves, Gregorio Sorrentino, Mathilde Van Durme, Kevin Wendo

Pole Contact Person:

Gaëtan Stoquart
gaetan.stoquart@uclouvain.be

HUMAN BIOMECHANICS

Biomechanics of human movement is a discipline that 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 collaboration between clinicians and researchers, this research group is dedicated to human Biomechanics: the study of neuro-musculoskeletal system in orthopaedic and neurologic patients, the rehabilitation in orthopedic and neurologic patients, and the assistive technologies for surgery and new standards for surgical accuracy measurements. Engineers, orthopaedic and maxillo-facial surgeons, physiotherapists and Physical Medicine & Rehabilitation specialists are founding a common scientific area to better understand the mechanisms of orthopaedic 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.

MyotonPro Is a Valid Device for Assessing Wrist Biomechanical Stiffness in Healthy Young Adults

Christine Detrembleur, Paul Fisette, Philippe Mahaudens, Anh Phong Nguyen, Clara Selves

BACKGROUND: The MyotonPro is a portable device for measuring biomechanical and viscoelastic properties in superficial soft tissues. The aims of this study are firstly to validate the MyotonPro compared to a reliable gold-standard frame and secondly to observe the influence of MyotonPro measurement on the total wrist viscoelasticity.

METHODS: Three silicone polymers with different elastic properties were assessed with the MyotonPro and with a reference rheometer (Universal Tribometer Mod). Then, a free oscillations method was used to measure the passive elastic and viscous stiffness of the wrist and compared to MyotonPro forearm measurements.

RESULTS: A one-way ANOVA demonstrated the validity of the MyotonPro's stiffness ($p = 0.001$), decrement ($p < 0.001$), and relaxation ($p = 0.008$) parameters for measuring the elastic stiffness (k) of the three polymers. The MyotonPro parameters demonstrated excellent reliability on the forearm. Proximal and distal anterior myofascial measurements of the MyotonPro were moderately correlated to the elastic stiffness ($p = 0.0027$-0.0275, absolute r = from 0.270 to 0.375) of the wrist while the postero-distal myofascial tissues of the forearm demonstrated a moderate correlation with the viscous stiffness of the wrist ($p = 0.0096$-0.0433, absolute r = from 0.257 to 0.326).

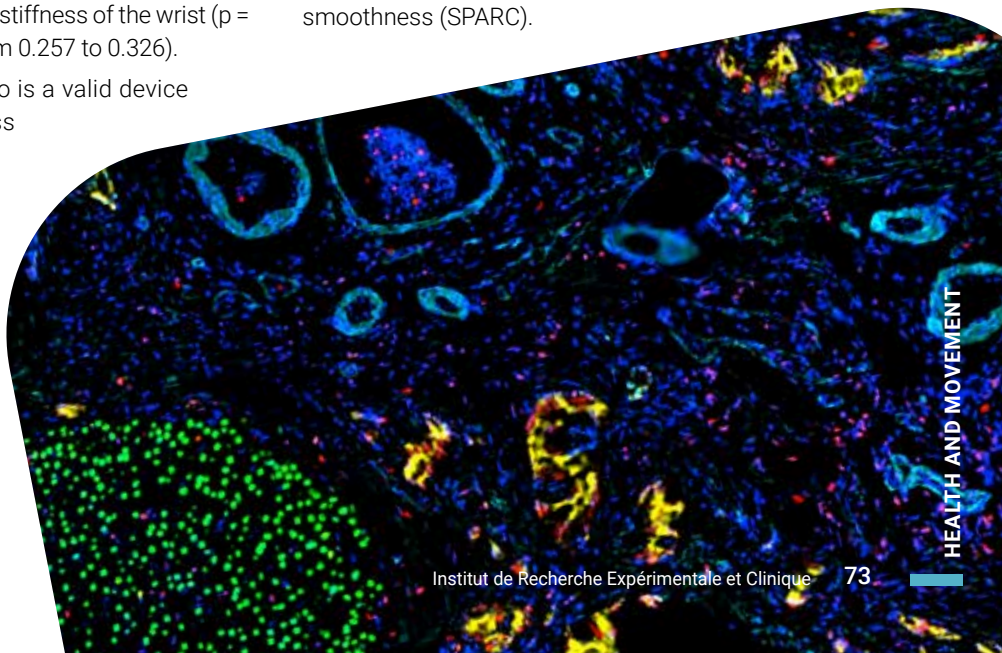
DISCUSSION: The MyotonPro is a valid device for measuring elastic stiffness as well as a portable, affordable, and easy-to-use tool for quantifying the biomechanical properties and viscoelasticity of myofascial tissue in healthy subjects.

Concurrent validity of an immersive virtual reality version of the Box and Block Test to assess manual dexterity among patients with stroke.

Thierry Lejeune, Martin Edwards, Stéphanie Dehem, Edouard Auvinet, Gauthier Everard, Yasmine Otmane-Tolba, Zélie Rosselli, Thomas Pellissier, Khawla Ajana, Stéphanie Dehem, Julien Lebleu

BACKGROUND: After a stroke, experts recommend regular monitoring and kinematic assessments of patients to objectively measure motor recovery. With the rise of new technologies and increasing needs for neurorehabilitation, an interest in virtual reality has emerged. In this context, we have developed an immersive virtual reality version of the Box and Block Test (BBT-VR). The aim of this study was to assess the concurrent validity of the BBT-VR among patients with stroke and healthy participants

METHODS: Twenty-three healthy participants and 22 patients with stroke were asked to perform the classical Box and Block Test (BBT) and BBT-VR three times with both hands. Concurrent validity was assessed through correlations between these two tests and reliability of the BBT-VR through correlation on test-retest. Usability of the BBT-VR was also evaluated with the System Usability Scale. Hand kinematic data extracted from controller's 3D position allowed to compute mean velocity (Vmean), peak velocity (Vpeak) and smoothness (SPARC).



RESULTS: Results showed strong correlations between the number of blocks displaced with the BBT and the BBT-VR among patients with stroke for affected ($r = 0.89$; $p < 0.001$) and less-affected hands ($r = 0.76$; $p < 0.001$) and healthy participants for dominant ($r = 0.58$; $p < 0.01$) and non-dominant hands ($r = 0.68$; $p < 0.001$). Reliability for test-retest was excellent (ICC > 0.8; $p < 0.001$) and usability almost excellent (System Usability Scale = 79 ± 12.34%). On average participants moved between 30 and 40% less blocks during the BBT-VR than during the BBT. Healthy participants demonstrated significantly higher kinematic measures (Vmean = 0.22 ± 0.086 ms-1; Vpeak = 0.96 ± 0.341 ms-1; SPARC = - 3.31 ± 0.862) than patients with stroke (Vmean = 0.12 ± 0.052 ms-1; Vpeak = 0.60 ± 0.202 ms-1; SPARC = - 5.04[- 7.050 to - 3.682]).

CONCLUSION: The BBT-VR is a usable, valid and reliable test to assess manual dexterity, providing kinematic parameters, in a population of patients with stroke and healthy participants.

ORTHOPEDIC SURGERY

Our team is involved in the development of new surgical techniques, and in the improvement of current techniques. One important concern is infection prevention is post-operative care. Post-operative infection is a devastating complication of joint or spine surgeries. In joint surgeries, the treatment is complicated by the rapid formation of bacterial biofilms on the implants' surfaces. Therefore, new therapeutic options targeting biofilms are in development to improve the outcome of PJI.

Development of an innovative in vivo model of PJI treated with DAIR

Olivier Cornu, Hervé Poilvache, Françoise Van Bambeke

INTRODUCTION: Prosthetic Joint Infection (PJI) are catastrophic complications of joint replacement. Debridement, implant retention, and antibiotic therapy (DAIR) is the usual strategy in acute infections but fails in 45% of MRSA infections. We describe the development of a model of infected arthroplasty in rabbits, treated with debridement and a course of vancomycin with clinically relevant dosage.

MATERIALS AND METHODS: A total of 15 rabbits were assigned to three groups: vancomycin pharmacokinetics (A), infection (B), and DAIR (C). All groups received a tibial arthroplasty using a Ti-6Al-4V implant. Groups B and C were infected per-operatively with a 5.5 log10 MRSA inoculum. After 1 week, groups C infected knees were surgically debrided. Groups A and C received 1 week of vancomycin. Pharmacokinetic profiles were obtained in group A following 1st and 5th injections. Animals were euthanized 2 weeks after the arthroplasty. Implants and tissue samples were processed for bacterial counts and histology.

RESULTS: Average vancomycin AUC0-12 h were 213.0 mg*h/L (1st injection) and 207.8 mg*h/L (5th injection), reaching clinical targets. All inoculated animals were infected. CFUs were reproducible in groups B. A sharp decrease in CFU was observed in groups C. Serum markers and leukocytes counts increased significantly in infected groups.

CONCLUSION: We developed a reproducible rabbit model of PJI treated with DAIR, using vancomycin at clinically relevant concentrations. E

ADAPTIVE SPORTS

The objective of this project is to assess the feasibility and effectiveness of adaptive sports for individuals with acquired central neurological lesion, and to analyze the effects of this approach according to the domains of the International Classification of Functioning, Health and Disability (ICF). Adaptive sports seem to be a feasible, efficient, and cost-effective complement to conventional rehabilitation. Significant effects can be found on all domains of the ICF. The effect of COVID-19 on physical activity of these patients was also analysed.

Effect of the COVID-19 pandemic lockdown on physical activity of individuals with a spinal cord injury in Belgium: observational study.

Gaëtan Stoquart, Thierry Lejeune, Louise Declerck, Jean-François Kaux, Céline Loiselet, Marc Vanderthommen

INTRODUCTION: Being physically active on a regular basis is vital to good physical and mental health. For individuals with spinal cord injury (SCI), PA rehabilitates impairments, autonomy and quality of life (QoL) [2]. The access to PA was limited during the COVID-19 pandemic. The primary aim of our study was to investigate how the COVID-19 lockdown affected PA levels of 2 groups: active and inactive Belgians with a SCI. The secondary aim was to identify the effect of the lockdown on social participation, QoL, pain and fatigue in the same population.

METHODS: The research sample consisted of 18- to 70-year-old community dwellers with SCI who were living

in Belgium and used a manual wheelchair. Two visits were organized for each patient, the first one before the second lockdown in late 2020, and the second one during the second lockdown in early 2021. Participants were asked to complete different questionnaires in French, including the Physical Activity Scale for Individuals with a Physical Disability (PASIPD) and the Reintegration to Normal Living Index (RNLI). For analysis, the participants were divided into 2 groups (active and inactive groups) based on the self-reported number of minutes of PA they performed each week before the lockdown.

RESULTS: In total, 34 participants were recruited: 20 in the active group and 14 in the inactive group. During the second lockdown, regarding the PASIPD, the active group showed significantly decreased leisure PA, by 15.21 MET hr/day (p = 0.00), and household PA, by 0.53 MET hr/day (p = 0.02). The total PASIPD score also significantly decreased from 27.77 to 15.44 MET hr/day (p = 0.00). The inactive group did not show significant changes in PA level for the domains of the PASIPD. However, the total PASIPD significantly decreased by 4.22 MET hr/day during the second lockdown (p = 0.03). For secondary outcomes, only social participation showed significant changes due to the second lockdown: RNLI scores decreased by 14.5 points (p = 0.00) and 19 points (p = 0.00) for the active and inactive groups.

CONCLUSION: Our results demonstrate that individuals with SCI significantly reduced their PA level during Belgium's second COVID-19 lockdown. These findings add knowledge regarding the impact of the lockdown among individuals with PD

NEUROLOGICAL REHABILITATION

Neurological rehabilitation is an important concern of our team. A huge number of papers have been published in the past. Currently, our team focuses its work on new technologies for rehabilitation.

New technologies promoting active upper limb rehabilitation after stroke: an overview and network meta-analysis

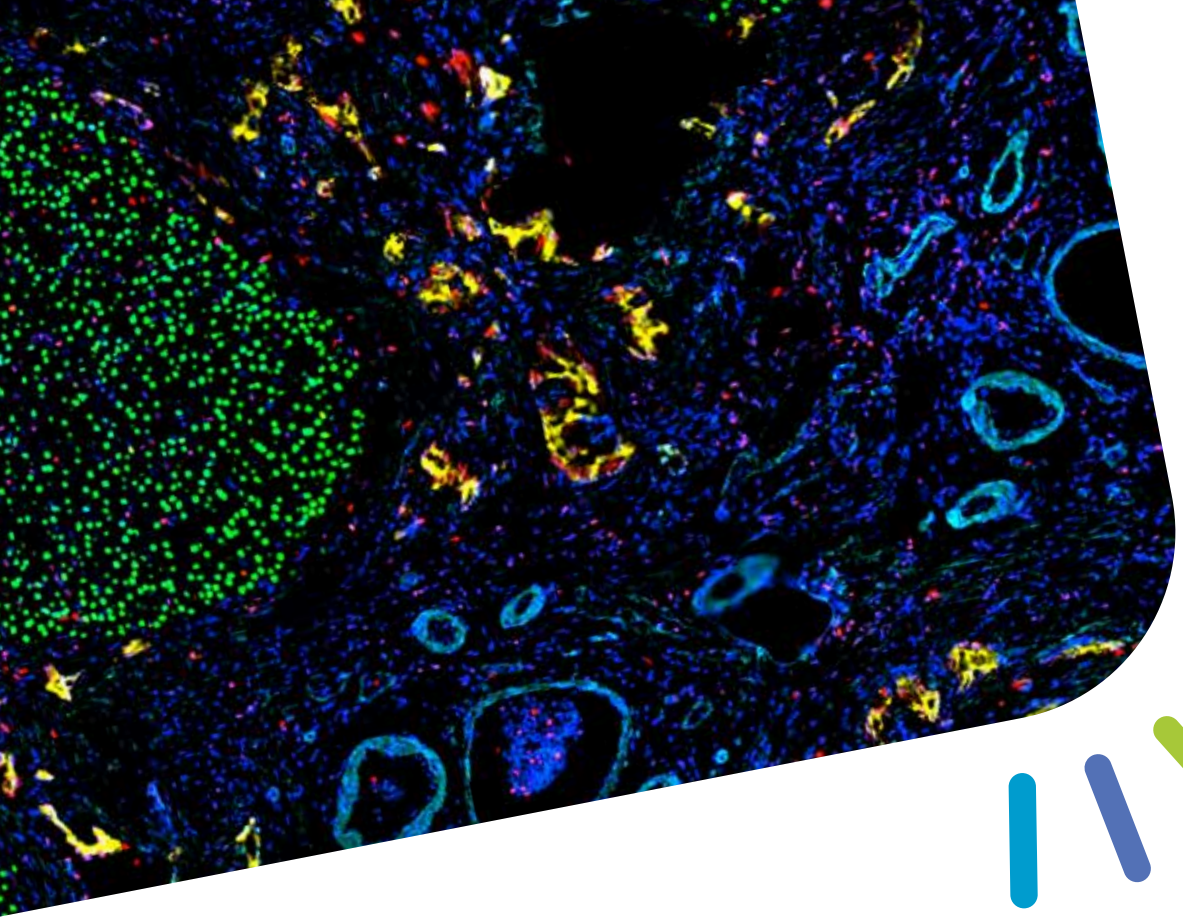
Thierry Lejeune, Gaëtan Stoquart, Stéphanie Dehem, Gauthier Everard, Ioannis Doumas

INTRODUCTION: The primary aim of this work was to summarize and compare the effects of active rehabilitation assisted by new technologies (virtual reality [VR], robot-assisted therapy [RAT] and telerehabilitation [TR]) on upper limb motor function and everyday living activity during the subacute and chronic phases of stroke. The secondary aims were to compare the effects of these technologies according to the intervention design (in addition to or in substitution of conventional therapy), the duration of active rehabilitation and the severity of patients' motor impairments.

EVIDENCE ACQUISITION: Several databases, namely PubMed, Scopus, Embase and Cochrane Library, were searched. Studies were included if they were meta-analyses with a moderate to high level of confidence (assessed with AMSTAR-2) that compared the effects of a new technology promoting active rehabilitation to that of a conventional therapy program among patients with stroke. Network meta-analyses were conducted to compare the effects of the new technologies.

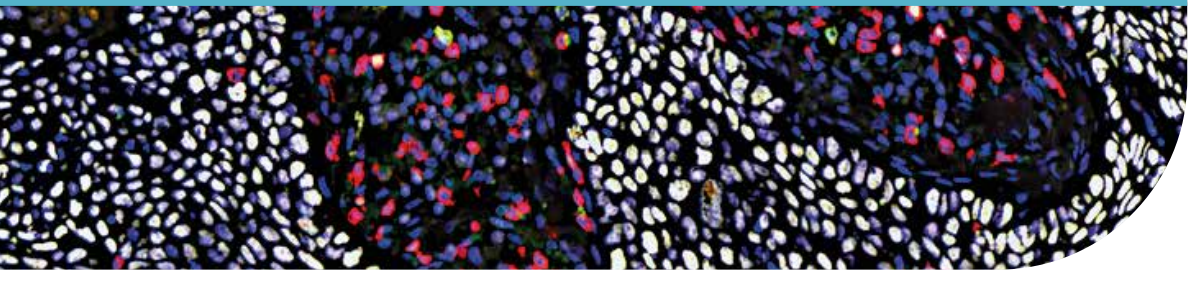
EVIDENCE SYNTHESIS: Eighteen different meta-analyses were selected and fifteen included in the quantitative analysis. In total these 15 meta-analyses were based on 189 different randomized controlled trials. VR (SMD≥0.25; P<0.05), RAT (SMD≥0.29; P≤0.29) and TR (SMD≥-0.08; P≤0.64) were found to be at least as effective as conventional therapy. During the subacute phase, RAT's greatest effect was observed for patients with severe-moderate impairments whereas VR and TR's greatest effects were observed for patients with mild impairments. During the chronic phase, the highest effects were observed for patients with mild impairments, for all studies technologies. Network meta-analyses showed that VR and RAT were both significantly superior to TR in improving motor function during the chronic phase but revealed no significant difference between VR, RAT and TR effectiveness on both motor function (during the subacute phase) and activity (during both chronic and subacute phase).

Conclusions: This overview provides low-to-moderate evidence that rehabilitation assisted with technologies are at least as effective as conventional therapy for patients with stroke. While VR and RAT seem to be more efficient during the subacute phase, all technologies seem to be as efficient as one another in the chronic phase.



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
- Gait Lab: instrumented treadmill fitted with 3D force sensors, 8 infrared 3D cameras, 16 channels of Wifi
- EMG, ergospirometer
- Artificial lung
- Rheometer
- Lung function equipment
- 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



POLE OF PNEUMOLOGY (PNEU)

Audag Nicolas, PT, PhD

William Poncin, PT, PhD

Gregory Reychler, PT, PhD

Pole Contact Person

Gregory Reychler
gregory.reychler@uclouvain.be

Researchers :

Aubriot Anne-Sophie, Cnockaert Pierre, Latiers Fabien, Latiers Anne-Claire, Maerckx Guillaume, Martin Ines, Nguyen Ngoc Minh, Thibon Christophe

PhD :

Audag Nicolas, Caty Gilles, Michotte Jean-Bernard, Morales Mestre Natalia, Piraux Elise, Poncin William, Reychler Gregory

Research Projects

PHYSIOTHERAPY

The effect of tongue elevation muscle training in patients with obstructive sleep apnea: A randomised controlled trial

William Poncin, Nils Correvon, Jonathan Tam, Jean-Christian Borel, Mathieu Berger, Giuseppe Liistro, Benny Mwenge, Raphael Heinzer, Olivier Contal

BACKGROUND: Oropharyngeal myofunctional therapy is a multi-component therapy effective to reduce the severity of obstructive sleep apnoea (OSA). However, existing protocols are difficult to replicate in the clinical setting. There is a need to isolate the specific effectiveness of each component of the therapy.

OBJECTIVE: To assess the effects of a 6 weeks tongue elevation training programme in patients with OSA.

METHODS: We conducted a multicentre randomised controlled trial. Eligible participants were adults diagnosed with moderate OSA who presented low adherence to continuous positive airway pressure therapy (mean use <4 h per night). The intervention group completed a 6 weeks tongue elevation training protocol that consisted in anterior tongue elevation strength and endurance tasks with the Iowa Oral Performance Instrument. The control group completed a 6 weeks sham training protocol that involved expiratory muscle training at very low intensity. Polygraphy data, tongue force and endurance, and OSA symptoms were evaluated pre- and post-intervention. The primary outcome was apneoa-hypopnea index (AHI).

RESULTS: Twenty-seven patients (55 ± 11 years) were recruited. According to modified intention-to-treat analysis (n = 25), changes in AHI and c did not significantly differ between groups. Daytime sleepiness (Epworth Sleepiness Scale) and tongue endurance significantly improved in the intervention group compared to the control group (p = .015 and .022, respectively). In the intervention group, 75% of participants had a decrease in daytime sleepiness that exceeded the minimal clinically important difference.

CONCLUSION: Six weeks of tongue elevation muscle training had no effect on OSA severity.

Consensus on Nasal Irrigation in Infants: A Delphi Study

Nicolas Audag, Pierre Cnockaert, Gregory Reychler, William Poncin

INTRODUCTION: Nasal irrigation is regularly used in infants to relieve upper airway symptoms. However, because there is no consensus on good practice, nasal irrigation in infants is described and applied heterogeneously among clinicians and between clinical trials.

OBJECTIVE: The aim of this study was to establish consensus regarding the use of nasal irrigation in infants.

METHODS: A panel of Belgian physiotherapists and physicians experienced in performing nasal irrigation in infants were surveyed using the Delphi technique. Three survey rounds were used. Participants rated their level of (dis)agreement to each statement in each round using a 6-point Likert scale. Consensus was defined for statements which collected at least 75% of responses in agreement or disagreement. The questionnaire of Round 1 was built on nasal irrigation practice habits previously collected from parents, childcare workers, and healthcare professionals. Questionnaires from rounds 2 and 3 were amended based on experts written feedback.

RESULTS: Thirty experts (12 physicians and 18 physiotherapists) completed all 3 questionnaires. Consensus was achieved for 47 of 75 statements (63%) distributed over the following domains: "contraindications," "indications and frequency of use," "irrigation means," "solution preparation," "solution volume," "realization of the technique," and "assessment of the efficacy of nasal irrigation."

CONCLUSION: This study provides the first well-constructed consensus on good practice on nasal irrigation in infants. Consensus on several statements across different domains were established but require validation in future trials. This study also proposes direction for future research focusing on statements that did not reach consensus.

AEROSOL

Effects of surgical facemasks on perceived exertion during submaximal exercise test in healthy children

Project Team Gregory Reychler, Marie Standaert, Nicolas Audag, Gilles Caty, Annie Robert, William Poncin

Only a few data associated to wearability of facemask during exercise are available in children. The aim of the study was to evaluate the effect of wearing a facemask on perceived exertion (primary aim), dyspnea, physical performance, and cardiorespiratory response during a submaximal exercise test in children aged between 8 and 12 years. This study was performed in 2021 in healthy volunteer children from 8 to 12 years. They performed prospectively two 1-min sit-to-stand tests (STST), with or without a surgical facemask. The perceived exertion (modified Borg scale), dyspnea (Dalhousie scale), heart rate, and pulsed oxygen saturation were recorded before and after STST. The STST measured the submaximal performance. Thirty-eight healthy children were recruited (8-9 years: n = 19 and 10-11 years: n = 19). After the STST, the perceived exertion increased with or without a facemask (8-9 years group: + 1 [0.6; 1.4] and + 1.6 [1.0; 2.1] - 10-11 years group: + 1.3 [0.7; 1.8] and + 1.9 [1.3; 2.6]) and it was higher with the facemask. The difference between the two conditions in perceived exertion was not clinically relevant in any group (mBorgf: 0.56 pts and 0.68 pts, respectively). The different domains of dyspnea assessed with Dalhousie scale were not influenced by the facemask. The submaximal performance measured by the STST was not changed by the mask whatever the age group. The cardio-respiratory demand was not clinically modified.Conclusion: The surgical facemask had no impact on dyspnea, cardiorespiratory parameters, and exercise performance during a short submaximal exercise in healthy children.

Impact of surgical mask on performance and cardiorespiratory responses to submaximal exercise in COVID-19 patients near hospital discharge: A randomized crossover trial

William Poncin, Adrien Schalkwijk, Charlie Vander Straeten, Frédéric Braem, Fabien Latiers, Gregory Reychler

BACKGROUND: Wearing a surgical mask in hospitalized patients has become recommended during care, including rehabilitation, to mitigate coronavirus disease 2019 (COVID-19) transmission. However, the mask may increase dyspnoea and raise concerns in promoting rehabilitation activities in post-acute COVID-19 patients.

OBJECTIVE: To evaluate the impact of the surgical mask on dyspnoea, exercise performance and cardiorespiratory response during a 1-min sit-to-stand test in hospitalized COVID-19 patients close to discharge.

METHODS: COVID-19 patients whose hospital discharge has been planned the following day performed in randomized order two sit-to-stand tests with or without a surgical mask. Outcome measures were recorded before, at the end, and after two minutes of recovery of each test. Dyspnoea (modified Borg scale), cardiorespiratory parameters and sit-to-stand repetitions were measured.

RESULTS: Twenty-eight patients aged 52 ± 10 years were recruited. Compared to unmasked condition, dyspnoea was significantly higher with the mask before and at the end of the sit-to-stand test (mean difference[95%-CI]: 1.0 [0.6, 1.4] and 1.7 [0.8, 2.6], respectively). The difference was not significant after the recovery period. The mask had no impact on cardiorespiratory parameters nor the number of sit-to-stand repetitions.

CONCLUSION: In post-acute COVID-19 patients near hospital discharge, the surgical mask increased dyspnoea at rest and during a submaximal exercise test but had no impact on cardiorespiratory response or exercise performance. Patients recovering from COVID-19 should be reassured that wearing a surgical facemask during physical or rehabilitation activities is safe. These data may also mitigate fears to refer these patients in rehabilitation centres where mask-wearing has become mandatory.

EXERCISE MEDICINE

High-intensity aerobic interval training and resistance training are feasible in rectal cancer patients undergoing chemoradiotherapy: a feasibility randomized controlled study

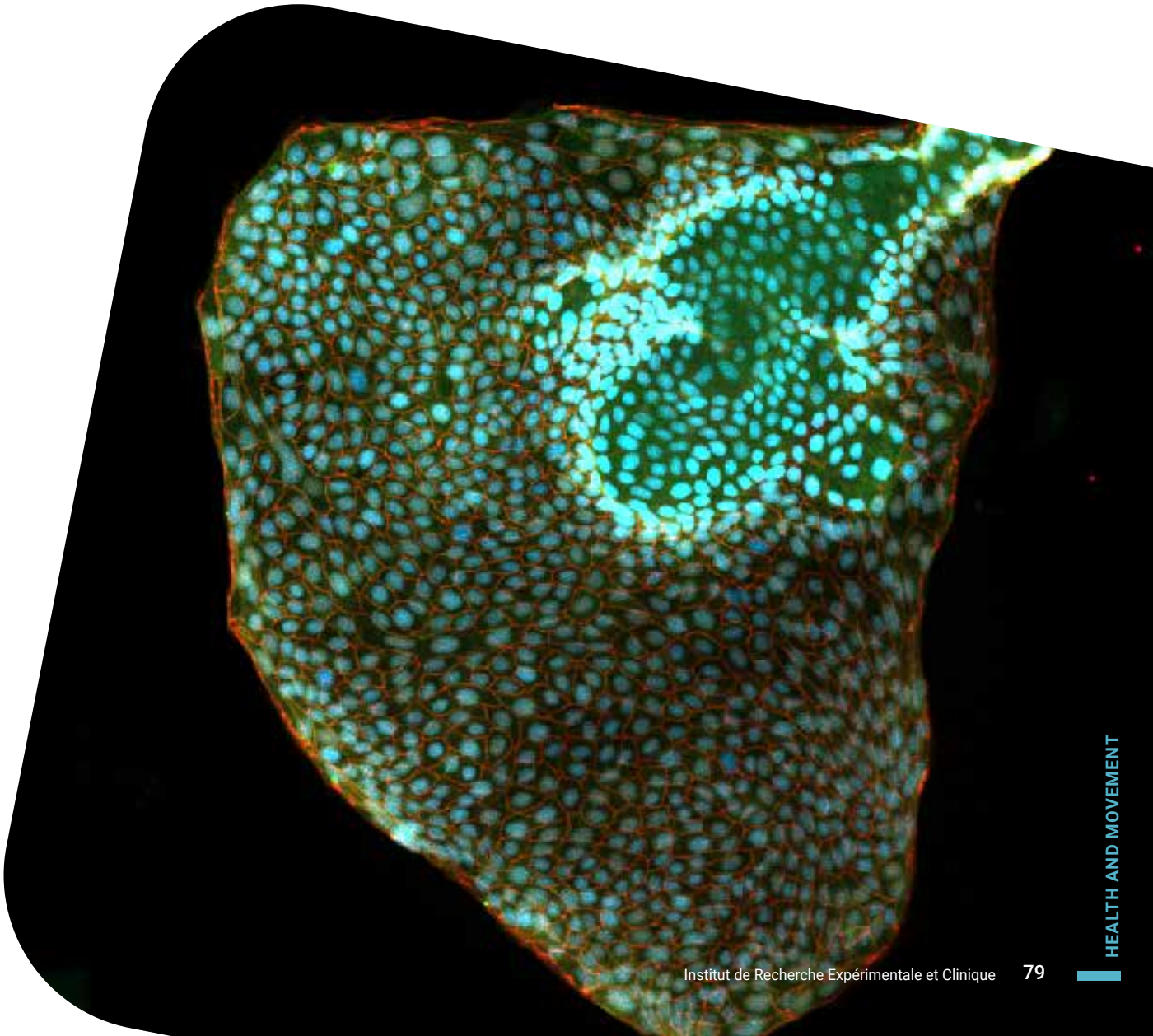
Elise Piraux, Gregory Reychler, David Vancraeynest, Xavier Geets, Daniel Léonard, Gilles Caty

BACKGROUND: There has been growing evidence of the benefits of high-intensity aerobic interval training (HIIT) and resistance training (RES) for populations with cancer. However, these two modalities have not yet been performed alone in rectal cancer patients undergoing neoadjuvant chemoradiotherapy (NACR T). Therefore, this study aimed to determine the feasibility of HIIT and RES in rectal cancer patients undergoing NACR T.

MATERIALS AND METHODS: Rectal cancer patients set to undergo NACRT were randomly assigned to HIIT intervention, RES intervention, or the usual care. Feasibility of HIIT and RES was assessed by measuring recruitment rate, adherence (retention rate, attendance rate, and exercise sessions duration and intensity), and adverse events. Endpoints (changes in fatigue, health-related quality of life, depression, daytime sleepiness, insomnia, sleep quality, functional exercise capacity, and executive function) were assessed at baseline and at week 5.

RESULTS: Among the 20 eligible patients, 18 subjects were enrolled and completed the study, yielding a 90% recruitment rate and 100% retention rate. Attendance at exercise sessions was excellent, with 92% in HIIT and 88% in RES. No exercise-related adverse events occurred.

CONCLUSION: This study demonstrated that HIIT and RES are feasible in rectal cancer patients undergoing NACR T.



POLE OF MORPHOLGY (MORF)

Catherine Behets
MD, PhD

Benoît Lengelé
MD, PhD, FRCS

Christine Galant
MD, PhD

Selena Toma
DDS, PhD

Researchers:
Marie-Christine Many, Daniel Manicourt, Julie Fosséprez, Grégoire André, Aybegüm Balci

Post-Doc:
Julie Craps

PhD:
Antoine Chretien, Guillaume Glaudot, Louis Maistriaux, Julie Manon

Technicians:
Christine de Ville de Goyet, Lies Fievé, Bettina Islamaj, Mélanie Beersaerts

Body donation team:
Michelle Cougnon, Walter Hudders, Bernard Caelen, Nicolas Charles-Pirlot

Pole Contact Person

Catherine Behets
catherine.behets@uclouvain.be

Research Projects

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 the spinal cord to allow better clinical assessment**

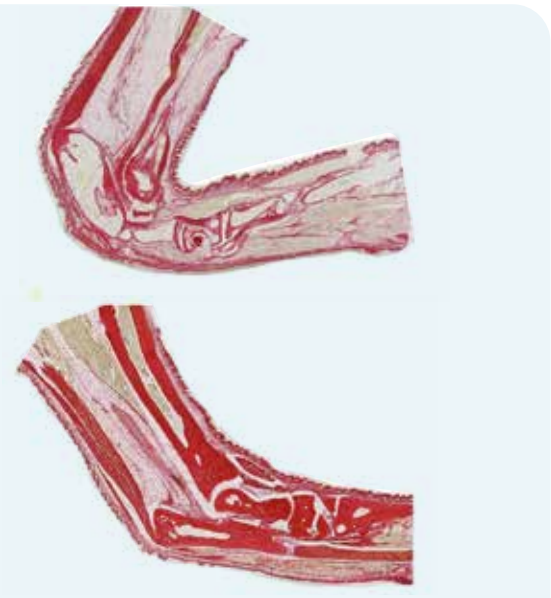


Figure 1. Sagittal section through triceps surae of oim (up) and WT (under) mice, showing fracture of calcaneus, thinner bones and thinner Achilles' tendon in oim than WT. Sirius red staining.

Osteogenesis imperfecta: characterization of bone-tendon unit in oim mouse

Antoine Chretien, Julie Fosséprez, Grégoire André, Jean Lebacq, Daniel Manicourt, Catherine Behetss

Osteogenesis imperfecta (OI) is a genetic connective tissue disorder characterized by low bone mass and spontaneous fractures. OI patients also present extra-skeletal manifestations such as dental anomalies, blue sclera, hearing loss and joint hypermobility. Several case reports have described tendon ruptures in patients with OI. We would like to characterize the phenotype of tendon to bone unit in oim mice, a validated model of type III OI. In the study we conducted, the oim mice showed avulsion fractures in high tendinous strain areas. The relative bone surface and the mineral density of epiphysis were significantly lower than those of WT mice. The cross-sectional area of oim tendons were significantly smaller but tenomodulin expression was not modified. Mechanical analyzes show that oim tendons are less stiff, less viscous but more stretchable than WT ones. Our data suggest that tendon to bone

unit is affected in oim mice, which could explain tendon ruptures in patients. It will be interesting to evaluate the effect of treatments on this complex. We have just set up a collaboration with the Inserm UMR_S 1229 RMeS - Equipe REGOS (Angers) in order to evaluate the effectiveness of a gastro-intestinal peptide.

Morphometric study of human spinal cord segments

Guillaume Glaudot, Anthony Nunès, Aleksandar Jankovski, Catherine Behets

Definition of the spinal cord (SC) areas in patients is currently based on the adjacent vertebrae. This study aims to develop a morphometric dataset allowing SC segment localization on MRI.
Thirty-two SC were dissected from 18 female and 14 male embalmed bodies (88±8.2 and 82±8.3 years old at death, respectively). Each individual SC segment was delimited and its anterior and posterior length, thickness and width were measured by two examiners. The data were analysed with ICC test, T-test (to compare the average of two samples) and Pearson test (for correlation) performed with Sigmaplot software.
Female whole SC length was significantly shorter than male one. The cranial (C4) and caudal (T1/T2) limits of the cervical enlargement as well as its maximal width (C6-C7) are identified by combining segment width and thickness. The thoracic region from T2 to T12 can also be identified using width and thickness values. The length of the lumbosacral region from L2 to S5 is particularly constant, irrespective from SC length and sex. Only segment thickness highlights the lumbar enlargement between L2 and S1 culminating in L3-L4-L5. Finally, from S2 to S5, width equals thickness and both decrease by 1mm per segment.
In conclusion, morphometric analysis of 32 human SC provided a dataset allowing statistical analysis of segment dimensions. A combined approach using mostly width and thickness provides landmarks to locate SC segment subsets of potential interest in standard clinical MRI setting.

REFERENCES 2022

NMSK

Samadi, Bahare ; Raison, Maxime ; Mahaudens, Philippe ; Detrembleur, Christine ; Achiche, Sofiane. *A preliminary study in classification of the severity of spine deformation in adolescents with lumbar/thoracolumbar idiopathic scoliosis using machine learning algorithms based on lumbosacral joint efforts during gait.* In: *Computer Methods in Biomechanics and Biomedical Engineering*, Vol. Na, no.Na, p. 1-12 (2022). doi:10.1080/10255842.2022.2117547. http://hdl.handle.net/2078.1/265219

Saragih, Ita ; Everard, Gauthier ; Lee, Bih-O. *A systematic review and meta-analysis of randomized controlled trials on the effect of serious games on people with dementia*. In: *Ageing Research Reviews*, Vol. 00, no.00, p. 00 (2022). doi:10.1016/j.arr.2022.101740. http://hdl.handle.net/2078.1/265612

Rauschen, Hannah ; arnaud randoux ; Nguyen, Anh Phong. *A systematic review of current surgical and conservative treatment in lower limb chronic exertional compartment syndrome. Sports Orthopaedics and Traumatology*. In: *Sports Orthopaedics and Traumatology*, (2022). doi:10.1016 (Accepté/Sous presse). http://hdl.handle.net/2078.1/266237

Borges, Flavia K ; Devereaux, P J ; Cuerden, Meaghan ; Sontrop, Jessica M ; Bhandari, Mohit ; Guerra-Farfán, Ernesto ; Patel, Ameen ; Sigamani, Alben ; Umer, Masood ; Neary, John ; Tiboni, Maria ; Tandon, Vikas ; Ramokgopa, Mmampapatla Thomas ; Sancheti, Parag ; Lawendy, Abdel-Rahman ; Balaguer-Castro, Mariano ; Jenkinson, Richard ; Ślęczka, Paweł ; Nur, Aamer Nabi ; Wood, Gavin C A ; Feibel, Robert J ; McMahon, John Stephen ; Biccard, Bruce M ; Ortalda, Alessandro ; Szczeklik, Wojciech ; Wang, Chew Yin ; Tomás-Hernández, Jordi ; Vincent, Jessica ; Harvey, Valerie ; Pettit, Shirley ; Balasubramanian, Kumar ; Slobogean, Gerard ; Garg, Amit X. *Accelerated Surgery Versus Standard Care in Hip Fracture (HIP ATTACK-1): A Kidney Substudy of a Randomized Clinical Trial.,* collab. HIP ATTACK-1 Investigators ; Veevaete, Laurent ; Le Polain de Waroux, Bernard ; Lavand'homme, Patricia ; Cornu, Olivier ; Tribak, Karim ; Yombi, Jean Cyr ; Touil, Nassim. In: *American journal of kidney diseases*, Vol. 80, no.5, p. 686-689 (2022). doi:10.1053/j.ajkd.2022.01.431. http://hdl.handle.net/2078.1/269864

Jakus, Lien ; Docquier, Pierre-Louis ; Veyckemans, Francis ; Reding, Raymond. *Anesthesia and World War II: When the Battlefield Becomes a Research Field-A Bibliometric Analysis of the Influence of World War II on the Development of Anesthesiology.*. In: *Anesthesia and Analgesia*, Vol. 134, no.1, p. 216-224 (2022). doi:10.1213/ANE.0000000000005745. http://hdl.handle.net/2078.1/257594

Huard, Maxime ; Hustin,Louis ; Detrembleur, Christine ; Letartre, Romain. *Are running stitches needed in DT4 Single Anteromedial Bundle Biological Augmentation transplant preparation ?*. In: *Acta Orthopaedica Belgica*, Vol. 88, no.2, p. 1-4 (2022). doi:10.52628/88.2.8982. http://hdl.handle.net/2078.1/261884

Van Cauter, Maïté ; Pirlot, Pierre ; Guilmot, Pierre-Philippe ; Thoreau, Loïc ; Bonnelance, Maxime ; Beckers, Gautier ; Poilvache, Hervé ; Morcillo, Daniel ; Druez, Vincent ; Dubuc, Jean-Emile ; Irda, Nadia ; Kaminski, Ludovic ; Vandergugten, Simon ; Sirbu, Alin ; Tribak, Karim ; Putineanu, Dan Constantin ; Mathieu, David ; Schubert, Thomas ; Yombi, Jean Cyr ; de Wouters d'Oplinter, Solange ; Docquier, Pierre-Louis ; Libouton, Xavier ; Thienpont, Emmanuel ; Banse, Xavier ; Barbier, Olivier ; Cornu, Olivier. *Chirurgie orthopédique et traumatologie: que retenir en 2021?.*

In: *Louvain médical*, Vol. 141, no.2, p. 120-127 (2022). http://hdl.handle.net/2078.1/268176

Everard, Gauthier ; Otmane-Tolba, Yasmine ; Rosselli, Zélie ; Pellissier, Thomas ; Ajana, Khawla ; Dehem, Stéphanie ; Auvinet, Edouard ; Edwards, Martin ; Lebleu, Julien ; Lejeune, Thierry. *Concurrent validity of an immersive virtual reality version of the Box and Block Test to assess manual dexterity among patients with stroke.* In: *Journal of NeuroEngineering and Rehabilitation*, Vol. 19, no.7, p. 1-11 (2022). doi:10.1186/s12984-022-00981-0. http://hdl.handle.net/2078.1/257527

Beckmann, Johannes ; Barrett, David ; Thienpont, Emmanuel. *Cutting-Edge Approaches in Arthroplasty: Before, during and after Surgery.*. In: *Journal of personalized medicine*, Vol. 12, no.10, p. 1671 [1-5] (2022). doi:10.3390/jpm12101671. http://hdl.handle.net/2078.1/269261

Poilvache, Hervé ; Van Bambeke, Françoise ; Cornu, Olivier. *Development of an innovative model of PJI treated with DAIR.*. In: *Frontiers in medicine*, Vol. 9, p. 984814 [1-14] (2022). doi:10.3389/fmed.2022.984814. http://hdl.handle.net/2078.1/268169

Luc, Alexandre. *Do the kinematics and sensorimotor control of people with chronic non-specific neck pain differ from those of healthy individuals when assessed in an immersive virtual reality environment? A systematic review*. In: *Physical Therapy Reviews*, Vol. 00, no.00, p. 00 (2022). doi:10.1080/10833196.2022.2143211. http://hdl.handle.net/2078.1/266602

Gabriel, Charlotte ; Barbier, Olivier ; David, Mathieu ; Manon, Julie ; Detrembleur, Christine ; Libouton, Xavier. *Effect of splint on pain, function and quality of life in trapeziometacarpal osteoarthritis patients?*. In: *Acta Orthopaedica Belgica*, Vol. 88, no. 1, p. 179-185 (2022). doi:10.52628/88.1.22. http://hdl.handle.net/2078.1/263518

Declerck, Louise ; Loiselet, Céline ; Kaux, Jean-François ; Lejeune, Thierry ; Vanderthommen, Marc ; Stoquart, Gaëtan. *Effect of the COVID-19 pandemic lockdown on physical activity of individuals with a spinal cord injury in Belgium: observational study*. In: *Annals of Physical and Rehabilitation Medicine*, p. 101649 (2022). doi:10.1016/j.rehab.2022.101649 (Accepté/Sous presse). http://hdl.handle.net/2078.1/259276

Asquini, Giacomo ; Pitance, Laurent ; Michelotti, Ambra ; Falla, Deborah. *Effectiveness of manual therapy applied to craniomandibular structures in temporomandibular disorders: A systematic review.*. In: *Journal of oral rehabilitation*, Vol. 49, no. 4, p. 442-455 (2022). doi:10.1111/joor.13299. http://hdl.handle.net/2078.1/272542

Saragih, Ita Daryanti ; Everard, Gauthier ; Tzeng, Huey-Ming ; Saragih, Ice Septriani ; Lee, Bih-0. *Efficacy of Robots-Assisted Therapy in Patients With Stroke - A Meta-analysis Update.* In: *The Journal of Cardiovascular Nursing*, Vol. 00, no. 00, p. 00 (2022). doi:10.1097/JCN.0000000000000945. http://hdl.handle.net/2078.1/265400

Erratum: Recommendations from the ICM-VTE: General., collab. ICM-VTE General Delegates ; Thienpont, Emmanuel. In: *The Journal of bone and joint surgery. American volume*, Vol. 104, no.15, p. e69 (2022). doi:10.2106/JBJS.ER.21.01531. http://hdl.handle.net/2078.1/269268

Bom, Frank ; Barbier, Olivier ; Libouton, Xavier ; Docquier, Pierre-Louis. *Forearm deformity in multiple hereditary exostosis. Radiologic predictors of radial head dislocation.*. In: *Orthopaedics & traumatology, surgery & research*, , p. 103445 (2022). doi:10.1016/j.otsr.2022.103445 (Accepté/Sous presse). http://hdl.handle.net/2078.1/268122

Roussel, Nathalie ; Chantrain, Valérie-Anne ; Foubert, Anthe ; Lambert, Catherine ; Hermans, Cédric ; Meeus, Mira ; Guillaume, Sylvain ; Lecouvet, Frédéric ; Krüger, Steffen ; Hilberg, Thomas ; Lobet, Sébastien. *Gaining more insight into ankle pain in haemophilia: A study exploring pain, structural and functional evaluation of the ankle joint*. In: *Haemophilia*, Vol. 28, no. 3, p. 480-490 (2022). doi:10.1111/hae.14544. http://hdl.handle.net/2078.1/259576

Hermans, Cédric ; Noone, Declan ; Benson, Gary ; Dolan, Gerry ; Eichler, Hermann ; Jiménez-Yuste, Víctor ; Königs, Christoph ; Lobet, Sébastien ; Pollard, Debra ; Zupančić-Šalek, Silva ; Mancuso, Maria Elisa. *Hemophilia treatment in 2021: Choosing the"optimal" treatment using an integrative, patient-oriented approach to shared decision-making between patients and clinicians.* In: *Blood Reviews*, Vol. 52, p. 100890 [1-9] (2022). doi:10.1016/j.blre.2021.100890. http://hdl.handle.net/2078.1/253477

Ruiz-Sorribas, Albert ; Poilvache, Hervé ; Kamarudin, Nur Hidayatul Nazirah ; Braem, Annabel ; Van Bambeke, Françoise. *Hydrolytic Enzymes as Potentiators of Antimicrobials against an Inter-Kingdom Biofilm Model.* In: *Microbiology Spectrum*, Vol. 10, no.1, p. e0258921 (2022). doi:10.1128/spectrum.02589-21. http://hdl.handle.net/2078.1/259572

Miesbach, Wolfgang ; Barcenilla, Sara Garcia ; Golan, Gaby ; Lobet, Sébastien. *Implications of haemophilia gene therapy for the changing role of the multidisciplinary team.*. In: *Haemophilia* : the official journal of the World Federation of Hemophilia, Vol. 28, no.1, p. e12-e14 (2022). doi:10.1111/hae.14440. http://hdl.handle.net/2078.1/263636

Chantrain, Christophe ; Docquier, Pierre-Louis ; Lejeune, Gauthier. *Influence de l'âge, du potentiel de croissance et de la fonctionnalité dans la prise en charge des tumeurs osseuses de l'enfant : exemple de la plastie de rotation.* In: *Revue medicale de Liege*, Vol. 77, no.3, p. 139-145 (2022). http://hdl.handle.net/2078.1/259608

Perez-Abadia, Gustavo ; Pindur, Lukas ; Frank, Johannes ; Marzi, Ingo ; Sauerbier, Michael ; Carroll, Sean M ; Schnapp, Luis ; Mendez, Manuel ; Sepulveda, Sergio ; Werker, Paul ; Libouton, Xavier ; Barbier, Olivier ; Dehoux, Jean-Paul ; Maquieira, Marcelo E ; Espriella, Cuahutemoc Marques ; Joshua, Irving ; Ovadja, Zachri N ; Spingler, Markus ; Barker, John H. *Intensive hands-on microsurgery course provides a solid foundation for performing clinical microvascular surgery.*. In: *European Journal of Trauma and Emergency Surgery*, (2022). doi:10.1007/s00068-022-02040-8 (Accepté/Sous presse). http://hdl.handle.net/2078.1/264158

Caudron, Martin ; Detrembleur, Christine ; Van Cauter, Maite. *Is simultaneous bilateral total hip arthroplasty deleterious in a biomechanical point of view? A comparative gait analysis study*. In: *BMC Musculoskeletal Disorders*, Vol. 23, no.903, p. 1-9 (2022). doi:10.1186/s12891-022-05856-y. http://hdl.handle.net/2078.1/265698

El Khoury, Ghady ; Barbier, Olivier ; Vanderlinden, Antoine ; Libouton, Xavier. *La rhizarthrose : que proposer au patient pour une douleur de la base du pouce ?*. In: *Louvain médical*, Vol. 141, no. 6, p. 320-324 (2022). http://hdl.handle.net/2078.1/269492

Kouassi, Kouamé Jean-Eric ; Akobé, Jean Régis ; Kouassi, Adélaide Aya ; Fonkoué, Loïc ; Detrembleur, Christine ; Kodo, Michel ; Cornu, Olivier. *Locally developed external fixators as definitive treatment of open tibia diaphyseal fractures: a clinical prospective study conducted in Ivory Coast.*. In: *International orthopaedics*, Vol. 46, no.1, p. 79-87 (2022). doi:10.1007/s00264-021-05073-7. http://hdl.handle.net/2078.1/256239

David, Mercedes ; Raison, Maxime ; Paul, Stéphanie ; Cartiaux, Olivier ; Detrembleur, Christine ; Mahaudens, Philippe. *Locoregional lung ventilation distribution in girls with adolescent idiopathic scoliosis and healthy adolescents. The immediate effect of Schroth 'derotational breathing' exercise in a controlled-trial.* In: *Physiotherapy Theory and Practice*, Vol. 1, no.1, p. 1-16 (2022). doi:10.1080/09593985.2022.2033896. http://hdl.handle.net/2078.1/258243

Madoki, Alexandre ; Tuerlinckx, Clément ; Rausin, Gauthier ; Guiraud, Kevin ; Docquier, Pierre-Louis. *Lower limb deformities and limb length discrepancies in hereditary multiple exostoses.*. In: *Acta orthopaedica Belgica*, Vol. 88, no.1, p. 198-205 (2022). doi:10.52628/88.1.25. http://hdl.handle.net/2078.1/266739

Dubail, Angélique ; Galant, Christine ; Borbath, Ivan ; Lecouvet, Frédéric ; Chaouki, Amine ; Barbier, Olivier ; Baldin, Paméla. *Metastatic cancer in an uncommon location: importance of clinico-pathological correlation.*. In: *Acta gastro-enterologica Belgica*, Vol. 85, no. 2, p. 408-409 (2022). doi:10.51821/85.2.10156. http://hdl.handle.net/2078.1/263709

Rialet-Micoulau, Joséphine ; Lucas, Valoris ; Demoulin, Christophe ; Pitance, Laurent. *Misconceptions of physical therapists and medical doctors regarding the impact of lifting a light load on low back pain.* In: *Brazilian Journal of Physical Therapy*, Vol. 26, no.1, p. 100385 (2022). doi:10.1016/j.bjpt.2021.100385. http://hdl.handle.net/2078.1/263712

Nguyen, Anh Phong ; Detrembleur, Christine ; Fisette, Paul ; Selves, Clara ; Mahaudens, Philippe. *MyotonPro Is a Valid Device for Assessing Wrist Biomechanical Stiffness in Healthy Young Adults.* In: *Frontiers in Life Science : frontiers of interdisciplinary research in the life sciences,* (2022). doi:10.3389/fspor.2022.797975. http://hdl.handle.net/2078.1/258846

Everard, Gauthier ; Declerck, Louise ; Detrembleur, Christine ; Léonard Sophie ; Bower, Glenn ; Dehem, Stéphanie ; Lejeune, Thierry. *New technologies promoting active upper limb rehabilitation after stroke. An overview and network meta-analysis.* In: *European Journal of Physical and Rehabilitation Medicine*, Vol. 58, no. 04, p. 530-48 (2022). doi:10.23736/S1973-9087.22.07404-4. http://hdl.handle.net/2078.1/261607

Brismée, Jean-Michel ; Froment, Frédéric P. ; Bellot, Nicolas ; Mambriani, Aurore ; Chauvet, Guillaume ; Chevrier, Solenne ; Desjardins, Thibault ; Riquier, Sylvain ; Rakotoarivelo, Lanto Harisoa ; Datoussaid, Kader ; Pitance, Laurent. *OMT-France publishes the first French physiotherapy guide for triage of patients with neuromusculoskeletal conditions – a step toward direct access in French speaking countries.* In: *Journal of Manual & Manipulative Therapy*, Vol. 30, no. 5, p. 259-260 (2022). doi:10.1080/10669817.2022.2119348. http://hdl.handle.net/2078.1/272541

Wendo, Kevin ; Barbier, Olivier ; Bollen, Xavier ; Schubert, Thomas ; Lejeune, Thierry ; Raucent, Benoît ; Olszewski, Raphael. *Open-Source 3D Printing in the Prosthetic Field—The Case of Upper Limb Prostheses: A Review.* In: *Machines*, Vol. 10, no.6, p. 413 [1-35] (2022). doi:10.3390/machines10060413. http://hdl.handle.net/2078.1/261906

Delieux, Louise ; Detrembleur, Christine ; Mahaudens, Philippe ; Esculier, Jean Francois ; Nguyen, Anh Phong ; Gillain, Loris. *Opinions about running shoes in runners and non-runners.* In: *Footwear Science*, (2022). doi:10.1080/19424280.2022.2144468. http://hdl.handle.net/2078.1/266871

Goetz, Pierre-Emmanuel ; Dumitriu, Dana Ioana ; Galant, Christine ; Docquier, Pierre-Louis. *Osteofibrous dysplasia-like adamantinoma of isolated fibula in a child mimicking chronic osteomyelitis with pathological fracture.*. In: *Journal of surgical case reports*, Vol. 2022, no.6, p. rjac196 [1-4] (2022). doi:10.1093/jscr/rjac196. http://hdl.handle.net/2078.1/263032

Banse, Xavier ; Kaminski, Ludovic ; Irda, Nadia ; Briquet, Caroline ; Cornu, Olivier ; Yombi, Jean Cyr. P*MMA-cement anterior column reconstruction in surgical treatment of spondylodiscitis.*. In: *Brain & spine*, Vol. 2, p. 101186 [1-8] (2022). doi:10.1016/j.bas.2022.101186. http://hdl.handle.net/2078.1/266750

Foubert, Anthe ; Roussel, Nathalie ; Chantrain, Valérie-Anne ; Hermans, Cédric ; Lambert, Catherine ; Lobet, Sébastien ; Meeus, Mira. *Pain coping behaviour strategies in people with haemophilia: A systematic literature review.* In: *Haemophilia*, Vol. 28, no. 6, p. 902-9016 (2022). doi:10.1111/hae.14627. http://hdl.handle.net/2078.1/264238

Paulmier, Amaury ; Raad, Mathieu ; Verhelle, Charles-Edouard ; Paul, Laurent ; Docquier, Pierre-Louis. *Patient-Specific Instruments for Forearm Sarcoma Resection and Allograft Reconstruction in Children: Results in 4 Cases.*. In: *Sarcoma*, Vol. 2022, p. 7005629 [1-8] (2022). doi:10.1155/2022/7005629. http://hdl.handle.net/2078.1/267220

Burton, Quentin ; Lejeune, Thierry ; Dehem, Stéphanie ; Lebrun, Noémie ; Ajana, Khawla ; Edwards, Martin Gareth ; Everard, Gauthier. *Performing a shortened version of the Action Research Arm Test in immersive virtual reality to assess post-stroke upper limb activity.* In: *Journal of NeuroEngineering and Rehabilitation*, Vol. 19, no.1, p. 1-12 (2022). doi:10.1186/s12984-022-01114-3. http://hdl.handle.net/2078.1/267923

Manon, Julie ; Evrard, Robin ; Maistriaux, Louis ; Fievé, Lies ; Heller, Ugo ; Magnin, Delphine ; Boisson, Jean ; Kadlub, Natacha ; Schubert, Thomas ; Lengelé, Benoît ; Behets Wydemans, Catherine ; Cornu, Olivier. *Periosteum and fascia lata: Are they so different?*. In: *Frontiers in bioengineering and biotechnology,* Vol. 10, p. 944828 [1-16] (2022). doi:10.3389/fbioe.2022.944828. http://hdl.handle.net/2078.1/266748

Ruiz-Sorribas, Albert ; Poilvache, Hervé ; Van Bambeke, Françoise. *Pharmacodynamics of Moxifloxacin, Meropenem, Caspofungin, and Their Combinations*

against In Vitro Polymicrobial Interkingdom Biofilms. In: *Antimicrobial Agents and Chemotherapy*, Vol. 66, no.2, p. e02149-21 (2022). doi:10.1128/aac.02149-21. http://hdl.handle.net/2078.1/262724

Vanderlinden, Antoine ; El Khoury, Ghady ; Bonnelance, Maxime ; Libouton, Xavier ; Barbier, Olivier. *Prise en charge d'une fracture du radius distal chez l'adulte : le bon traitement pour le bon patient*. In: *Louvain médical*, Vol. 141, no.5, p. 269-275 (2022). http://hdl.handle.net/2078.1/268819

Evrard, Robin ; Schubert, Thomas ; Paul, Laurent ; Docquier, Pierre-Louis. *Quality of resection margin with patient specific instrument for bone tumor resection.*. In: *Journal of bone oncology*, Vol. 34, p. 100434 [1-5] (2022). doi:10.1016/j.jbo.2022.100434. http://hdl.handle.net/2078.1/263036

de Wouters d'Oplinter, Solange ; Detrembleur, Christine ; Durnez, Anne ; Mahaudens, Philippe ; Henry, Brice ; Schrooyen, Jean ; Docquier, Pierre-Louis. *Quantitative gait analysis in children with osteogenesis imperfecta: relationship between gait deviations and clinical features.* In: *Acta orthopaedica Belgica*, Vol. 88, no.2, p. 255-262 (2022). doi:10.52628/88.2.9117. http://hdl.handle.net/2078.1/264612

Recommendations from the ICM-VTE: General., collab. *ICM-VTE General Delegates* ; Thienpont, Emmanuel. In: *The Journal of bone and joint surgery. American volume*, Vol. 104, no.Suppl 1, p. 4-162 (2022). doi:10.2106/JBJS.21.01531. http://hdl.handle.net/2078.1/269267

Luc, Alexandre ; Antoine, François ; Bekkering, Geertruida ; Detrembleur, Christine ; Pitance, Laurent. *Relationship between leisure time physical activity, weight, and the onset and persistence of non-specific neck pain: A systematic review.* In: *Journal of Orthopaedic and Sports Physical Therapy*, Vol. 52, no. 12, p. 777-791 (2022). doi:10.2519/jospt.2022.11137. http://hdl.handle.net/2078.1/264435

Declerck, Louise ; Schutz, Xavier ; Kaux, Jean-François ; Stoquart, Gaëtan ; Lejeune, Thierry ; Vanderthommen, Marc ; Cayrol, Timothée ; Selves, Clara ; Van Beveren, Julien ; Beaudart, Charlotte. *Standard error of measurement and minimal detectable change of the French physical activity scale for individuals with physical disabilities.*. In: *Annals of physical and rehabilitation medicine*, Vol. 65, no.3, p. 101583 (2022). doi:10.1016/j.rehab.2021.101583. http://hdl.handle.net/2078.1/273270

Raad, Mathieu ; Van Cauter, Maïte ; Detrembleur, Christine ; Cornu, Olivier ; Vandemeulebroecke, Guillaume. *Survey regarding prevention of surgical site infection after orthopaedic surgery in Belgium: are we on the right track?*. In: *Acta Orthopaedica Belgica*, Vol. 88, no.4, p. 645-654 (2022). doi:10.52628/88.4.9722. http://hdl.handle.net/2078.1/274383

Mancus Maria Elisa ; Holstein Khatarina ; O'Donnell James ; Lobet, Sébastien ; Klamroth, Robert ; *On behalf of the FVIII Think Tank Study Group. Synovitis and joint health in patients with haemophilia: Statements from a European e-Delphi consensus study.* In: *Haemophilia* (Print), Vol. 1, no.1, p. 1-10 (2022). doi:10.1111/hae.14734. http://hdl.handle.net/2078.1/271430

Valet, Maxime ; Pierchon, Laura ; Lejeune, Thierry. *The 2-min walk test could replace the 6-min walk test in ambulant persons with subacute or chronic stroke: a two-stage retrospective study.*. In: *International journal of rehabilitation research*, Vol. /, no./, p. / (2022). doi:10.1097/MRR.0000000000000556 (Accepté/Sous presse). http://hdl.handle.net/2078.1/267707

Issa, Julien ; Olszewski, Raphael ; Dyszkiewicz-Konwińska, Marta. *The Effectiveness of Semi-Automated and Fully Automatic Segmentation for Inferior Alveolar Canal Localization on CBCT Scans: A Systematic Review.*. In: *International journal of environmental research and public health*, Vol. 19, no.1, p. 1-10 (2022). doi:10.3390/ijerph19010560. http://hdl.handle.net/2078.1/263850

St-Louis, Jean ; Abad, Audrey ; Funk, Sharon ; Tilak, Merlyn ; Classey, Stephen ; Zourikian, Nichan ; McLaughlin, Paul ; Lobet, Sébastien ; Hernandez, Grace ; Akins, Stacie ; Wells, Anna J. ; Manco-Johnson, Marilyn ; John, Judy ; Austin, Steve ; Chowdary, Pratima ; Hermans, Cédric ; Nugent, Diane ; Bakeer, Nihal ; Mangles, Sarah ; Hilliard, Pamela ; Blanchette, Victor S. ; Feldman, Brian M.. The Hemophilia Joint Health Score version 2.1 Validation in Adult Patients Study: A multicenter international study. In: Research and practice in thrombosis and haemostasis, Vol. 6, no. 2, p. e12690 [1-11] (2022). doi:10.1002/rth2.12690. http://hdl.handle.net/2078.1/260274

Greenbaum, Tzvika ; Pitance, Laurent ; Kedem, Ron ; Emodi-Perlman, Alona. The mouth-opening muscular performance in adults with and without temporomandibular disorders: A systematic review. In: Journal of Oral Rehabilitation, (2022). doi:10.1111/joor.13303. http://hdl.handle.net/2078.1/257962

El Khoury, Ghady ; Libouton, Xavier ; De Boeck, Florian ; Barbier, Olivier. *Use of a 3D-printed splint for the treatment of distal radius fractures: A randomized controlled trial.*. In: *Orthopaedics & traumatology, surgery & research* : OTSR, Vol. 136, no.1, p. 103326 (2022). doi:10.1016/j.otsr.2022.103326. http://hdl.handle.net/2078.1/263877

Devis, Marine ; Stoquart, Gaëtan ; Géonet, Marie ; London, Frédéric ; van Pesch, Vincent. *Validation of the French version of the Multiple Sclerosis Intimacy And Sexuality Questionnaire-19: A preliminary study.*. In: *Multiple sclerosis and related disorders*, Vol. 65, no.1, p. 103986 (2022). doi:10.1016/j.msard.2022.103986. http://hdl.handle.net/2078.1/273272

Rodriguez Tapia, Gonzalo ; Doumas, Ioannis ; Lejeune, Thierry ; Previnaire, Jean-Gabriel. *Wearable powered exoskeletons for gait training in tetraplegia: a systematic review on feasibility, safety and potential health benefits.* In: *Acta Neurologica Belgica*, (2022). doi:10.1007/s13760-022-02011-1. http://hdl.handle.net/2078.1/263651

Sanchez, Christelle ; Zappia, Jérémie ; Lambert, Cécile ; Foguenne, Jacques ; Dierckxsens, Yvan ; Dubuc, Jean-Emile ; Delcour, Jean-Pierre ; Gothot, André ; Henrotin, Yves. *and Extracts Modulate Different and Complementary Pathways on Human Chondrocytes : Deciphering of a Transcriptomic Study.*. In: *Frontiers in pharmacology*, Vol. 13, p. 931914 [1-14] (2022). doi:10.3389/fphar.2022.931914. http://hdl.handle.net/2078.1/271000

PNEU

Piraux E, Reychler G, Vancraeynest D, Geets X, Léonard D, **Caty G.**, High-intensity aerobic interval training and resistance training are feasible in rectal cancer patients undergoing chemoradiotherapy: a feasibility randomized controlled study, Rep Pract Oncol Radiother. 2022 May 19;27(2):198-208. doi: 10.5603/RPOR.a2022.0036. eCollection 2022.

Hardy S, Berardis S, Aubriot AS, **Reychler G**, Gohy S., One-minute sit-to-stand test is practical to assess and follow the muscle weakness in cystic fibrosis, Respir Res. 2022 Sep 23;23(1):266. doi: 10.1186/s12931-022-02176-6.

Reychler G, Piraux E, Beaumont M, **Caty G**, Liistro G., Telerehabilitation as a Form of Pulmonary Rehabilitation in Chronic Lung Disease: A Systematic Review, Healthcare (Basel). 2022 Sep 17;10(9):1795. doi: 10.3390/healthcare10091795.

Poncin W, Correvon N, Tam J, Borel JC, Berger M, Liistro G, Mwenge B, Heinzer R, Contal O., The effect of tongue elevation muscle training in patients with obstructive sleep apnea: A randomised controlled trial, J Oral Rehabil. 2022 Nov;49(11):1049-1059. doi: 10.1111/joor.13369. Epub 2022 Sep 21.

Duprez F, Bruyneel A, Vanhelleputte K, Meurant V, Raquet B, Dupriez F, de Terwangne C, Tortora R, Jacques JM, Greef J, **Poncin W.**, Comparison of the Arterial Oxygenation Between Two Oxygen Masks, Respir Care. 2022 Jul 19:respcare.09898. doi: 10.4187/respcare.09898. Online ahead of print.

Audag N, Cnockaert P, Reychler G, Poncin W., Consensus on Nasal Irrigation in Infants: A Delphi Study, Ann Otol Rhinol Laryngol. 2022 Jul 14:34894221112514. doi: 10.1177/00034894221112514. Online ahead of print.

Van Hove O, Gillet A, Tack J, **Reychler G**, Guatteri M, Ballarin A, Thomas J, Espinoza R, Bonnier F, Norrenberg M, Daniel P, Toussaint M, Leduc D, Bonnechère B, Taton O., Development of a Medium Care Unit Using an Inexperienced Respiratory Staff: Lessons Learned during the COVID-19 Pandemic, Int J Environ Res Public Health. 2022 Jun 15;19(12):7349. doi: 10.3390/ijerph19127349.

Poncin W, Lebret M, **Maerckx G.**, [Pneumatic instrumental airway clearance techniques: Description, settings and indications], Rev Mal Respir. 2022 Jun;39(6):534-546. doi: 10.1016/j.rmr.2022.04.006. Epub 2022 Jun 20.

Hammer S, Toussaint M, Vollsæter M, Nesbjørg Tvedt M, Drange Røksund O, **Reychler G**, Lund H, Andersen T., Exercise Training in Duchenne Muscular Dystrophy: A Systematic Review and Meta-Analysis, J Rehabil Med. 2022 Jan 11;54:jrm00250. doi: 10.2340/jrm.v53.985.

Reychler G, Beaumont M, Contal O, Georges M., [Respiratory physiotherapy in 2022: A multimodal approach], Rev Mal Respir. 2022 Apr;39(4):319-320. doi: 10.1016/j.rmr.2022.04.009.

Burton M, Valet M, **Caty G**, Aboubakar F, **Reychler G.**, Telerehabilitation physical exercise for patients with lung cancer through the course of their disease: A systematic review, J Telemed Telecare. 2022 May 12:1357633X221094200. doi: 10.1177/1357633X221094200. Online ahead of print.

Duprez F, De Terwangne C, **Poncin W**, Bruyneel A, De Greef J, Wittebole X., A Modified Aerosol Mask Could Significantly Save Oxygen Supplies during SARS COV 2 Pandemic, J Emerg Nurs. 2022 May;48(3):248-250. doi: 10.1016/j.jen.2021.08.002.

Poncin W, Schalkwijk A, Vander Straeten C, Braem F, **Latiers F, Reychler G.**, Impact of surgical mask on performance and cardiorespiratory responses to submaximal exercise in COVID-19 patients near hospital discharge: A randomized crossover trial, Clin Rehabil. 2022 Aug;36(8):1032-1041. doi: 10.1177/02692155221097214. Epub 2022 Apr 27.

Thibon C, Vecellio L, Dubus JC, Kabamba B, **Reychler G.**, Nebulization and COVID-19: Is the risk of spread actual?, Respir Med. 2022 Jun;197:106854. doi: 10.1016/j.rmed.2022.106854. Epub 2022 Apr 20.

Reychler G, Standaert M, **Audag N, Caty G**, Robert A, **Poncin W**., Effects of surgical facemasks on perceived exertion during submaximal exercise test in healthy children, Eur J Pediatr. 2022 Jun;181(6):2311-2317. doi: 10.1007/s00431-022-04430-x. Epub 2022 Mar 3.

Poncin W, Baudet L, Braem F, **Reychler G**, Duprez F, Liistro G, Belkhir L, Yombi JC, De Greef J., Systems on Top of Nasal Cannula Improve Oxygen Delivery in Patients with COVID-19: a Randomized Controlled Trial, J Gen Intern Med. 2022 Apr;37(5):1226-1232. doi: 10.1007/s11606-022-07419-2. Epub 2022 Feb 8.

Cnockaert P, Audag N, Poncin W., Nasal irrigation practice habits in infants: A Belgian survey: Nasal irrigation practice habits in infants, Arch Pediatr. 2022 Apr;29(3):200-206. doi: 10.1016/j.arcped.2022.01.010. Epub 2022 Jan 31.

Schurmans G, **Caty G, Reychler G.**, Is the Peri-Bariatric Surgery Exercise Program Effective in Adults with Obesity: a Systematic Review, Obes Surg. 2022 Feb;32(2):512-535. doi: 10.1007/s11695-021-05693-3. Epub 2022 Jan 4.

Audag N, Toussaint M, Liistro G, Vandervelde L, Cugy E, **Reychler G**., European Survey: Dysphagia Management in Patients with Neuromuscular Diseases, Dysphagia. 2022 Oct;37(5):1279-1287. doi: 10.1007/s00455-021-10392-3. Epub 2022 Jan 3.

Duprez F, de Terwangne C, Bellemans V, **Poncin W, Reychler G**, Sorgente A, Cuvelier G, Mashayekhi S, Wittebole X., High-flow nasal cannula therapy, factors affecting effective inspired oxygen fraction: an experimental adult bench model, J Clin Monit Comput. 2022 Oct;36(5):1441-1448. doi: 10.1007/s10877-021-00784-z. Epub 2021 Dec 8.

Combret Y, Prieur G, Boujibar F, Gravier FE, Smondack P, Le Roux P, Bonnevie T, Medrinal C, **Reychler G.**, Validity and reliability of the one-minute sit-to-stand test for the measurement of cardio-respiratory responses in children with cystic fibrosis, Pulmonology. 2022 Mar-Apr;28(2):137-139. doi: 10.1016/j.pulmoe.2021.10.005. Epub 2021 Nov 26.

Duprez F, Dupriez F, De Greef J, Gabriel J, Bruyneel A, **Reychler G**, De Terwangne C, **Poncin W.**, Performance of Different Low-Flow Oxygen Delivery Systems, Respir Care. 2022 Mar;67(3):322-330. doi: 10.4187/respcare.09312. Epub 2021 Oct 20.

Prieur G, Delorme M, Lebret M, Combret Y, Machefert M, Medrinal C, Smondack P, Gravier FE, Lamia B, Bonnevie T, **Reychler G.**, Nasal High-Flow Therapy during Exercise in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis, Ann Am Thorac Soc. 2022 Feb;19(2):291-302. doi: 10.1513/AnnalsATS.202104-436SR.

Combret Y, Medrinal C, Prieur G, Robledo Quesada A, Gillot T, Gravier FE, Bonnevie T, Lamia B, Le Roux P, **Reychler G**., Oxygen uptake kinetics during treadmill walking in adolescents with clinically stable cystic fibrosis, Physiother Theory Pract. 2022 Oct;38(10):1389-1397. doi: 10.1080/09593985.2020.1868029. Epub 2021 Jan 4.

MORF

Craps, Julie ; Joris, Virginie ; Baldeschi, Lelio ; Daumerie, Chantal ; Camboni, Alessandra ; Buemi, Antoine ; Lengelé, Benoît ; Behets, Catherine ; Boschi, Antonella ; Mourad, Michel ; Many, Marie-Christine ; Dessy, Chantal. miR-199a *Downregulation as a Driver of the NOX4/HIF-1α/VEGF-A Pathway in Thyroid and Orbital Adipose Tissues from Graves' Patients.. In: International Journal of Molecular Sciences*, Vol. 23, no.1, p. 153 (2021). doi:10.3390/ijms23010153. http://hdl.handle.net/2078.1/256419

Hepp, Michael ; Wérion, Alexis ; De Greef, Axel ; de Ville de Goyet, Christine ; de Bournonville, Marc ; Behets, Catherine ; Lengelé, Benoît ; Daumerie, Chantal ; Mourad, Michel ; Ludgate, Marian ; Many, Marie-Christine ; Joris, Virginie ; Craps, Julie. Oxidative Stress-Induced Sirtuin1 Downregulation Correlates to HIF-1α, GLUT-1, and VEGF-A Upregulation in Th1 Autoimmune Hashimoto's Thyroiditis.. In: International Journal of Molecular Sciences (Print), Vol. 22, no. 8, p. 3806 (2021). doi:10.3390/ijms22083806. http://hdl.handle.net/2078.1/245677

Van Regemorter, Elliott ; Joris, Virginie ; Van Regemorter, Victoria ; Marique, Lancelot ; Behets, Catherine ; Lengelé, Benoit ; Boschi, Antonella ; Baldeschi, Lelio ; Daumerie, Chantal ; Many, Marie-Christine ; Craps, Julie. Downregulation of Caveolin-1 and Upregulation of Deiodinase 3, Associated with Hypoxia-Inducible Factor-1α Increase, Are Involved in the Oxidative Stress of Graves' Orbital Adipocytes. In: Thyroid, Vol. 31, no. 4, p. 627 (2021). doi:10.1089/thy.2020.0238

Cardinal, Mickaël ; Chretien, Antoine ; Roels, Thomas ; Lafont, Sébastien ; Ominsky, Michael S. ; Devogelaer, Jean-Pierre ; Manicourt, Daniel ; Behets, Catherine. Gender-Related Impact of Sclerostin Antibody on Bone in the Osteogenesis Imperfecta Mouse. In: Front Genet. 2021 Aug 10;12:705505. doi: 10.3389/fgene.2021.705505. http://hdl.handle.net/2078.1/250046

Van Bockstal, Mieke ; Libbrecht, Louis ; Galant, Christine. Comment on: "Pathological features of 11,337 patients with primary ductal carcinoma in situ (DCIS) and subsequent events: results from the UK Sloane Project".. In: British journal of cancer,, p. [1-2] (2021). doi:10.1038/s41416-021-01280-6. http://hdl.handle.net/2078.1/244704

Lasserre, Jérôme ; Brecx, Michel ; Toma, Selena. Implantoplasty Versus Glycine Air Abrasion for the Surgical Treatment of Peri-implantitis: A Randomized Clinical Trial.. In: The International journal of oral & maxillofacial implants, Vol. 35, no. 35, p. 197-206 (2021). doi:10.11607/jomi.6677. http://hdl.handle.net/2078.1/252025

Stanciu Pop, Claudia Maria ; Nollevaux, Marie-Cécile ; Berlière, Martine ; Duhoux, François ; Fellah, Latifa ; Galant, Christine ; Van Bockstal, Mieke. Morphological intratumor heterogeneity in ductal carcinoma in situ of the breast. In: Virchows Archiv, Vol. 479, no. 1, p. 33-43 (2021). doi:10.1007/s00428-021-03040-6. http://hdl.handle.net/2078.1/242701

Seijnhaeve, Elsa ; Galant, Christine ; Van Bockstal, Mieke. Nuclear Insulinoma-Associated Protein 1 Expression as a Marker of Neuroendocrine Differentiation in Neoplasms of the Breast.. In: International journal of surgical pathology, (2021). doi:10.1177/1066896920985938 (Accepté/Sous presse). http://hdl.handle.net/2078.1/246460

Wabik, Amélie ; Van Bockstal, Mieke ; Berlière, Martine ; Galant, Christine. Periductal Stromal Tumors and Phyllodes Tumors Represent a Spectrum of Fibroepithelial Lesions: What Is in a Name?. In: International journal of surgical pathology, Vol. 29, no.1, p. 97-101 (2021). doi:10.1177/1066896920929086. http://hdl.handle.net/2078.1/246459

Van Bockstal, Mieke ; Libbrecht, Louis ; Galant, Christine. The 5-Year Paradigm in DCIS of the Breast: Unexpected Lessons From the NSABP B-43 Trial.. In: Journal of clinical oncology, Vol. 39, no.30, p. 3409-3410 (2021). doi:10.1200/JCO.21.00968. http://hdl.handle.net/2078.1/252303

De Pelsemaeker, Marie-Caroline ; Guiot, Yves ; Vanderveken, Jonathan ; Galant, Christine ; Van Bockstal, Mieke. The Impact of the COVID-19 Pandemic and the Associated Belgian Governmental Measures on Cancer Screening, Surgical Pathology and Cytopathology.. In: Pathobiology, Vol. 88, no.1, p. 46-55 (2021). doi:10.1159/000509546. http://hdl.handle.net/2078.1/246456

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.

Pole Contact Persons

Olivier Devuyst
olivier.devuyst@uclouvain.be

Johann Morelle
johann.morelle@uclouvain.be

Michel Jadoul
michel.jadoul@uclouvain.be

Sébastien Druart
sebastien.druart@uclouvain.be

Olivier Devuyst, MD, PhD, Head

Michel Jadoul, MD

Johann Morelle MD, PhD

Eric Goffin, MD

Nada Kanaan, MD

Laura Labriola, MD

Nathalie Demoulin, MD

Valentine Gillion, MD

Arnaud Devresse, MD

Nathalie Godefroid, MD

Technicians:

Sébastien Druart
Sophie Ligot

Secretary:

Sébastien Druart

IREC - Pôle de Néphrologie

B1.54.03 Avenue Hippocrate 54
B-1200 Brussels
T : +32 2 764 54 50
F : +32 2 764 54 55

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)**

REFERENCES 2021

Devresse A, Lhommel R, Godefroid N, **Goffin E, Kanaan N.** *18-Fluorodeoxyglucose positron emission computed tomography for systemic oxalosis in primary hyperoxaluria type 1.. In: American Journal of Transplantation,* (2021).

Labriola L, Scohy A, Seghers F, Perlot Q, De Greef J, Desmet C, Romain C, **Morelle J,** Yombi JC, Kabamba-Mukadi B, Rodriguez-Villalobos H, **Jadoul M.** *A Longitudinal, 3-Month Serologic Assessment of SARS-CoV-2 Infections in a Belgian Hemodialysis Facility.. In: Clinical journal of the American Society of Nephrology,* Vol. 16, no. 4, p. 613-614 (2021).

Mehrotra R, Stanaway IB, Jarvik GP, Lambie M, **Morelle J,** Perl J, Himmelfarb J, Heimburger O, Johnson DW, Imam TH, Robinson B, Stenvinkel P, **Devuyst O**, Davies SJ. *A genome-wide association study suggests correlations of common genetic variants with peritoneal solute transfer rates in patients with kidney failure receiving peritoneal dialysis., collab.* Bio-PD Consortium. In: *Kidney international,* (2021).

Morelle J, Marechal C, Yu Z, Debaix H, Corre T, Lambie M, Verduijn Marion, Dekker F, Bovy P, Evenepoel P, Bammens B, Selgas R, Bajo MA, Coester AM, Sow A, Hautem N, Struijk DG, Krediet RT, Balligand JL, **Goffin E**, Crott R, Ripoche P, Davies S, **Devuyst O**. *AQP1 Promoter Variant, Water Transport, and Outcomes in Peritoneal Dialysis.* In: *New England Journal of Medicine,* Vol. 385, no.17, p. 1570-1580 (2021).

Goffin E, Candellier Alexandre, Vart P, Noordzij M, Arnol M, Covic A, Lentini P, Malik S, Reichert LJ, Sever MS, Watschinger B, Jager KJ, Gansevoort RT. *COVID-19 related mortality in kidney transplant and hemodialysis patients: a comparative, prospective registry based study.,* collab. **Labriola L, Devresse A**, ERACODA Collaborators ; **Kanaan N.** In: *Nephrology, Dialysis, Transplantation,* Vol. 36, no. 11, p. 2094-2105 (2021).

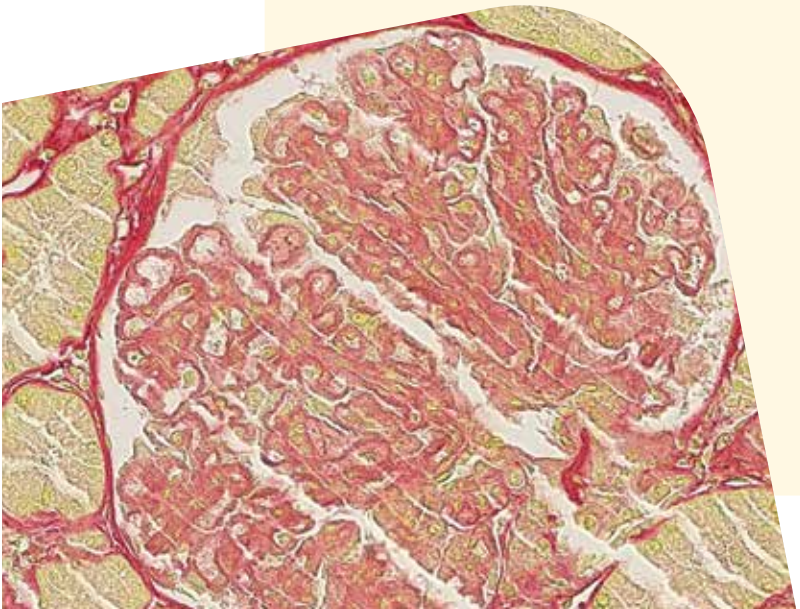
Labriola L, Ruelle J, Scohy A, Seghers F, Perlot Q, De Greef J, Desmet C, Romain C, Yombi JC, Rodriguez-Villalobos H, Kabamba Mukadi B, **Jadoul M.** *Dynamics of spreading of SARS-CoV-2 in a Belgian hemodialysis facility: The importance of the analysis of viral strains.* In: *Journal of medical virology*, (2021).

Morelle J, Stachowska-Pietka J, Öberg C, Gadola L, La Milia V, Yu Z, Lambie M, Mehrotra R, de Arteaga J, Davies S. *ISPD recommendations for the evaluation of peritoneal membrane dysfunction in adults: Classification, measurement, interpretation and rationale for intervention.* In: *Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis,* Vol. 41, no. 4, p. 352-372 (2021).

Ponte B, Sadler MC, Olinger E, Vollenweider P, Bochud M, Padmanabhan S, Hayward C, Kutalik Z, **Devuyst O**. *Mendelian randomization to assess causality between uromodulin, blood pressure and chronic kidney disease.* In: *Kidney International,* Vol. 100, no.6, p. 1282-1291 (2021).

Demoulin N, Aydin S, **Gillion V, Morelle J**, **Jadoul M.** *Pathophysiology and Management of Hyperoxaluria and Oxalate Nephropathy: A Review..* In: *American journal of kidney diseases : the official journal of the National Kidney Foundation,* (2021).

Schaeffer C, **Devuyst O**, Rampoldi L. *Uromodulin: Roles in Health and Disease.* In: *Annual Review of Physiology,* Vol. 83, no.1, p. 477-501 (2021).



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.

In 2022, Olivier Feron and Pierre Sonveaux, both from the FATH pole, were selected to be part of the WELBIO department within the WEL Research Institute (WELRI). WELBIO is an inter-university research institute subsidized by Wallonia, the missions of which are to support fundamental research in life sciences and to promote the industrial valorization of scientific discoveries into biomedical applications.

Olivier Feron also obtained a Eos grant together with colleagues from UGent, the EOS-program aims to promote joint research between researchers in the Flemish and French-speaking communities. Pierre Sonveaux was appointed Belgian National Delegate to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).

Research Poles

POLE OF PHARMACOLOGY AND THERAPEUTICS (FATH)

Cyril Corbet, PhD

Olivier Feron, PhD

Pierre Sonveaux, PhD

Olivier Feron's team:

Léo Aubert, PhD
Sébastien Ibanez, PhD
Anouk Lepez, PhD
Ophélie Renoult, PhD
Philippine Bruno, PhD student (ARC)
Charline Degavre, PhD student (FRIA)
Marine Deskeuvre, PhD student (Assist. UCLouvain)
Clémence François, PhD student (PDR-Télévie)
Katarzyna Glowacka, PhD student (FRIA)
Kubra Ozkan, PhD student (Télévie)
Perrine Vermonden, PhD student (Aspirante FNRS)
Céline Guilbaud, Techn
Florine Laloux, Techn

Cyril Corbet's team:

Françoise Derouane, PhD student (Fondation St Luc)
*Elena Richiardone, PhD student (FRIA)**
*Valentin Van den bossche, PhD student (Asp.FNRS)**
Julie Vignau, PhD student (Aspirante FNRS)
Engy Vigneron, PhD student (Télévie)
*(*co-supervision with O. Feron)*

Pierre Sonveaux's team:

Tania Isabel De Miranda Capeloa, PhD
Mauricio Da Silva Morais, PhD
Marine Blackman, PhD student (Télévie)
Chiara Brustenga, PhD student (Télévie)
Arthur Colson, MD, PhD student (FRIA)
Ilaria Colauzzi (ITN Marie Curie)
Sara Lipari, PhD student (ITN Marie Curie)
Barbara Matthieu, PhD student (ARC)
Justin Rondeau, PhD student (ITN Marie Curie)
Perrine Savoyen, PhD student (Assistante)
Justine Van de Velde, PhD student (Assistante)
Luca Zampieri, PhD student (ITN Marie Curie)
Marie Bedin, Techn
Loïc Hamelin, Techn
Emmanuel Vandenhooft, Techn
Thibaut Vazeille, Techn

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

POLE OF MOLECULAR IMAGING, RADIOTHERAPY AND ONCOLOGY (MIRO)

Jean-François Baurain, MD, PhD

François Duhoux, MD, PhD

Xavier Geets, MD, PhD

François Jamar, MD, PhD

John A. Lee, PhD

Renaud Lhommel, MD

Jean-Pascal Machiels, MD, PhD

Véronique Roelants, MD, PhD

Sandra Schmitz, MD, PhD

Edmond Sterpin, PhD

Marc Van Den Eynde, MD, PhD

Researchers:

Ana Barragan, PhD
Simon Beyaert, PhD student
Elena Borderias, PhD
Maureen Ciccarelli, PhD student
Chuxin Zhang, PhD student
Françoise Derouane, PhD student
Sylvain Deffet, PhD
Dario Di Perri, MD PhD
Camille Draguet, PhD student
Rachel Galot, MD, PhD
Natasha Honoré, PhD student
Margerie Huet, PhD student
Nicolas Huyghe, PhD student
Eléonore Longton, MD, PhD
Finoula Maestre, MD, PhD student
Marina Orts-Sanz, PhD student
Julien Pierrard, MD PhD student
Danah Pross, PhD student
Benjamin Roberfroid
Philippe Stevens, PhD student
Athenais van der Elst, PhD student
Loïc Van der Veken, MD, PhD student
Cédric van Marcke, MD, PhD
Geneviève Van Ooteghem, MD, PhD
Lies Verpoest, PhD student
Sophie Wuyckens, PhD student

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

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

- Pole of Pneumology, ENT and dermatology (PNEU), S. Ocak, F. Aboubakar
- Pole of Hepato-Gastroenterology (GAEN), I. Borbath, I. Leclercq, P. Starkel
- Louvain Centre for Toxicology and Applied Pharmacology (LTAP), F. Huaux

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

MAJOR FUNDINGS

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

- **Welbio investigators (2022-2024) :** O. Feron (Acidosis and Drug tolerant persister cells) and P. Sonveaux (Understanding the metabolic control of brain-specific cancer metastasis)
- **Eos grant (2022-2025) :** O. Feron (Harnessing tumor acidosis and immunogenic ferroptosis for an innovative treatment of peritoneal carcinomatosis), together with A. Skirtach and D Krysko (UGent)
- **F.R.S.-FNRS-PDR-Télévie (2022-25) :** O. Feron (Interplay between tumor metabolism and new generation of immune checkpoints) together with M. Herfs (Uliège, GIGA cancer)
- **F.R.S.-FNRS-PDR-Télévie (2021-2024)** C. Corbet (Targeting microenvironment-mediated metabolic vulnerabilities to overcome the oncogene-driven resistance to anti-EGFR therapy in colorectal cancers), together with A. Bellahcène (ULiège, GIGA-Cancer).
- **Action de recherches concertées (ARC) (2019-2024)** O. Feron, L. Bindels, P. Cani, B. Jordan, Y. Larondelle. The role of diet-, microbiota- and adipocyte-derive lipids in cancer progression (LIPOCAN).
- **Action de recherches concertées (ARC) (2021-2026)** P. Sonveaux, E. Sterpin, AC. Heuskin, B Gallez. Metabolic control of different responses of human cancer cells to X-ray and proton radiotherapy (MetaRad).
- **Fondation Belge Contre le Cancer (2020-2024):** Fundamental Research Grant. O. Feron. To reconcile the location of tumor microenvironment-driven mesenchymal-like cancer cells and their contribution to cancer progression.
- **Fondation Belge Contre le Cancer (2019-2022):** Fundamental Research Grant. P. Sonveaux, R. Frédérick. Lactate dehydrogenase B (LDHB) inhibition for anticancer treatment
- **RW BEWARE** (Industrial collaboration) (2022-2024): P. Sonveaux (Preclinical development of a lactate tracer for medical cancer imaging)
- **Industrial collaboration (2022-2024):** P. Sonveaux and R. Frédérick (Development of small molecule inhibitors
- **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).
- **WALLinov (2018-2022).** JP Machiels. Predictive biomarkers for CDK4 inhibition in cancer.
- **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.
- **RW Pôles Biowin & Mecatech EPT (2020-2024):** E.Sterpin & J.Lee. Emerging Proton Therapy (high-rate dose a.k.a. "Flash").
- **RW Pôles Biowin & Mecatech D-CAF (2021-2025):** E.Sterpin & J.Lee. Detectors for Carbon, Arc, and Flash Therapies.

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. The main research topic in the group of O. Feron consists of the study of different aspects of the tumor (lipid) metabolism impacting on, or influenced by the tumor microenvironment. In particular, hypoxia and acidosis parameters are integrated in all the studies by using a variety of 3D tumor models. Recent research axes of the O. Feron lab include the interplay between circadian rhythm, nutrition and cancer progression, and the search for the most promising combination of metabolism-targeting drugs with either chemotherapy or second-generation immune checkpoint inhibitors. 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 a hypoxia-related prognostic biomarkers and lactate tracers for PET scan**
- **Chronobiological characterization of tumor metabolism and related chronotherapy optimization**

REFERENCES 2022 (selected)

Lan J, Cadassou O, **Corbet C**, Riant O, **Feron O.** Discovery of Mitochondrial Complex I Inhibitors as Anticancer and Radiosensitizer Drugs Based on Compensatory Stimulation of Lactate Release. Cancers (Basel). 2022 Nov 6;14(21):5454.

Deskeuvre M, Lan J, Dierge E, Messens J, Riant O, **Corbet C, Feron O**, Frédérick R. Targeting cancer cells in acidosis with conjugates between the carnitine palmitoyltransferase 1 inhibitor etomoxir and pH (low) insertion peptides. Int J Pharm. 2022 Aug 25;624:122041.

Cappellesso F, Orban MP, Shirgaonkar N, Berardi E, Serneels J, Neveu MA, Di Molfetta D, Piccapane F, Caroppo R, Debellis L, Ostyn T, Joudiou N, Mignion L, Richiardone E, Jordan BF, Gallez B, Corbet C, Roskams T, DasGupta R, Tejpar S, Di Matteo M, Taverna D, Reshkin SJ, Topal B, Virga F, Mazzone M. Targeting the bicarbonate transporter SLC4A4 overcomes immunosuppression and immunotherapy resistance in pancreatic cancer. Nat Cancer. 2022 Dec;3(12):1464-1483.

Pisapia P, Li Z, **Corbet C**. Editorial: The effect of anticancer drug therapies in the treatment of lung cancer. Front Oncol. 2022 Oct 19;12:1035245.

Derouane F, van Marcke C, Berlière M, Gerday A, Fellah L, Leconte I, Van Bockstal MR, Galant C, **Corbet C**, Duhoux FP. Predictive Biomarkers of Response to Neoadjuvant Chemotherapy in Breast Cancer: Current and Future Perspectives for Precision Medicine. Cancers (Basel). 2022 Aug 11;14(16):3876.

Buyse C, Joudiou N, Warscotte A, Richiardone E, Mignion L, **Corbet C**, Gallez B. Evaluation of Syrosingopine, an MCT Inhibitor, as Potential Modulator of Tumor Metabolism and Extracellular Acidification. Metabolites. 2022 Jun 17;12(6):557.

Capeloa T, Van de Velde JA, d'Hose D, Lipari SG, Derouane F, Hamelin L, Bedin M, Vazeille T, Duhoux FP, Murphy MP, Porporato PE, Gallez B, **Sonveaux P.** Inhibition of Mitochondrial Redox Signaling with MitoQ Prevents Metastasis of Human Pancreatic Cancer in Mice. Cancers (Basel). 2022 Oct 7;14(19):4918.

d'Hose D, Mathieu B, Mignion L, Hardy M, Ouari O, Jordan BF, **Sonveaux P,** Gallez B. EPR Investigations to Study the Impact of Mito-Metformin on the Mitochondrial Function of Prostate Cancer Cells. Molecules. 2022 Sep 10;27(18):5872.

Blackman MCNM, Capeloa T, Rondeau JD, Zampieri LX, Benyahia Z, Van de Velde JA, Fransolet M, Daskalopoulos EP, Michiels C, Beauloye C, **Sonveaux P.** Mitochondrial Protein Cox7b Is a Metabolic Sensor Driving Brain-Specific Metastasis of Human Breast Cancer Cells. Cancers (Basel). 2022 Sep 8;14(18):4371.

Weber DD, Aminzadeh-Gohari S, Thapa M, Redtenbacher AS, Catalano L, Capelôa T, Vazeille T, Emberger M, Felder TK, Feichtinger RG, Koelblinger P, Dallmann G, **Sonveaux P,** Lang R, Kofler B. Ketogenic diets slow melanoma growth in vivo regardless of tumor genetics and metabolic plasticity. Cancer Metab. 2022 Jul 18;10(1):12.

Macchi C, Moregola A, Greco MF, Svecla M, Bonacina F, Dhup S, Dadhich RK, Audano M, **Sonveaux P,** Mauro C, Mitro N, Ruscica M, Norata GD. Monocarboxylate transporter 1 deficiency impacts CD8+ T lymphocytes proliferation and recruitment to adipose tissue during obesity. iScience. 2022 May 23;25(6):104435.

Ippolito L, **Sonveaux P,** Chiarugi P. Unconventional roles of lactate along the tumor and immune landscape. Trends Endocrinol Metab. 2022 Apr;33(4):231-235.

Capeloa T, Krzystyniak J, d'Hose D, Canas Rodriguez A, Payen VL, Zampieri LX, Van de Velde JA, Benyahia Z, Pranzini E, Vazeille T, Fransolet M, Bouzin C, Brusa D, Michiels C, Gallez B, Murphy MP, Porporato PE, **Sonveaux P.** MitoQ Inhibits Human Breast Cancer Cell Migration, Invasion and Clonogenicity. Cancers (Basel). 2022 Mar 16;14(6):1516.

Capeloa T, Krzystyniak J, Rodriguez AC, Payen VL, Zampieri LX, Pranzini E, Derouane F, Vazeille T, Bouzin C, Duhoux FP, Murphy MP, Porporato PE, **Sonveaux P.** MitoQ Prevents Human Breast Cancer Recurrence and Lung Metastasis in Mice. Cancers (Basel). 2022 Mar 15;14(6):1488.

MIRO

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

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

Radiation Oncology -delivered as single modality or in combination with surgery and/or medical treatments- represents one of the most effective options to cure cancer at a local or loco-regional stage. It also has a prominent palliative role for the management of patients with metastatic disease. Although indisputable progresses have been made over the last few decades in the treatment of cancer, patients still die from uncontrolled loco-regional disease. Inaccurate definition of the target volumes, insufficient or sub-optimal radiation dose distribution, and intrinsic radiation resistance are, among others, factors that explain these treatment failures. In this framework, the Laboratory of Molecular Imaging and Radiation Oncology developed several lines of research aiming at 1) improving the radiation delivery, 2) at a better understanding of the role of tumour microenvironment in radiation response, 3) at integrating molecular imaging with various PET tracers in the radiation treatment process, and 4) automating key steps of treatment planning with artificial intelligence (deep convolutional neural networks) to come up with clinical decision support system for patient referral (e.g. to photon or proton proton therapy). 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..

- **Robust planning and adaptive treatment in proton therapy**
- **Calorimetry in hadron beams**
- **Automatic segmentation of CT images using a registration-free atlas**
- **Preclinical in *vivo* imaging**

REFERENCES 2022 (selected)

Wuyckens S, Zhao L, Saint-Guillain M, Janssens G, **Sterpin E**, Souris K, Ding X, Lee JA. Bi-criteria Pareto optimization to balance irradiation time and dosimetric objectives in proton arc therapy. Phys Med Biol. 2022 Dec 13;67(24).

Buti G, Shusharina N, Ajdari A, **Sterpin E**, Bortfeld T. Exploring trade-offs in treatment planning for brain tumor cases with a probabilistic definition of the clinical target volume. Med Phys. 2023 Jan;50(1):410-423.

Opalinski L, **Schmitz S**, Van Eeckhout P, d'Abadie P, **Gheysens O**. Hyoepiglottic Rheumatoid Nodule Mimicking Head and Neck Malignancy on 18 F-FDG PET/CT. Clin Nucl Med. 2023 Feb 1;48(2):e80-e81.

Draguet C, Barragán-Montero AM, Vera MC, Thomas M, Populaire P, Defraene G, Haustermans K, Lee JA, **Sterpin E**. Automated clinical decision support system with deep learning dose prediction and NTCP models to evaluate treatment complications in patients with esophageal cancer. Radiother Oncol. 2022 Nov;176:101-107.

Elhamiasl M, Salvo K, Poels K, Defraene G, Lambrecht M, **Geets X, Sterpin E**, Nuyts J. Low-dose CT allows for accurate proton therapy dose calculation and plan optimization. Phys Med Biol. 2022 Sep 30;67(19).

Wuyckens S, Saint-Guillain M, Janssens G, Zhao L, Li X, Ding X, **Sterpin E, Lee JA**, Souris K. Treatment planning in arc proton therapy: Comparison of several optimization problem statements and their corresponding solvers. Comput Biol Med. 2022 Sep;148:105609.

d'Abadie P, Walrand S, Hesse M, Borbath I, **Lhommel R, Jamar F**. TCP post- radioembolization and TCP post-EBRT in HCC are similar and can be predicted using the in vitro radiosensitivity. EJNMMI Res. 2022 Jul 8;12(1):40.

Grham R, Moreira AP, Glaudemans AWJM, Jensen LT, Mihaïlovic J, Nazarenko S, Ozcan Z, Piciu D, Wadsak W, Kunikowska J, **Jamar F**. 2022 follow-up: impact of the COVID-19 pandemic on nuclear medicine departments in Europe. Eur J Nucl Med Mol Imaging. 2022 Aug;49(10):3309-3315.

Primakov SP, Ibrahim A, van Timmeren JE, Wu G, Keek SA, Beuque M, Granzier RWY, Lavrova E, Scrivener M, Sanduleanu S, Kayan E, Halilaj I, Lenaers A, Wu J, Monshouwer R, **Geets X**, Gietema HA, Hendriks LEL, Morin O, Jochems A, Woodruff HC, Lambin P. Automated detection and segmentation of non-small cell lung cancer computed tomography images. Nat Commun. 2022 Jun 14;13(1):3423.

Allignet B, Sunyach MP, **Geets X,** Waissi W. Is there a place for definitive radiotherapy in the treatment of unresectable soft-tissue sarcoma? A systematic review. Acta Oncol. 2022 Jun;61(6):720-729.

van der Heyden B, Heymans SV, Carlier B, Collado-Lara G, **Sterpin E**, D'hooge J. Deep learning for dose assessment in radiotherapy by the super-localization of vaporized nanodroplets in high frame rate ultrasound imaging. Phys Med Biol. 2022 May 27;67(11).

d'Abadie P, Walrand S, Lhommel R, Hesse M, Borbath I, **Jamar F.** Optimization of the Clinical Effectiveness of Radioembolization in Hepatocellular Carcinoma with Dosimetry and Patient-Selection Criteria. Curr Oncol. 2022 Mar 29;29(4):2422-2434.

Barragán-Montero A, Bibal A, Dastarac MH, Draguet C, Valdés G, Nguyen D, Willems S, Vandewinckele L, Holmström M, Löfman F, Souris K, **Sterpin E, Lee JA**. Towards a safe and efficient clinical implementation of machine learning in radiation oncology by exploring model interpretability, explainability and data- model dependency. Phys Med Biol. 2022 May 27;67(11):10.1088/1361-6560/ac678a.

Borderías-Villarroel E, Taasti V, Van Elmpt W, Teruel-Rivas S, **Geets X, Sterpin E**. Evaluation of the clinical value of automatic online dose restoration for adaptive proton therapy of head and neck cancer. Radiother Oncol. 2022 May;170:190-197.

Boutaghane N, Hesse M, Bouzid B, Zaidi H, **Jamar F,** Walrand S. Dual-layer collimator for improved spatial resolution in SPECT with CZT camera: an analytical and Monte Carlo study. Phys Med Biol. 2022 Mar 11;67(6).

Charlier F, Descamps T, Lievens Y, **Geets X**, Remouchamps V, Lambrecht M, Moretti L. ProCaLung - Peer review in stage III, mediastinal node-positive, non- small-cell lung cancer: How to benchmark clinical practice of nodal target volume definition and delineation in Belgium*. Radiother Oncol. 2022 Feb;167:57-64.

Lecouvet FE, Vekemans MC, Van Den Berghe T, Verstraete K, Kirchgesner T, Acid S, Malghem J, Wuts J, Hillengass J, Vandecaveye V, **Jamar F, Gheysens O**, Vande Berg BC. Imaging of treatment response and minimal residual disease in multiple myeloma: state of the art WB-MRI and PET/CT. Skeletal Radiol. 2022 Jan;51(1):59-80.

MIRO (2/2) - Laboratory of Medical Oncology

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

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

REFERENCES 2022 (selected)

Berliere M, Coche M, Lacroix C, Riggi J, Coyette M, Coulie J, Galant C, Fellah L, Leconte I, Maiter D, **Duhoux FP**, François A. Effects of Hormones on Breast Development and Breast Cancer Risk in Transgender Women. Cancers (Basel). 2022 Dec 30;15(1):245.

Alexis LG, Dano H, Dekairelle AF, Van Marcke C, **Van den Eynde M**. Acquired microsatellite instability status and loss of HER2 positivity during treatment of gastro-esophageal junction adenocarcinoma. Dig Liver Dis. 2023 Mar;55(3):426-428.

van Herpen C, Vander Poorten V, Skalova A, Terhaard C, Maroldi R, van Engen A, Baujat B, Locati LD, Jensen AD, Smeele L, Hardillo J, Martineau VC, Trama A, Kinloch E, Even C, **Machiels JP**; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Salivary gland cancer: ESMO-European Reference Network on Rare Adult Solid Cancers (EURACAN) Clinical Practice Guideline for diagnosis, treatment and follow-up. ESMO Open. 2022 Dec;7(6):100602.

Psyrri A, Fayette J, Harrington K, Gillison M, Ahn MJ, Takahashi S, Weiss J, **Machiels JP**, Baxi S, Vasilyev A, Karpenko A, Dvorkin M, Hsieh CY, Thungappa SC, Segura PP, Vynnychenko I, Haddad R, Kasper S, Mauz PS, Baker V, He P, Evans B, Wildsmith S, Olsson RF, Yovine A, Kurland JF, Morsli N, Seiwert TY; KESTREL Investigators. Durvalumab with or without tremelimumab versus the EXTREME regimen as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck: KESTREL, a randomized, open-label, phase III study. Ann Oncol. 2023 Mar;34(3):262-274.

Bossi P, Chan AT, Even C, **Machiels JP**; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.

org. ESMO-EURACAN Clinical Practice Guideline update for nasopharyngeal carcinoma: adjuvant therapy and first-line treatment of recurrent/metastatic disease. Ann Oncol. 2023 Mar;34(3):247-250.

Lee VH, Adham M, Ben Kridis W, Bossi P, Chen MY, Chitapanarux I, Gregoire V, Hao SP, Ho C, Ho GF, Kannarunimit D, Kwong DL, Lam KO, Lam WKJ, Le QT, Lee AW, Lee NY, Leung TW, Licitra L, Lim DW, Lin JC, Loh KS, Lou PJ, **Machiels JP**, Mai HQ, Mesía R, Ng WT, Ngan RK, Tay JK, Tsang RK, Tong CC, Wang HM, Wee JT. International recommendations for plasma Epstein-Barr virus DNA measurement in nasopharyngeal carcinoma in resource-constrained settings: lessons from the COVID-19 pandemic. Lancet Oncol. 2022 Dec;23(12):e544-e551.

Migden M, Loquai C, Robert C, **Baurain JF**, Squittieri N, Arntz R, Dierlamm J, Dréno B. Sonidegib improved quality of life in patients with advanced basal cell carcinoma: Results from the phase 2 Basal cell carcinoma outcomes with LDE225 treatment trial through 73 weeks. JAAD Int. 2022 Oct 18;10:31-33.

Mehra N, Fizazi K, de Bono JS, Barthélémy P, Dorff T, Stirling A, **Machiels JP**, Bimbatti D, Kilari D, Dumez H, Buttigliero C, van Oort IM, Castro E, Chen HC, Di Santo N, DeAnnuntis L, Healy CG, Scagliotti GV. Talazoparib, a Poly(ADP- ribose) Polymerase Inhibitor, for Metastatic Castration-resistant Prostate Cancer and DNA Damage Response Alterations: TALAPRO-1 Safety Analyses. Oncologist. 2022 Oct 1;27(10):e783-e795.

Aparicio T, Bouché O, Etienne PL, Barbier E, Mineur L, Desgrippes R, Guérin- Meyer V, Hocine F, Martin J, Le Brun-Ly V, Cretin J, Desramé J, Rinaldi Y, Cany L, Falandry C, Lefevre LB, Marous M, Terrebonne E, Mosser L, Turpin J, Turpin A, Bauguion L, Reichling C, **Van den Eynde M**, Carola E, Hiret S. Preliminary tolerance analysis of adjuvant chemotherapy in older patients after resection of stage III colon cancer from the PRODIGE 34-FFCD randomized trial. Dig Liver Dis. 2022 Sep 14:S1590-8658(22)00662-4.

Luyckx M, Squifflet JL, Bruger AM, **Baurain JF**. Recurrent High Grade Serous Ovarian Cancer Management. In: Lele S, editor. Ovarian Cancer [Internet]. Brisbane (AU): Exon Publications; 2022 Sep 8. Chapter 6.

Derouane F, van Marcke C, Berlière M, Gerday A, Fellah L, Leconte I, Van Bockstal MR, Galant C, Corbet C, **Duhoux FP**. Predictive Biomarkers of Response to Neoadjuvant Chemotherapy in Breast Cancer: Current and Future Perspectives for Precision Medicine. Cancers (Basel). 2022 Aug 11;14(16):3876.

Mignion L, Desmet CM, Harkemanne E, Tromme I, Joudiou N, Wehbi M, **Baurain JF**, Gallez B. Noninvasive detection of the endogenous free radical melanin in human skin melanomas using electron paramagnetic resonance (EPR). Free Radic Biol Med. 2022 Sep;190:226-233.

Simonelli M, Garralda E, Eskens F, Gil-Martin M, Yen CJ, Obermannova R, Chao Y, Lonardi S, Melichar B, Moreno V, Yu ML, Bongiovanni A, Calvo E, Rottey S, **Machiels JP**, Gonzalez-Martin A, Paz-Ares L, Chang CL, Mason W, Lin CC, Reardon DA, Vieito M, Santoro A, Meng R, Abbadessa G, Menas F, Lee H, Liu Q, Combeau C, Ternes N, Ziti-Ljajic S, Massard C. Isatuximab plus atezolizumab in patients with advanced solid tumors: results from a phase I/II, open-label, multicenter study. ESMO Open. 2022 Oct;7(5):100562.

Thouvenin J, Van Marcke C, Decoster L, Raicevic G, Punie K, Vandenbulcke M, Salgado R, Van Valckenborgh E, Maes B, Joris S, Steichel DV, Vranken K, Jacobs S, Dedeurwaerdere F, Martens G, Devos H, **Duhoux FP**, Rasschaert M, Pauwels P, Geboes K, Collignon J, Tejpar S, Canon JL, Peeters M, Rutten A, Van de Mooter T, Vermeij J, Schrijvers D, Demey W, Lybaert W, Van Huysse J, Mebis J, Awada A, Claes KBM, Hebrant A, Van der Meulen J, Delafontaine B, Bempt IV, Maetens J, de Hemptinne M, Rottey S, Aftimos P, De Grève J. PRECISION: the Belgian molecular profiling program of metastatic cancer for clinical decision and treatment assignment. ESMO Open. 2022 Aug;7(4):100524.

Bregni G, Pretta A, Senti C, Acedo Reina E, Vandeputte C, Trevisi E, Gkolfakis P, Kehagias P, Deleporte A, Van Laethem JL, Vergauwe P, **Van den Eynde M**, Deboever G, Janssens J, Demolin G, Holbrechts S, Clausse M, De Grez T, Peeters M, D'Hondt L, Geboes K, Besse-Hammer T, Rothé F, Flamen P, Hendlisz A, Sclafani F. Circulating DNA in the neoadjuvant setting of early stage colon cancer. Acta Oncol. 2022 Oct;61(10):1223-1229.

Vergote I, Denys H, Altintas S, Kerger J, **Baurain JF,** Bours V, Henry S, Van de Vijver K, Lambrechts D, Gennigens C. Homologous recombination repair deficiency (HRD) testing in newly diagnosed advanced-stage epithelial ovarian cancer: A Belgian expert opinion. Facts Views Vis Obgyn. 2022 Jun;14(2):111-120.

Saad F, de Bono J, Barthélémy P, Dorff T, Mehra N, Scagliotti G, Stirling A, **Machiels JP,** Renard V, Maruzzo M, Higano CS, Gurney H, Healy C, Bhattacharyya H, Arondekar B, Niyazov A, Fizazi K. Patient-reported Outcomes in Men with Metastatic Castration-resistant Prostate Cancer Harboring DNA Damage Response Alterations Treated with Talazoparib: Results from TALAPRO-1. Eur Urol. 2023 Apr;83(4):352-360.

Houssiau H, **Duhoux FP**, François D, Seront E. Radium-223 as an Additional Therapeutic Strategy in Highly Selected Patients With Metastatic Breast Cancer: A Case Report. Front Oncol. 2022 May 27;12:896301.

Agostinetto E, Nader-Marta G, Paesmans M, Ameye L, Veys I, Buisseret L, Neven P, Taylor D, Fontaine C, Duhoux FP, Canon JL, Denys H, Coussy F, Chakiba C, Ribeiro JM, Piccart M, Desmedt C, Ignatiadis M, Aftimos P. ROSALINE: a phase II, neoadjuvant study targeting ROS1 in combination with endocrine therapy in invasive lobular carcinoma of the breast. Future Oncol. 2022 Jul;18(22):2383-2392.

Gomez-Roca C, Cassier P, Zamarin D, **Machiels JP**, Perez Gracia JL, Stephen Hodi F, Taus A, Martinez Garcia M, Boni V, Eder JP, Hafez N, Sullivan R, Mcdermott D, Champiat S, Aspeslagh S, Terret C, Jegg AM, Jacob W, Cannarile MA, Ries C, Korski K, Michielin F, Christen R, Babitzki G,

Watson C, Meneses-Lorente G, Weisser M, Rüttinger D, Delord JP, Marabelle A. Anti-CSF-1R emactuzumab in combination with anti-PD-L1 atezolizumab in advanced solid tumor patients naïve or experienced for immune checkpoint blockade. J Immunother Cancer. 2022 May;10(5):e004076.

Huyghe N, Benidovskaya E, Stevens P, **Van den Eynde M.** Biomarkers of Response and Resistance to Immunotherapy in Microsatellite Stable Colorectal Cancer: Toward a New Personalized Medicine. Cancers (Basel). 2022 Apr 29;14(9):2241.

Bouaoud J, Bossi P, Elkabets M, **Schmitz S**, van Kempen LC, Martinez P, Jagadeeshan S, Breuskin I, Puppels GJ, Hoffmann C, Hunter KD, Simon C, **Machiels JP**, Grégoire V, Bertolus C, Brakenhoff RH, Koljenović S, Saintigny P. Unmet Needs and Perspectives in Oral Cancer Prevention. Cancers (Basel). 2022 Apr 2;14(7):1815.

Delaloge S, Dureau S, D'Hondt V, Desmoulins I, Heudel PE, **Duhoux FP**, Levy C, Lerebours F, Mouret-Reynier MA, Dalenc F, Frenel JS, Jouannaud C, Venat-Bouvet L, Nguyen S, Callens C, Gentien D, Rapinat A, Manduzio H, Vincent-Salomon A, Lemonnier J, Cottu P; French Breast cancer Intergroup Unicancer-UCBG. Survival outcomes after neoadjuvant letrozole and palbociclib versus third generation chemotherapy for patients with high-risk oestrogen receptor-positive HER2-negative breast cancer. Eur J Cancer. 2022 May;166:300-308.

Gombos A, Venet D, Ameye L, Vuylsteke P, Neven P, Richard V, **Duhoux FP**, Laes JF, Rothe F, Sotiriou C, Paesmans M, Awada A, Guiot T, Flamen P, Piccart-Gebhart M, Ignatiadis M, Gebhart G. Author Correction: FDG positron emission tomography imaging and ctDNA detection as an early dynamic biomarker of everolimus efficacy in advanced luminal breast cancer. NPJ Breast Cancer. 2022 Mar 16;8(1):38.

Tesileanu CMS, Sanson M, Wick W, Brandes AA, Clement PM, Erridge SC, Vogelbaum MA, Nowak AK, **Baurain JF**, Mason WP, Wheeler H, Chinot OL, Gill S, Griffin M, Rogers L, Taal W, Rudà R, Weller M, McBain C, van Linde ME, Aldape K, Jenkins RB, Kros JM, Wesseling P, von Deimling A, Hoogstrate Y, de Heer I, Atmodimedjo PN, Dubbink HJ, Brouwer RWW, van IJcken WFJ, Cheung KJ, Golfinopoulos V, Baumert BG, Gorlia T, French PJ, van den Bent MJ. Temozolomide and Radiotherapy versus Radiotherapy Alone in Patients with Glioblastoma, IDH-wildtype: Post Hoc Analysis of the EORTC Randomized Phase III CATNON Trial. Clin Cancer Res. 2022 Jun 13;28(12):2527-2535.

Baldin P, Carrasco J, Beniuga G, Jouret-Mourin A, Demolin G, Roland S, D'Hondt L, Vergauwe P, Van Daele D, Mailleux M, Sinapi I, De Cuyper A, Blétard N, Massart B, Delos M, Castella ML, van Maanen A, **Van den Eynde M**. Randomized Phase 2 Study Comparing Pathological Responses of Resected Colorectal Cancer Metastases after Bevacizumab with mFOLFOX6 or FOLFIRI (BEV-ONCO Trial). Cancers (Basel). 2022 Feb 24;14(5):1183.

Devaux A, **Baurain JF**. Management of metastatic melanoma with new immunotherapy approaches beyond PD-1/CTLA-4 inhibitors. Curr Opin Oncol. 2022 Mar 1;34(2):123-130.

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).

REPRODUCTIVE MEDICINE

Our research into reproductive medicine focuses on various aspects of female reproduction:

- **Fertility preservation involving ovarian tissue cryopreservation and transplantation to maintain and restore fertility in cancer patients.**
- **Development of artificial gonadal organs.**
- **Investigation of benign gynecological diseases affecting reproduction; like endometriosis, adenomyosis and uterine fibroids.**

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

They work in close collaboration with the gynecology, hemato-oncology and anatomo-pathology departments of Cliniques Universitaires Saint-Luc.

Thematic Group Contact Person

Marie-Madeleine Dolmans
marie-madeleine.dolmans@uclouvain.be
Tel. 32 (0) 2.764.52.87

Research Pole

POLE OF GYNECOLOGY UNIT (GYNE)

Marie-Madeleine Dolmans, MD, PhD

Researchers and Technicians

Alessandra Camboni, MD, PhD
Luciana Cacciottola, MD, PhD
Camille Hossay, MD, PhD student
Marie d'Argent, MD, PhD student
Francisco Vitale, MD, PhD student
Thi Yen Thu Nguyen, MD, PhD student
Christina Anna Stratopoulou, PhD student
Margherita Zipponi, PhD student
Dongyun Lee, MD, PhD
Lara Houeis, PhD student
Maria Dolores Gonzalez, technician
Sarah Storder, technician
Olivier Van Kerk, technician
Mira Hryniuk, BA, English language editor
Dora Ourives Sereno, logistics and finance
Deborah Godefroidt, secretary

OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION

Cryobanking

Houeis L, Dolmans MM

Cancer treatments like chemotherapy and/or radiotherapy can induce premature menopause in young cancer patients, especially if alkylating agents or bone marrow transplantation are needed. In such cases, fertility preservation options include cryopreservation of oocytes or ovarian tissue freezing (1,2). Oocyte vitrification is offered to post-pubertal patients prior to administration of chemotherapy if and when the timeframe allows (3). The first live birth after fertility preservation using this technique was reported in a woman with mosaic Turner syndrome in 2022 (4).

In prepubertal patients, the only fertility preservation alternative is ovarian tissue cryopreservation (OTC) and subsequent transplantation (OTT) (2), placing thawed cortical strips on to the ovary or into a specially created peritoneal pocket (5). This technique is most commonly performed before initiation of treatment, but because primordial follicles are quiescent and more resistant to damage, it may also be an option after chemotherapy. Indeed, the live birth rate was found to be similar in both groups, as presented at two international congresses (1,6). Moreover, as MM Dolmans was president of the International Society for Fertility Preservation (ISFP) at its biannual meeting, we had the pleasure of hosting this event in Brussels in November 2022 (7).

The ovarian tissue bank at Cliniques Universitaires Saint-Luc (one of the first and largest in the world) contains tissue from more than 750 patients. The pregnancy rate after autotransplantation is 38%, as indicated by the from 5 leading European centers in the field, which is highly encouraging (8).

.

Ovarian follicle pool decline in women

Cacciottola L, Camboni A, Dolmans MM

While there are different pathways of controlled cell death, apoptosis and autophagy are known to be implicated in follicle loss. Apoptosis participates in eliminating damaged follicles, such as those impaired by chemotherapy, but its involvement in physiological age-related follicle decline is less well understood. Autophagy has proved crucial to follicle quiescence maintenance in murine models, yet its contribution to human follicle pool modulation is still unclear. Our work has sought to elucidate how these cell death pathways play a role in both physiological age-related ovarian reserve decline, and pathological follicle depletion triggered by inflammation or a pro-oxidant environment. A retrospective study on a large cohort of patients (age range 1-35 years) with non-ovarian pathologies evidenced a role for apoptosis and autophagy in age-related ovarian reserve decline, the latter being critical before puberty. Data also revealed a different response to non-physiological follicle death, with higher apoptosis rates only in prepubertal patients who had undergone some previous chemotherapy. This confirms that the apoptotic pathway is activated by drugs that induce DNA damage in oocytes, like alkylating agents (9)..

Effect of freezing and in vitro culture on ovarian tissue activation

Hossay C, Cacciottola L, Dolmans MM

OTC and OTT constitute an effective strategy for fertility preservation and restoration, but massive burnout of primordial follicles occurring after transplantation limits graft longevity and, in turn, the effectiveness of the procedure. We investigated potential causes of primordial follicle pool depletion in cryopreserved human ovarian tissue by assessing the impact of freezing, in vitro culture (IVC), and grafting to chick

chorioallantoic membrane (CAM) on early follicle dynamics (10) (Figure 1). Our data proved that IVC induces primordial follicle depletion, but there is no additional impact of freezing. Grafting to CAM preserves the primordial follicle pool by curbing follicle activation, apoptosis and autophagy, probably thanks to rapid graft revascularization and/or circulating embryonic anti-Müllerian hormone. These findings highlight the importance of enhancing neoangiogenesis in ovarian grafts and investigating the potential benefits of administering anti-Müllerian hormone to prevent primordial follicle burnout.

Effects of chemotherapy on ovarian tissue

Houeis L, Dolmans MM

There is now sufficient evidence to support the feasibility and efficacy of OTC and subsequent OTT for both fertility preservation and restoration of ovarian endocrine function. Prior chemotherapy is usually considered a contraindication to further OTC, but tissue cannot always be frozen before chemotherapy. Indeed, surgery may be contraindicated due to mass compression as in case of lymphoma, or when immediate chemotherapy is required for blood cancers like leukemia. In such cases, tissue may be frozen between chemotherapy sessions or when the patient is in complete remission. Recent publications report that undergoing OTC after some chemotherapy yields the same, or even higher, pregnancy rates compared to no chemotherapy at all before OTC (8). We aim to shed light on the effects of chemotherapy on ovarian tissue, as no research to date has been able to explain these unexpected results. Ovarian tissue from patients previously subjected to chemotherapy will be analyzed and compared with tissue from patients free of any chemotherapy. Since induction with cortisone is often part of chemotherapy protocols and has an impact on the immune system and inflammation, we will study its effects on ovarian tissue and the follicle environment by investigating inflammation and its consequences (fibrosis, neovascularization, immune system), as well as follicle status and characteristics.

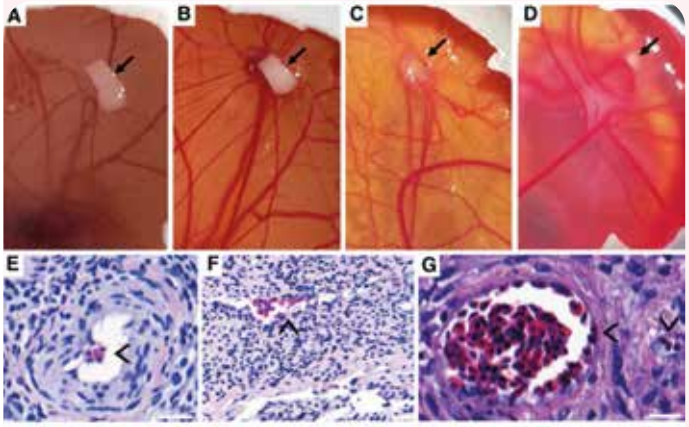


Figure 1. Macroscopic and microscopic evaluation of cryopreserved human ovarian tissue grafted to chorioallantoic membrane (CAM). Macroscopic aspect of ovarian tissue grafted to the traumatized CAM of a 7-day-old chick embryo on day 0 **(A)**, day 1**(B)** and day 6 **(C,D)**. Note the wheel-spoke pattern of CAM blood vessels around the ovarian graft on day 1 **(B)**. By day 6, the grafts were covered with a second layer of CAM **(C)** and most of them penetrated the egg **(D)**. Histology of ovarian tissue grafted to CAM with avian erythrocytes detected in vessels from ovarian grafts on day 1 **(E,F)** and day 6 **(G)**. Arrows point to ovarian grafts **(A-D)**. Arrowheads indicate avian erythrocytes **(E-G)**. Scale bar: 20 µm.

Importance of oxygen tension in human ovarian tissue in vitro culture

Vitale F, Cacciottola L, Dolmans MM

While there is enough evidence to support the feasibility of OTC and OTT, there is a risk of reintroducing malignant cells along with the grafted tissue, especially in certain types of cancer like leukemia. These patients could potentially benefit from an IVC system able to support complete in vitro development of early-stage follicles from cryopreserved ovarian tissue into fertilizable oocytes. Unfortunately, IVC of human follicles remains challenging, mainly due to poor viability.

The primordial follicle pool resides within the ovarian cortex, where in vivo oxygen (O2) tension ranges between 2% and 8%. Lowering O2 tension closer to physiological levels could therefore be considered a strategy to improve follicle outcomes. We investigated follicle survival and quality within ovarian cortical tissue cultured at 20% vs 5% O2 tension for 6 days. To this end, we performed (i) cleaved caspase-3 immunostaining to identify follicle apoptosis; (ii) 8-hydroxy-2-deoxyguanosine (8-OHdG) and gamma-H2AX (γH2AX) immunolabeling to detect oxidative stress damage and DNA double-strand breaks (DSBs) respectively; and (iii) β-galactosidase staining to assess follicle senescence. Our findings demonstrated that IVC at 5% O2 yields higher follicle survival and quality than at 20% O2, mainly by causing fewer oxidative stress-related lesions and less DNA DSB damage (11).

REFERENCES

1. **Dolmans MM**, Demeestere I, Anckaert E, De Vos M. Proceedings of the Oncofertility Congress of the "Freezing Ovarian Tissue and Oocytes" (FOTO) Consortium Brussels. J Assist Reprod Genet. 2022;39(8):1715-1725.
2. **Cacciottola L**, Donnez J, **Dolmans MM**. Ovarian tissue and oocyte cryopreservation prior to iatrogenic premature ovarian insufficiency. Best Pract Res Clin Obstet Gynaecol. 2022;81:119-133.
3. **Cacciottola L, Dolmans MM**, Schattman GL. A synopsis of the 2021 International Society of Fertility Preservation bi-annual meeting. J Assist Reprod Genet. 2022;39(8):1727-1732.
4. Strypstein L, Van Moer E, Nekkebroeck J, Segers I, Tournaye H, Demeestere I, **Dolmans MM**, Verpoest W, De Vos M. First live birth after fertility preservation using vitrification of oocytes in a woman with mosaic Turner syndrome. J Assist Reprod Genet. 2022;39(2):543-549.
5. **Hossay C**, Pirard C, Laurent P, Kluyskens C, Donnez J, **Dolmans MM**. Transplantation of Refrozen Ovarian Cortical Strips Retrieved from a Cryopreserved Whole Ovary: Proof of Feasibility. J Clin Med. 2022;11(17):4942.
6. Ataman LM, Laronda MM, Gowett M, Trotter K, Anvari H, Fei F, Ingram A, Minette M, Suebthawinkul C, Taghvaei Z, Torres-Vélez M, Velez K, Adiga SK, Anazodo A, Appiah L, Bourlon MT, Daniels N, **Dolmans MM**, Finlayson C, Gilchrist RB, Gomez-Lobo V, Greenblatt E, Halpern JA, Hutt K, Johnson EK, Kawamura K, Khrouf M, Kimelman D, Kristensen S, Mitchell RT, Moravek MB, Nahata L, Orwig KE, Pavone ME, Pépin D, Pesce R, Quinn GP, Rosen MP, Rowell E, Smith K, Venter C, Whiteside S, Xiao S, Zelinski M, Goldman KN, Woodruff TK, Duncan FE. A synopsis of global frontiers in fertility preservation. J Assist Reprod Genet. 2022;39(8):1693-1712.
7. **Houeis L, Dolmans MM**. Summary of the ISFP congress, Brussels, 10-12 November, 2022. J Assist Reprod Genet. 2023;40(3):433-442.
8. **Dolmans MM**, von Wolff M, Poirot C, et al. Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. Fertil Steril. 11:1102-1115, 2021.
9. **Cacciottola L, Camboni A, Cernogoraz A**, Donnez J, Dolmans MM. Role of apoptosis and autophagy in ovarian follicle pool decline in children and women diagnosed with benign or malignant extra-ovarian conditions. Hum Reprod. 2023;38(1):75-88.
10. **Hossay C**, Tramacere F, **Cacciottola L, Camboni A**, Squifflet JL, Donnez J, **Dolmans MM**. Follicle outcomes in human ovarian tissue: effect of freezing, culture, and grafting. Fertil Steril. 2023;119(1):135-145.
11. **F Vitale, L Cacciottola, FS Yu, M Barretta, C Hossay**, J Donnez, **MM Dolmans**. Importance of oxygen tension in human ovarian tissue in vitro culture. Human Reproduction. 2023 (Submitted).

ENDOMETRIOSIS

Dolmans MM, Cacciottola L

Endometriosis is a female reproductive disorder characterized by growth of uterine tissue in distant sites, affecting around 2-10% of reproductive-age women and causing chronic pelvic pain and infertility. Its pathogenesis is complex and still partially unexplained, so there is a pressing need for a comprehensive understanding of the disease to be able to detect and investigate events that take place in the microenvironment of the uterus. We aim to characterize the various pathogenetic (MIRA: pathogenic?) mechanisms that contribute to initiation and development of endometriosis (1). This involves elucidating new biological targets like reactive oxygen species (2) and paracrine signaling of microRNAs, and identifying novel therapeutic approaches as adjuvants to hormonal treatments.

Exosomes in endometriosis: a possible mechanism of damage to the ovarian reserve by ovarian endometriomas themselves

Lee DY, Cacciottola L, Dolmans MM

It is widely known that surgery for ovarian endometriomas depletes the ovarian reserve. However, increasing evidence shows that ovarian endometriomas themselves can also diminish the follicle pool through a variety of possible mechanisms. Exosomes, which are now thought to play a key role in cell-to-cell interactions, could be involved in the deleterious effect that ovarian endometriomas have on the follicle pool, but it has never been investigated.

We will culture tissue from ovarian endometriomas for 4 days to acquire the supernatant. After isolating exosomes by ultracentrifugation and characterizing them using nanoparticle tracking analysis and transmission electron microscopy, we will label them with a dye. Labeled exosomes will then be co-cultured with healthy ovarian tissue for 6 days. Finally, various parameters related to ovarian damage, including follicle classification, density, growth and survival, as well as macrophage accumulation and PI3K pathway markers, will be calculated and compared after confirming the presence of labeled exosomes in healthy ovarian tissue.

We anticipate that our research will provide a new pathogenesis for ovarian damage caused by ovarian endometriomas themselves, offering both the insight and orientation needed to develop a therapeutic strategy to prevent damage to adjacent tissue.

REFERENCES 2022

1. Donnez J, **Cacciottola L**. Endometriosis: an inflammatory disease that requires new therapeutic options. Int J Mol Sci. 2022;23(3):1518.

2. **Cacciottola L**, Donnez J, **Dolmans MM**. Can endometriosis-related oxidative stress pave the way for new treatment targets? Int J Mol Sci. 2021;22(13):7138.

ADENOMYOSIS AND ENDOMETRIOSIS

Stratopoulou CA, Zipponi M, d'Argent M, Camboni A, Dolmans MM

Uterine adenomyosis is a chronic benign disorder estimated to affect up to 20% of gynecology patients, causing heavy menstruation with subsequent anemia, severe pelvic pain and infertility (1, 2). Although the pathogenesis of adenomyosis has not been fully elucidated, the most widely accepted theory suggests invasion of the surrounding myometrium by endometrial cells, establishing ectopic lesions of endometrial glands and stroma. Our team aims to shed light on the complex mechanisms underlying endometrial invasiveness, with a view to acquiring a better understanding to be able to treat the condition.

Data increasingly point to an aberrant immune response in adenomyosis, and anti-inflammatory agents are commonly prescribed to manage disease symptoms (3). We previously detected excess infiltration of macrophages in adenomyosis compared to healthy endometrium (Figure 2), triggering our interest in the specific roles of these cells. We conducted an in vitro study, co-culturing activated macrophages with primary endometrial epithelial and stromal cells to investigate the impact of these interactions on endometrial cell invasiveness. We confirmed that macrophages promoted invasiveness in both endometrial cell populations, but this capacity was independent of breaks in cell-cell junctions and subsequent epithelial-mesenchymal transition. We therefore concluded that endometrial cells move and invade surrounding tissue in clusters, strongly suggesting collective cell migration to be the main mechanism underlying endometrial cell invasiveness in adenomyosis (4).

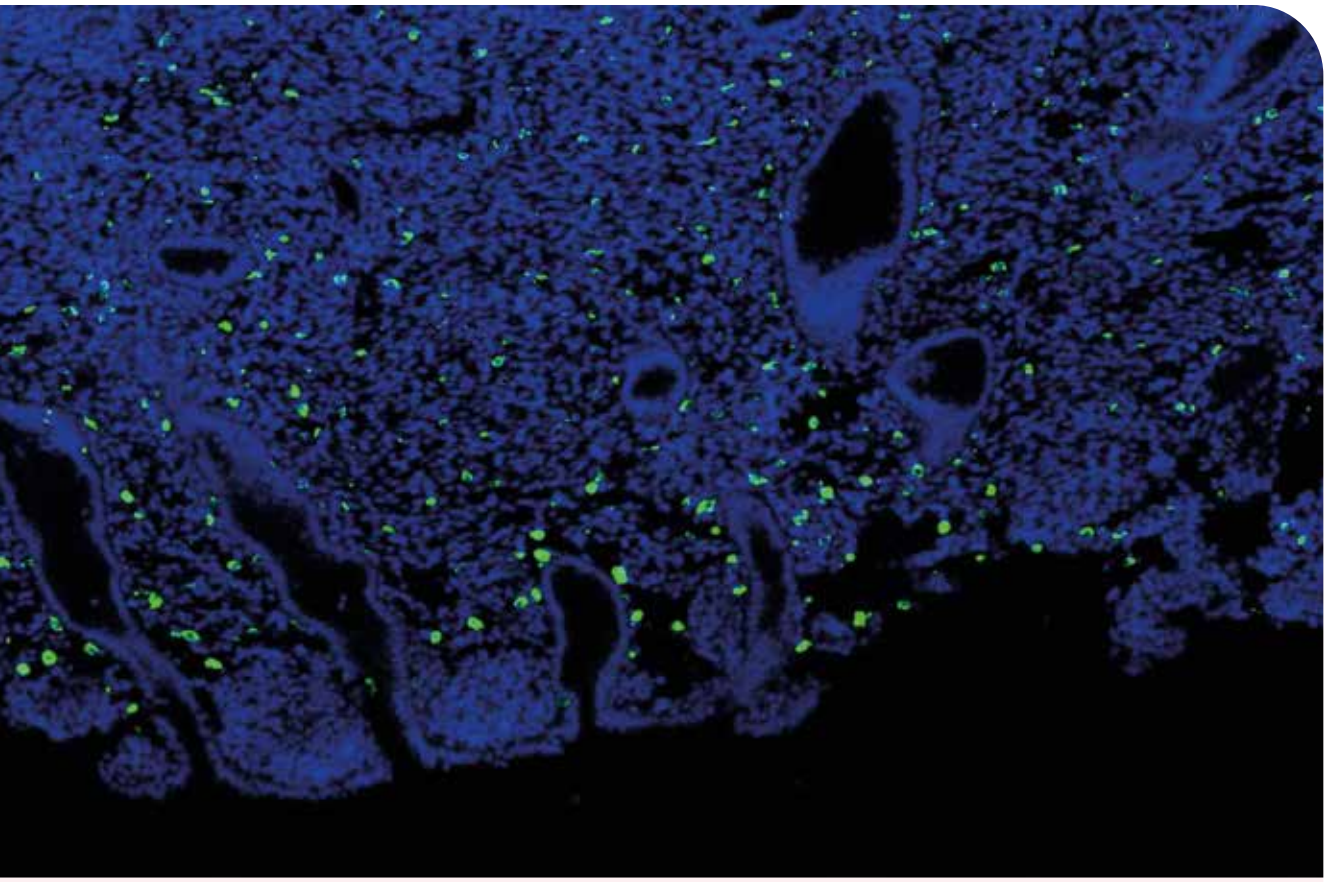


Figure 2. Accumulation of CD163-positive macrophages in endometrium of a patient with adenomyosis

Regarding lesion survival and progression, we found adenomyotic tissue to resist physiological cell death, as both apoptosis and autophagy showed decreased rates compared to healthy endometrium (5) (Figure 3). All in all, these findings indicate that adenomyosis may result from enhanced invasiveness and survival of endometrial tissue, paving the way for more rigorous research into its etiopathogenesis.

In any case, estrogens play a key role in the evolution of the disease and its symptoms. This is why gonadotropin-releasing hormone (GnRH) antagonists have emerged as potential treatment for endometriosis/adenomyosis, placing patients in a hypoestrogenic state (3, 6, 7). We are currently examining the role of paracrine signaling by stromal cells in the invasion process of the myometrium, looking to elucidate the pathophysiology of adenomyosis. Our focus is exosomal microRNAs actively secreted from endometrial stromal cells and their capacity to serve as biomarkers for the disease. The overall goal is to define appropriate noninvasive diagnostic tools for earlier disease identification and implementation of novel medical therapies for this relatively unknown and enigmatic disorder.

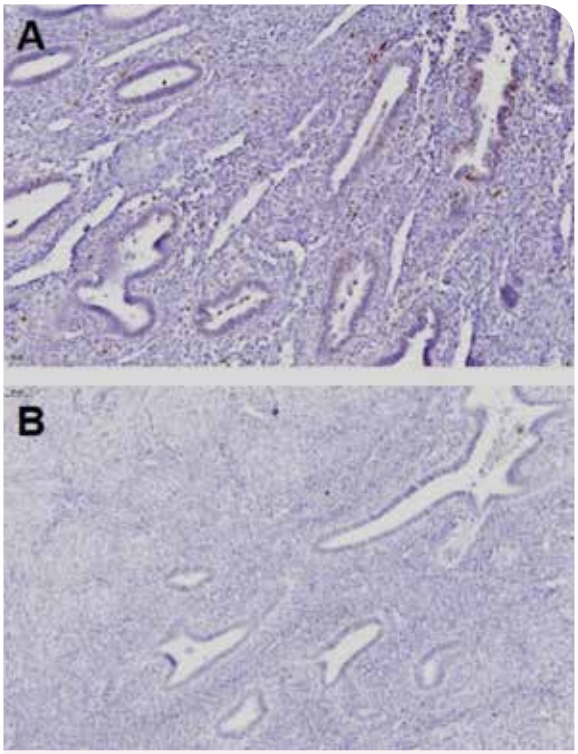


Figure 3. Apoptotic cells in normal menstrual endometrium (A) versus adenomyotic lesion (B).

REFERENCES 2022

1. Petraglia F, **Dolmans MM**. Iron deficiency anemia: Impact on women's reproductive health. Fertil Steril. 2022;118:605-606.

2. Donnez J, Carmona F, Maitrot-Mantelet L, **Dolmans MM**, Chapron C. Uterine disorders and iron deficiency anemia. Fertil Steril. 2022;118:615-624.

3. **Dolmans MM**, Donnez J. Emerging Drug Targets for Endometriosis. Biomolecules. 2022;12:1654.

4. **Stratopoulou CA, Cussac S, d'Argent M**, Donnez J, **Dolmans MM**. M2 macrophages enhance endometrial cell invasiveness by promoting collective cell migration in uterine adenomyosis. Reprod Biomed Online. 2023;S1472-6483(23)00003-2.

5. **d'Argent M, Stratopoulou CA, Cussac S, Camboni A**, Jadoul P, Donnez J, **Dolmans MM**. Are lower levels of apoptosis and autophagy behind adenomyotic lesion survival? 2022;submitted article.

6. Donnez J, **Dolmans MM**. GnRH Antagonists with or without Add-Back Therapy: A New Alternative in the Management of Endometriosis? Int J Mol Sci. 2021;22(21):11342.

7. Donnez J, **Cacciottola L**, Squifflet JL, **Dolmans MM**. Profile of Linzagolix in the Management of Endometriosis, Including Design, Development and Potential Place in Therapy: A Narrative Review. Drug Des Devel Ther. 2023;17:369-380.

MEDICAL MICROBIOLOGY

Although the research theme "Microbiology, Infectious Diseases and Antimicrobial Agents" is being developed, the pole of microbiology contributes 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 ***Clostridioides difficile and Borrelia***, including expertise in the diagnosis of ***Yersinia***. The group has also developed activities in the fields of Mycobacteriology, rapid diagnosis of septicemia, antimicrobial resistance, viral hepatitis and cytomegalovirus infection.

Thematic Group Contact Person

Pr Benoît KABAMBA-MUKADI
benoit.kabamba@uclouvain.be

Research Pole

MEDICAL MICROBIOLOGY

Benoît Kabamba-Mukadi, PhmD, PhD

Hector Rodriguez-Villalobos, MD, PhD

Alexia Verroken, MD, PhD

Ahalieyah Anantharajah, PhmD, PhD

Géraldine Dessilly, PhD

Researchers

Ahalieyah Anantharajah
Géraldine Dessilly
Anaïs Scohy

PhD students

Anais Scohy
Seydou Nakanabo
Daniel Valia

Technicians

Fairouz Boutachkourt
Sylvie Comblez
Najet Lamarti
Eléonore Ngyuvula Mantu
Anne-Thérèse Pâques
Kate Soumillion
Anne-Thérèse Vandenbroucke
Samuel van der Linden

Administrative staff

Anne Buchelot
Mélanie Coenen
Sylvie Debray

Pole Contact Person

Pr Benoît KABAMBA-MUKADI
benoit.kabamba@uclouvain.be

BACTERIOLOGY

Diagnosis and epidemiology of Clostridioides difficile Infections (CDI)

Ahalieyah Anantharajah, Eléonore Ngyuvula Mantu, Kate Soumillion, Anne-Thérèse Pâques, Michel Delmée, Sylvie Comblez

C. *difficile* is the main cause of hospital-acquired diarrhea and has become one of the most frequent bacterial pathogens isolated in healthcare settings. The 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. We have participated actively to the European nomenclature harmonization for the PCR-ribotyping. At the NRC, over six hundred different profiles have already been identified. Clinical isolates are analyzed for virulence genes (multiplex home-made PCR) and antimicrobial susceptibility to monitor the emergence of hypervirulent strains and/or - strains resistant to antibiotics commonly used for the treatment of CDI (vancomycin, metronidazole and fidaxomicin). Strains considered as possibly epidemiologically linked are sub-typed by MLVA (multilocus variable number tandem repeats analysis). Currently, the NRC is implementing genomic approaches such as WGS (Whole genome sequencing), in order to better understand the virulence of certain clinical isolates and the phenotypic differences within a single ribotype and to investigate the clonal links of clustered cases. In parallel, the NRC participates in the validation of new diagnostic methods through partnership with commercial companies and evaluate the accuracy of commercial molecular assays to identify hypervirulent strains. The NRC also participates in several European programs coordinated by the ECDC.

Development of Whole Genome Analysis for Typing and Detection of Virulence and Antibiotic Resistance Genes

Ahalieyah Anantharajah, Eléonore Ngyuvula Mantu, Kate Soumillion, Benoît Kabamba-Mukadi, Alexia Verroken, Hector Rodriguez-Villalobos

Multidrug-resistant pathogens present a major burden for hospitals. Rapid cluster identification and pathogen profiling, i.e., of antibiotic resistance and virulence genes by whole genome sequencing, are crucial for effective infection control and treatment. We have initiated a study on the whole genome sequencing of carbapenemase producing organisms to better understand the mechanisms involved in the persistence of these bacteria in patients and in the hospital environment.

Evaluation of the antibacterial activity of bacteriocins as a new therapeutic option for multiresistant microorganisms

Hector Rodriguez-Villalobos, Anandi Martin (Senior Project Manager - Infectious Disease, Syngulon), Alexia Verroken, Ahalieyah Anantharajah, Philippe Gabant (Syngulon)

Bacterial multiresistance is currently recognized as a major public health problem requiring urgent interventions in multiple areas. Parallel to the development of new antibiotics, other strategies are needed for the treatment of these multiresistant microorganisms. Antimicrobial peptides are natural molecules produced by animals, plants, protozoa, fungi or bacteria. Bacteriocins are thermostable antimicrobial peptides of 2-6KDa, synthesized by plasmid or ribosomal of gram-positive and negative bacteria. They protect the producing bacteria by promoting their own growth, at the expense of others present in the environment by their bactericidal or bacteriostatic properties.

In collaboration with the start-up Syngulon, the pole MBLG develops a novel line of research based on the antibacterial activity of synthetic bacteriocins. We explored the activity and synergy between bacteriocins, and antibiotics used for the treatment of these microorganisms, as a new way to overcome multi-resistance. Studies began in 2022 with a focus on multiresistance of Mycobacterium tuberculosis (Martin A et al Microb Drug Resist 2022) and Mycobacterium abcesus. Both are involved in significant global morbidity and mortality, especially in developing countries, immunosuppressed patients, and patients suffering from mucoviscidosis.

The results are promising, and we are currently analyzing this bactericidal and synergistic activity with antimicrobials also in additional groups of gram-positive and gram-negative microorganisms. We include vancomycin resistant enterococci (Antimicrobial activity of chemically synthetized bacteriocins against vancomycin-resistant clinical isolates of Enterococ-

cus faecium and Enterococcus faecalis, 41eme RICAI Dec 2022), extended spectrum ß-lactamases and carbapenemase producing Enterobacterales and other major pathogens (results in progress).

Study of candidiasis and biofilms of Candida in Burkina Faso

As part of the North-South cooperation (ARES PRD-2017) project, Prof Rodriguez-Villalobos is the promoter of the doctoral thesis of Dr Seydou Nakanabo Diallo, in co-supervision with Prof.Sanata Bamba (l'Université Nazi-Boni. Bobo Dioulasso . Burkina Faso.

Candidiasis is the main fungal infection in human pathology. However, the species involved in Burkina Faso as well as their virulence capacity and sensitivity profile to antifungals are not well known. The main objectives of this thesis project are a) the optimization of the diagnosis of candidiasis in Burkina Faso; b) the epidemiological analysis of invasive and relevant clinical candidiasis in Burkina Faso; c) the evaluation of the activity of different antifungals in an in vitro model; and d) analysis of biofilm production capacity and susceptibility of yeast-produced biofilms to antifungals to better adapt the treatment in this context.

Community as starting point of antibiotic resistance emergence and spread in low-resource setting: risk factors assessment

As part of the North-South cooperation, Prof Rodriguez-Villalobos is the promoter of the doctoral thesis of Dr Daniel Valia together with Professor Annie Robert (co-promoter, UCLouvain/SSS/IREC/EPID), in collaboration with the Clinical research unit of Nanoro (Burkina Faso), and the Institut of Tropical medicine (Antwerp). This PhD project is supported by the Conseil de l'Action International (CAI) of the Université Catholique de Louvain)

While death attributable to antimicrobial resistance worldwide is already high, it is expected to keep increasing in LMICs (Low and Middle Income Countries) carrying the highest burden without comprehensive action to optimize antibiotic use. In Burkina Faso, while antimicrobial stewardship programs most of the time target hospitals, little is known about antibiotic dispensing and use practices as well as the extent of resistance genes circulating in the community. The aim of this PhD project is therefore to provide a deep insight on antibiotic use as well as the extent of resistant strains of E. coli and K. pneumoniae, (two of the three pathogens most responsible of associated and attributable death in sub-Saharan Africa) in the community.

Development of metagenomic analysis of microbiome for clinical use

Benoît Kabamba-Mukadi, Eléonore Ngyuvula Mantu, Kate Soumillion

The 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.

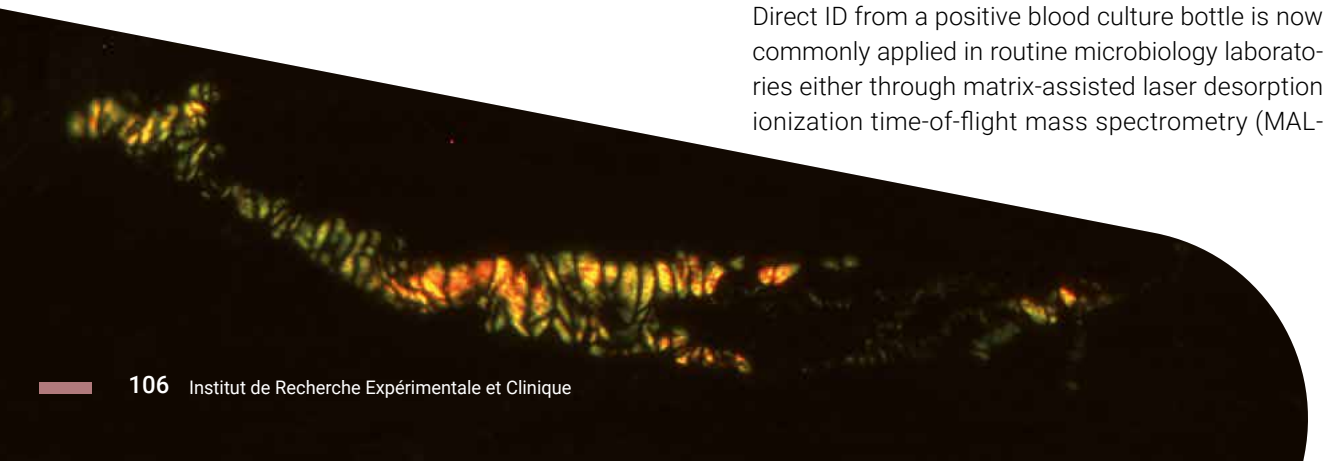
A research protocol called OPTICS (Oral Phage Therapy against Intestinal Carriage of Superbugs) is being conducted by Dr Brieuc Van Nieuwenhuyse at the pediatric hospitalization unit U92 as part of his doctoral thesis project. The concept is to treat children with digestive MDRO (Multidrug Resistant Organisms) with oral phage therapy before their liver transplant to hope that they will have fewer post-transplant bacterial complications.

Microbiological diagnosis of septicemia

Alexia Verroken, Ahalieyah Anantharajah, Hector Rodriguez-Villalobos

Sepsis remains a worldwide cause of mortality and morbidity with a reported 47-50 million cases and at least 11 million deaths per year. As time to appropriate antibiotherapy is a major factor to reduce sepsis mortality, a wide variety of tools have been developed to speed up identification (ID) and antimicrobial susceptibility test (AST) results from positive blood cultures.

Direct ID from a positive blood culture bottle is now commonly applied in routine microbiology laboratories either through matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MAL-



DI-TOF MS) either through the use of a molecular method yet detecting a limited panel of strains. These approaches combine very satisfying analytical performances and a 24-hour time gain compared to subculture.

Nevertheless, in this current era of increasing multi-resistance, ID results are frequently insufficient to decide on an optimal antimicrobial treatment and AST remains more than ever essential. Recently commercial rapid AST systems (RAST) with defined antibiotic panels and based on cellular imaging were marketed allowing results within 5 to 8 hours and reported overall agreement with routine AST between 91 and 95%.

We initiated a prospective single center randomized clinical study aiming to measure the microbiological and clinical performances of 3 RAST approaches including the Specific Reveal (bioMérieux), the dRAST (Quantamatrix) and the ASTar (Qlinea). Two hundred and forty adult hospitalized patients with a Gram-negative positive-detected blood culture will be included. Data analysis and comparison to routine microbiological results and turnaround times are ongoing.

Borrelia burgdorferi

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

A collaborative project focused on Lyme disease was set up in 2020 between a Belgian biotechnology company and the medical microbiology research unit of UCLouvain which conducted a set of experiments on Borrelia burgdorferi sensu lato: identification and species characterization, culture, strain selection, quantification, challenge tests, viability tests. This study aimed to test the effect of different candidate proteins (MBL, C1 complex, C1r,…) on the complement pathway with a view to improving the effectiveness of therapeutic management.

A PhD study was conducted by Laurence Geebelen with the overall objective of estimating the health and cost burden of Lyme borreliosis and other tick-borne infections in Belgium. The thesis defense took place on December 10th, 2021.

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). This study is part of ongoing PhD project of Raphaël Rousseau, with Professor Sophie Vanwambeke as the promoter (Faculty of Science/Ecole de géographie (SST/SC/GEOG); Earth and Life Institute/Earth & Climate (SST/ELI/ELIC)).

VIROLOGY

Antiretroviral drug resistance

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

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). A recent study has assessed the prevalence and evolution of transmitted HIV drug resistance mutations between 2013 and 2019. The prevalence was stable over the years, and comparable to the prevalence in other Western European countries. The high frequency of NNRTI mutations (11,4%) requires special attention with evidence for local clustered onward transmission of some frequently detected mutations (Mortier at al. Open Forum Infect Dis, 2022)

A retrospective study conducted by Stoffels et al. (J Infect Dis, 2020) showed that chronic and early antiretroviral therapy lead to more false-negative HIV test results. The study evaluated the reactivity of 3 HIV confirmatory assays (INNO-LIA, Geenius, and MP) and 7 HIV rapid tests in Belgium. In early-treated cohort (N=83) the confirmation assay sensitivities ranged from 87.5% to 95.2%, whereas rapid test assay sensitivities ranged from 75.9% to 100%. The fastest reversion was demonstrated after 4 months of treatment. Among the long-term treated cohort (N=390 HIV-1 patients with ≥ 9 years of undetectable viral load), the confirmation assay sensitivities ranged from 98.1% to 99.5%, whereas rapid test sensitivities ranged from 96.2% to 100%. Longer treatment increased nonreactivity of the HIV rapid tests (P = .033). Undetectable viral load decreases the sensitivities of HIV diagnostic tests, and further monitoring of the performance of serological assays is advised.

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. Since end of 2017, INSTI resistance mutations are investigated by the semi-automated NGS platform.

Indeed, the ARL of UCLouvain 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

Study on the HIV-1 provirus (Dr Géraldine Dessilly), that had 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

Project Team (Benoît Kabamba-Mukadi, Géraldine Dessilly, Anne-Thérèse Vandenbroucke, Najet Lamarti, Anne-Thérèse Pâques)

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.

Since 2020, new projects on HIV-2 have been launched, 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.

SARS-CoV-2 and COVID-19

Project Team (Benoît Kabamba-Mukadi, Géraldine Dessilly, Anne-Thérèse Vandenbroucke, Anne-Thérèse Pâques, Eléonore Ngyuvula Mantu, Kate Soumillion, Samuel van der Linden)

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 set up 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.

This project was included in the HYGIEIA project (HYpothesizing the Genesis of Infectious Diseases and Epidemics through an Integrated Systems Biology Approach), supported by corporate sponsorship of 2,700,000 euros (Sofina Covid Solidarity Fund) and designed to respond to the enormous challenges of the COVID-19 pandemic through a multi-omic approach supported supported by network medicine and the gigantic potential of AI (artificial intelligence). A true pioneer of the medicine of tomorrow.

It is hoped that in addition to investigating COVID-19, the logistics deployed within this project will be applicable to other infectious agents, pandemic-type situations, and also other complex, non-infectious diseases (Ward et al. viruses, 2022).

From September 2020 to November 2022, the MBLG research unit 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.

Since 2020, collaborations are ongoing to assess the antiviral effect of certain compounds (drug, disinfectant, UV disinfection, etc.) as well as the persistence of disinfectants on different surfaces (Dessilly et al. J Glob Antimicrob Resist. 2022).

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.

The project also includes genetic characterization of CMV strains implicated in congenital CMV infection (cCMV): (1) to assess the possible presence of drug resistance mutations in cCMV strains that may compromise secondary or tertiary prevention with valaciclovir (2) to characterize cCMV genotypes that, once acquired, can lead to severe disease progression, would allow for early diagnosis and prediction of outcome.

Viral Hepatitis

Benoît Kabamba-Mukadi, Géraldine Dessilly, Eléonore Ngyuvula Mantu, Kate Soumillion and Anne-Thérèse Vandenbroucke

Since 2019, the Medical Microbiology Research Unit of IREC has been active in monitoring drug resistance and determining the genotype and subgenotype of HCV. In collaboration with the National Reference Center (NRC), a consortium between the Cliniques Universitaires Saint-Luc and Sciensano, we perform these assays via a semi-automated NGS platform. Indeed, the laboratory is the first in Belgium to have validated, accredited according to the ISO 15189 Standard and used NGS in clinical routine for the identification of HCV resistance mutations and the determination of the HCV genotype.

An ongoing study is also investigating the utility of NGS for detecting HCV resistance mutations in treatment naive patients.

Project thesis on viral hepatitis (Infection by hepatitis B and C viruses in Lubumbashi, Democratic Republic of Congo: prevalence, viral markers and molecular characterization)

Doctoral thesis project by Mr Arsène Kabamba Tshikongo with Prof. Albert Longanga from the University of Lubumbashi (UNILU) in the Democratic Republic of Congo as promoter and Professor Benoît Kabamba Mukadi from UCLouvain as co-promoter, supervised by Dr Géraldine Dessilly, Mrs Anne-Thérèse Pâques, Najet Lamarti, Anne-Thérèse Vandenbroucke

As part of the North-South cooperation encouraged by UCLouvain, the Prof. B. Kabamba-Mukadi was the co-promoter on the thesis carried out locally by the PhD student, Mr Arsène Kabamba who obtained a scholarship from the Administration des Relations Internationales (ADRI) of UCLouvain. Since 2019, the candidate has been coming to the Microbiology research unit at IREC for several months a year to learn and carry out the molecular and serological tests related to the project, which has led to the publication of 3 scientific articles. The thesis defense took place on January 28th, 2022, in Lubumbashi (DR Congo).

EQUIPMENTS

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

REFERENCES 2022

L Wallemacq, Silvio ; Danwang, Celestin ; **Scohy, Anaïs** ; Belkhir, Leïla ; De Greef, Julien ; **Kabamba-Mukadi, Benoît** ; Yombi, Jean Cyr. A comparative analysis of the outcomes of patients with influenza or COVID-19 in a tertiary hospital in Belgium.. In: Journal of infection and chemotherapy, Vol. 28, no.11, p. 1489-1493 (2022). doi:10.1016/j.jiac.2022.07.012. http://hdl.handle.net/2078.1/268158

Yerbanga, Isidore W ; Nakanabo Diallo, Seydou ; Rouamba, Toussaint ; Denis, Olivier ; **Rodriguez-Villalobos**, Hector ; Montesinos, Maria Isabel ; Bamba, Sanata. A systematic review of epidemiology, risk factors, diagnosis, antifungal resistance, and management of invasive aspergillosis in Africa.. In: Journal de mycologie medicale, Vol. 33, no.1, p.101328 (2022). doi:10.1016/j.mycmed.2022.101328. http://hdl.handle.net/2078.1/266040

Manolache, Narcis-George ; Ursachi, Vasile ; **Scohy, Anaïs** ; Desmet, Charlotte ; Yombi, Jean Cyr ; Nzeusseu Toukap, Adrien ; Stoenoiu, Maria Simona. Attenuated anti-SARS-CoV-2 antibody response to vaccination in patients with rheumatic diseases.. In: The Journal of infection, Vol. 84, no. 2, p. e22-e23 (2022). doi:10.1016/j.jinf.2021.12.006.http://hdl.handle.net/2078.1/261631

Van Nieuwenhuyse, Brieuc ; Van der Linden, Dimitri ; Chatzis, Olga ; Lood, Cédric ; Wagemans, Jeroen ; Lavigne, Rob ; Schroven, Kaat ; Paeshuyse, Jan ; De Magnee, Catherine ; Sokal, Etienne ; Stéphenne, Xavier ; Scheers, Isabelle ; **Rodriguez-Villalobos, Hector** ; Djebara, Sarah ; Merabishvili, Maya ; Soentjens, Patrick ; Pirnay, Jean-Paul. Bacteriophage-antibiotic combination therapy against extensively drug-resistant Pseudomonas aeruginosa infection to allow liver transplantation in a toddler.. In: Nature communications, Vol. 13, no.1, p. 5725 (2022). doi:10.1038/s41467-022-33294-w. http://hdl.handle.net/2078.1/265577

Saad Albichr, Imane ; De Greef, Julien ; Van Den Neste, Eric ; Poire, Xavier ; Havelange, Violaine ; Vekemans, Marie-Christiane ; Bailly, Sarah ; Yombi, Jean Cyr ; Mzougui, Samy ; **Scohy, Anaïs ; Kabamba-Mukadi, Benoît**. Cellular response to COVID-19 vaccines in hematologic malignancies patients: a new hope for non-responders?. In: Leukemia & lymphoma, Vol. 63, no. 3, p. 743-746 (2022). doi:10.1080/10428194.2021.1998485. http://hdl.handle.net/2078.1/254705

Anantharajah, Ahalieyah ; Deltombe, Matthieu ; de Barsy, Marie ; Evrard, Stéphanie ; Denis, Olivier ; Bogaerts, Pierre ; Hallin, Marie ; Miendje Deyi, Véronique Yvette ; Pierard, Denis ; Bruynseels, Peggy ; Boelens, Jerina ; Glupczynski, Gerald ; Huang, Te-Din. Characterization of hypervirulent Klebsiella pneumoniae isolates in Belgium.. In: Journal of Clinical Investigation, Vol. 41, no. 5, p. 859-865 (2022). doi:10.1007/s10096-022-04438-z. http://hdl.handle.net/2078.1/259980

Choteau, Mathilde ; **Scohy, Anaïs** ; Messe, Stéphane ; Luyckx, Mathieu ; Dechamps, Mélanie ; Montiel, Virginie ; Yombi, Jean Cyr ; Gruson, Damien ; Limaye, Nisha ; Michiels, Thomas ; Dumoutier, Laure. Development of SARS-CoV2 humoral response including neutralizing antibodies is not sufficient to protect patients against fatal - 2 - infection.. In: Scientific reports, Vol. 12, no. 1, p. 2077 [1-12] (2022). doi:10.1038/s41598-022-06038-5. http://hdl.handle.net/2078.1/258443

Labriola, Laura ; Ruelle, Jean ; **Scohy, Anaïs** ; Seghers, François ; Perlot, Quentin ; De Greef, Julien ; Desmet, Christine ; Romain, Cécile ; Yombi, Jean Cyr ; **Rodriguez-Villalobos, Hector ; Kabamba Mukadi, Benoît** ; Jadoul, Michel. Dynamics of spreading of SARS-CoV-2 in a Belgian hemodialysis facility: The importance of the analysis of viral strains.. In: Journal of medical virology, Vol. 94, no.4, p. 1481-1487 (2022). doi:10.1002/jmv.27471. http://hdl.handle.net/2078.1/261587

Ward, Bradley ; Yombi, Jean Cyr ; Balligand, Jean-Luc ; Cani, Patrice D. ; Collet, Jean-François ; De Greef, Julien ; Dewulf, Joseph P. ; Gatto, Laurent ; Haufroid, Vincent ; Jodogne, Sébastien ; **Kabamba-Mukadi, Benoît** ; Pyr dit Ruys, Sébastien ; Vertommen, Didier ; Elens, Laure ; Belkhir, Leïla. HYGIEIA: HYpothesizing the Genesis of Infectious Diseases and Epidemics through an Integrated Systems Biology Approach. In: Viruses, Vol. 14, no. 7, p. 1373 [1-17] (2022). doi:10.3390/v14071373. http://hdl.handle.net/2078.1/262895

Lardinois, Benjamin ; Belkhir, Leïla ; **Verroken, Alexia**. Helicobacter canis: A Review of Microbiological and Clinical Features.. In: Frontiers in microbiology, Vol. 12, p. 814944 [1-8] (2022). doi:10.3389/fmicb.2021.814944. http://hdl.handle.net/2078.1/259738

Van Regemorter, Elliott ; **Scohy, Anais** ; Morelle, Johann ; Jadoul, Michel ; Labriola, Laura. Humoral responses to BNT162b2 SARS-CoV-2 and hepatitis B vaccines are associated in patients on maintenance hemodialysis: a single-centre experience in Belgium.. In: Clinical kidney journal, Vol. 15, no.2, p. 363-365 (2022). doi:10.1093/ckj/sfab221. http://hdl.handle.net/2078.1/259750

Lambert, Catherine ; **Scohy, Anaïs** ; Yombi, Jean Cyr ; Goffin, Eric ; Devresse, Arnaud. Impact of therapeutic plasma exchange on acquired vaccinal anti-SARS-CoV-2 antibodies.. In: European journal of internal medicine, Vol. 100, p.140-142 (2022). doi:10.1016/j.ejim.2022.02.014. http://hdl.handle.net/2078.1/261408

Fernandes, Guillaume ; Devresse, Arnaud ; **Scohy, Anaïs** ; De Greef, Julien ; Yombi, Jean Cyr ; Belkhir, Leïla ; Darius, Tom ; Mourad, Michel ; Buemi, Antoine ; **Kabamba-Mukadi, Benoît** ; Goffin, Eric ; Kanaan, Nada. In Reply to 'Kidney Transplant Recipients With COVID-19 and Monoclonal Antibody Therapy: Additional Considerations'.. In: Kidney medicine, Vol. 4, no.8, p. 100503 (2022). doi:10.1016/j.xkme.2022.100503. http://hdl.handle.net/2078.1/268159

Dessilly, Géraldine ; Pâques, Anne-Thérèse ; Vandenbroucke, Anne-Thérèse ; Hazée, Pierre ; Gaume, Alain ; Gindro, Katia ; Schnée, Sylvain ; Lakaye, Frédéric ; **Kabamba-Mukadi, Benoît**. In vitro evaluation of the virucidal activity of disodium citrate perhydrate (2SCP) disinfectant against SARS-CoV-2.. In: Journal of global antimicrobial resistance, Vol. 28, p. 158-160 (2022). doi:10.1016/j.jgar.2022.01.006. http://hdl.handle.net/2078.1/259730

Fernandes, Guillaume ; Devresse, Arnaud ; **Scohy, Anaïs** ; Yombi, Jean Cyr ; Belkhir, Leïla ; De Greef, Julien ; Darius, Tom ; Buemi, Antoine ; **Kabamba Mukadi, Benoît** ; Goffin, Eric ; Kanaan, Nada. Monoclonal Antibody Therapy for SARS-CoV-2 Infection in Kidney Transplant Recipients: A Case Series From Belgium.. In: Transplantation, Vol. 106, no. 1, p. e107-e108 (2022). doi:10.1097/TP.0000000000003974. http://hdl.handle.net/2078.1/252932

Fernandes, Guillaume ; Devresse, Arnaud ; **Scohy, Anaï**s ; De Greef, Julien ; Yombi, Jean Cyr ; Belkhir, Leïla ; Darius, Tom ; Mourad, Michel ; Buemi, Antoine ; **Kabamba Mukadi, Benoît** ; Goffin, Eric ; Kanaan, Nada. Monoclonal Antibody Therapy in Kidney Transplant Recipients With Delta and Omicron Variants of SARS-CoV-2: A Single-Center Case Series.. In: Kidney Medicine, Vol. 4, no. 6, p. 100470 (2022). doi:10.1016/j.xkme.2022.100470. http://hdl.handle.net/2078.1/260514

Deckers, Corentin ; Soleimani, Reza ; Denis, Olivier ; Bogaerts, Pierre ; BERHIN, Catherine ; **Rodríguez-Villalobos**, Hector ; Descy, Julie ; Hallin, Marie ; Nonhoff, Claire ; Desmet, Stefanie ; Magerman, Koen ; Vanden Abeele, Anne Marie ; Lissoir, Bénédicte ; Matheeussen, Veerle ; Vernelen, Kris ; Huang, Te-Din. Multicenter inter-laboratory analysis of routine susceptibility testing with a challenge panel of resistant strains., collab. Belgian National Antibiogram Committee. In: Journal of global antimicrobial resistance, no. 28, p. 125-129 (2022). doi:10.1016/j.jgar.2021.12.020. http://hdl.handle.net/2078.1/257280

Geebelen, Laurence ; Lernout, Tinne ; Devleesschauwer, Brecht ; **Kabamba-Mukadi, Benoît** ; Saegeman, Veroniek ; Belkhir, Leïla ; De Munter, Paul ; Dubois, Bénédicte ; Westhovens, Rene ; Van Oyen, Herman ; Speybroeck, Niko ; Tersago, Katrien ; Giot, Jean-Baptiste ; Léonard, Philippe ; Vangheluwe, Riet ; Wieërs, Grégoire ; Marot, Jean-Christophe ; Evrard, Frédéric ; Delaere, Bénédicte ; Noirhomme, Séverine ; Binnemans, Els ; Vanhoof, Johan. Non-specific symptoms and post-treatment Lyme disease syndrome in patients with Lyme borreliosis: a prospective cohort study in Belgium (2016–2020), collab. Humtick Hospital Group. In: BMC Infectious Diseases, Vol. 22, no. 1, p. 756 [1-14] (2022). doi:10.1186/s12879-022-07686-8. http://hdl.handle.net/2078.1/265849

Verroken, Alexia ; Hajji, Chaima ; Bressant, Florian ; Couvreur, Jonathan ; **Anantharajah, Ahalieyah** ; **Rodriguez-Villalobos, Hector**. Performance evaluation of the FAST System and the FAST-PBC Prep cartridges for speeded-up positive blood culture testing.. In: Frontiers in microbiology, Vol. 13, p. 982650 (2022). doi:10.3389/fmicb.2022.982650. http://hdl.handle.net/2078.1/273745

Ngougni Pokem, Perrin ; Wittebole, Xavier ; Collienne, Christine ; **Rodriguez-Villalobos, Hector** ; Tulkens, Paul M. ; Elens, Laure ; Van Bambeke, Françoise ; Laterre, Pierre-François. Population Pharmacokinetics of Temocillin Administered by Continuous Infusion in Patients with Septic Shock Associated with Intra-Abdominal Infection and Ascitic Fluid Effusion. In: Antibiotics, Vol. 11, no. 7, p. 898 [1-19] (2022). doi:10.3390/antibiotics11070898. http://hdl.handle.net/2078.1/264675

Mortier, Virginie ; Debaisieux, Laurent ; **Dessilly, Géraldine** ; Stoffels, Karolien ; Vaira, Dolores ; Vancutsem, Ellen ; Van Laethem, Kristel ; Vanroye, Fien ; Verhofstede, Chris. Prevalence and Evolution of Transmitted Human Immunodeficiency Virus Drug Resistance in Belgium Between 2013 and 2019.. In: Open forum infectious diseases, Vol. 9, no.7, p. ofac195 (2022). doi:10.1093/ofid/ofac195. http://hdl.handle.net/2078.1/273766

Martin, Anandi ; Bland, Michael J ; **Rodriguez-Villalobos, Hector** ; Gala, Jean-Luc ; Gabant, Philippe. Promising Antimicrobial Activity and Synergy of Bacteriocins Against Mycobacterium tuberculosis.. In: Microbial drug resistance (Larchmont, N.Y.), (2022). doi:10.1089/mdr.2021.0429. http://hdl.handle.net/2078.1/273846

Fernandes, Guillaume ; Devresse, Arnaud ; **Scohy, Anaïs** ; Yombi, Jean Cyr ; Belkhir, Leïla ; De Greef, Julien ; De Meyer, Martine ; Mourad, Michel ; Darius, Tom ; Buemi, Antoine ; **Kabamba Mukadi, Benoît** ; Goffin, Eric ; Kanaan, Nada. Rapid Decline in Vaccine Induced anti-SARS-CoV-2 Antibody Titers 3 Months After Kidney Transplantation: A Case Series From Belgium.. In: Transplantation, Vol. 106, no. 1, p. e98-e99 (2022). doi:10.1097/TP.0000000000003963. http://hdl.handle.net/2078.1/251378

Frère, Julie ; Chatzis, Olga ; Cremer, Kelly ; Merckx, Joanna ; De Keukeleire, Mathilde ; Renard, Florence ; Ribesse, Nathalie ; Minner, Frédéric ; Ruelle, Jean ; **Kabamba, Benoit ; Rodriguez-Villalobos, Hector** ; Bearzatto, Bertrand ; Delforge, Marie-Luce ; Henin, Coralie ; Bureau, Fabrice ; Gillet, Laurent ; Robert, Annie ; Van der Linden, Dimitri. SARS-CoV-2 Transmission in Belgian French-Speaking Primary Schools: An Epidemiological Pilot Study. In: Viruses, Vol. 14, no.10, p. 2199 (2022). doi:10.3390/v14102199. http://hdl.handle.net/2078.1/266110

Devresse, Arnaud ; Briol, Sébastien ; De Greef, Julien ; Lemaitre, Florian ; Boland, Lidvine ; Haufroid, Vincent ; **Scohy, Anaïs ; Kabamba-Mukadi, Benoît** ; Yombi, Jean Cyr ; Belkhir, Leïla ; Darius, Tom ; Buemi, Antoine ; De Potter, Kristell ; Mantegazza, Rebecca ; Bearzatto, Bertrand ; Goffin, Eric ; Kanaan, Nada. Safety, Efficacy and Relapse of Nirmatrelvir-Ritonavir in Kidney Transplant Recipients Infected with SARS-CoV-2.. In: Kidney International Reports, Vol. 8, no. 1, p. 2356-2363 (2022). doi:10.1016/j.ekir.2022.08.026. http://hdl.handle.net/2078.1/264855

Wang, Gang ; Brunel, Jean-Michel ; **Rodriguez-Villalobos, Hector** ; Bolla, Jean-Michel ; Van Bambeke, Françoise. The polyamino-isoprenyl potentiator NV716 revives disused antibiotics against Gram-negative bacteria in broth, infected monocytes, or biofilms, by disturbing the barrier effect of their outer membrane.. In: European journal of medicinal chemistry, Vol. 238, no.11, p. 114496 (2022). doi:10.1016/j.ejmech.2022.114496. http://hdl.handle.net/2078.1/264674

Valia, Daniel ; Ingelbeen, Brecht ; Kaboré, Bérenger ; Karama, Ibrahima ; Peeters, Marjan ; Lompo, Palpouguini ; Vlieghe, Erika ; Post, Annelies ; Cox, Janneke ; de Mast, Quirijn ; Robert, Annie ; van der Sande, Marianne A. B. ; **Rodriguez-Villalobos, Hector** ; van der Ven, Andre ; Tinto, Halidou ; Jacobs, Jan. Use of WATCH antibiotics prior to presentation to the hospital in rural Burkina Faso. In: Antimicrobial resistance and infection control, Vol. 11, no. 1, p. 59 [1-7] (2022). doi:10.1186/s13756-022-01098-8. http:///hdl.handle.net/2078.1/261799

Ward, Bradley; Yombi, Jean Cyr; Balligand, Jean-Luc; Cani, Patrice D; Collet, Jean-François; de Greef, Julien; Dewulf, Joseph P; Gatto, Laurent; Haufroid, Vincent; Jodogne, Sébastien; **Kabamba, Benoît;** Pyr dit Ruys, Sébastien; Vertommen, Didier; Elens, Laure and Belkhir, Leïla. HYGIEIA: HYpothesizing the Genesis of Infectious Diseases and Epidemics through an Integrated Systems Biology Approach. Viruses. 2022 Jul; 14(7): 1373. Published online 2022 Jun 23. doi: 10.3390/v14071373

CLINICAL TRIAL CENTER (CTC):

LINK TO UCLOUVAIN

Julie Vanacker
Academic support and central desk officer for UCLouvain
julie.vanacker@saintluc.uclouvain.be

Jean-Louis Vanoverschelde, MD, PhD
CUSL Medical Director
jean-louis.vanoverschelde@saintluc.uclouvain.be

Dominique Van Ophem
CTC director
dominique.vanophem@saintluc.uclouvain.be

CUSL INTERNAL LINKS

Coline De Grande
Legal officer
coline.degrande@saintluc.uclouvain.be

Aline Van Maanen
Statistician : Redcap suppo
and CUSL sponsored studi
aline.vanmaanen@saintluc.uclouvain.be

Kiswendsida Sawadogo-
Statistician : Redcap suppo
& CUSL sponsored studies
kiswendsida.sawadogo@saintluc.uclou

Alix Collard
Statistician : Redcap suppo
and CUSL sponsored studi
alix.collard@saintluc.uclouvain.be

Michel Van Hassel, MD
CTC deputy director, coordinator contracts, finance and reporting
michel.vanhassel@saintluc.uclouvain.be

Isabelle Beaufay
Coordinator quality and regulatory affairs
isabelle.beaufay@saintluc.uclouvain.be

Marie Masson
Assistant of the manager contracts, finance and reporting
marie.masson@saintluc.uclouvain.be

Sandra Cueto-Lopez
Central desk for Commercial Research
sandra.cuetolopez@uclouvain.be ;
guichetcommercial@saintluc.uclouvain.be

Enrico Tricanico
Contracts and finance officer
enrico.tricanico@saintluc.uclouvain.be

San Salvatore Livolsi
Contracts and finance officer
san.livolsi@saintluc.uclouvain.be

Pauline Stevaux
Contracts and finance officer
pauline.stevaux@saintluc.uclouvain.be

Céline Patti
Contracts and finance officer
celine.patti@saintluc.uclouvain.be

Paul Mourlhou
Reporting officer
paul.mourlhou@saintluc.uclouvain.be

Benoit Plichon
European academic projects officer
benoit.plichon@saintluc.uclouvain.be

Joëlle De Vriese
Academic support and central desk
joelle.devriese@saintluc.uclouvain.be
guichetacademique@saintluc.uclouvain.b

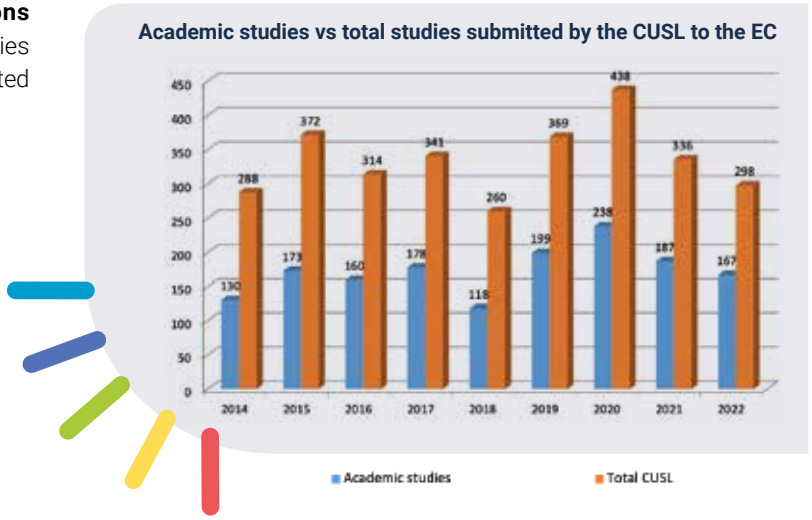
Tania Thirion
Academic support
tania.thirion@siantluc.uclouvain.be

Elise Bays
Academic CRA
elise.bays@saintluc.uclouvain.be

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

DEVELOPMENT OF CLINICAL RESEARCH AT THE CUSL

Ethics Committee (EC) submissions at the CUSL: in 2022, academic studies (master theses not included) represented 56% of the total submissions.



RESEARCH MANDATES

• NEW « FRC » STARTING GRANTS SINCE 2017

	2017	2018	2019	2020	2021	2022	2023	Total
Starting grant	4	4	5	3	2	3	**3**	**24**

"FRC" MANDATES FOR CLINICAL RESEARCHERS AND RESEARCHERS (NEW APPOINTMENTS AND RENEWALS) SINCE 2011 (TOTAL)

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	Total since 2011
TOTAL : Clinical researchers (CUSL)	3	8	5	14	18	13	26	20	30	**22**	**189**
Of which renewals :	0	4	2	5	5	6	11	6	17	**13**	**78**
TOTAL : Researchers (UCL)	3	12	11	8	10	7	2	0	0	**1**	**84**
Of which renewals :	1	2	2	3	6	3	2	0	0	**1**	**28**

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

	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total since 2011
TOTAL	9	10	12	10	8	6	6	7	**8**	**98**

FNRS MANDATES SINCE 2012 (NEW APPOINTMENTS AND RENEWAL)

	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total since 2012
Clinicians (Clinical service)	11	9	13	13	13	13	14	10	**10**	**123**
Researchers (Poles)	3	3	4	4	2	7	16	9	**22**	**79**

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 2022, the total FTE increased from 11.9 to 16.1 CUSL and still 0.7 FTE for the academic support to research performed by an UCLouvain researcher. The academic support for drug or device studies promoted by the CUSL has been developed: 1FTE for this specific academic desk; 1FTE academic CRA; 2.2 FTE statistical and Redcap support for academic studies and registries promoted by the CUSL.

Organization of the clinical research at the CUSL

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	2020	2021	2022
Commercial (new + amendments+ CDA+CTR)	291	309	282	344	484	441	**369**
Academic (external and internal agreements, MTA, DTA, grants, CTR)	74	77	165	183	257	219	**160**

In addition, 143 commercial grants, 5 sponsorship contracts were managed by the CTC..

EUROPEAN PROJECTS AND PUBLIC FINANCED PROJECTS SUPPORT (TYPE H2020)

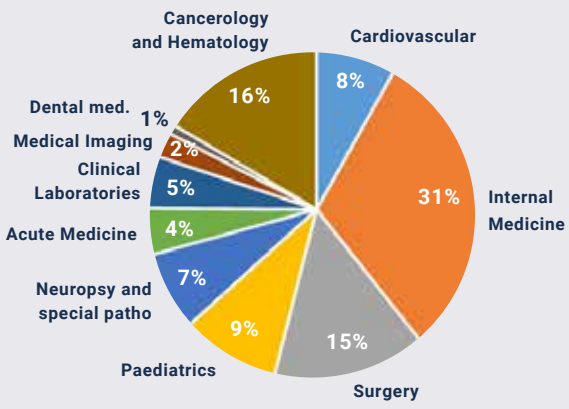
The European projects support officer coordinates the administrative management of research projects financed by European funds. .

Eleven European projects are ongoing on December 31, 2022

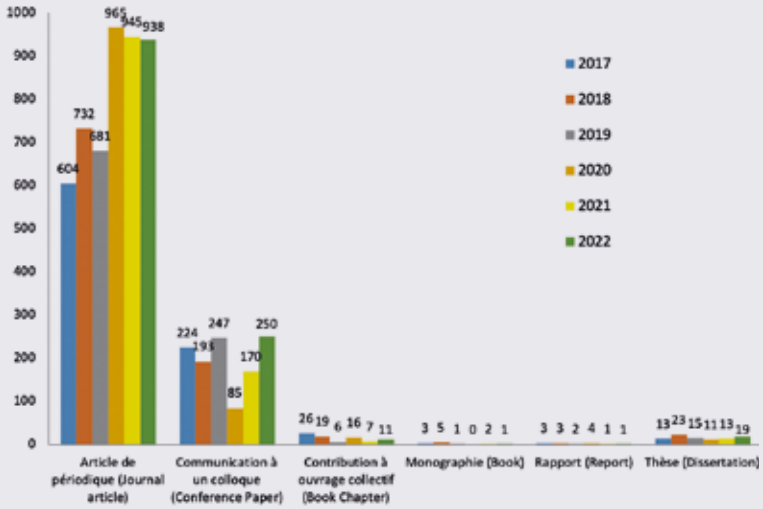
- Types of projects: 7 H2020/RIA (Research Innovation Action), 4 IMI (Innovative Medicine Initiative)
- Types of contracts : 1 where the CUSL are an UCLouvain affiliated entity and 10 where the CUSL are direct contractors.

REPORTING AND ACADEMIC INDICATORS FOR THE CUSL MEDICAL DEPARTMENTS

2022 total credits /department



Publications CUSL 2017 to 2022
(source: base de données précompte pro des chercheurs)



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 and to the contract team of the CTC.
- In 2022, 131 commercial studies were submitted to the Ethics Committee. Of these, 119 were submitted directly by the central desk. In addition, 4 CTR pilot studies and 8 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 2022

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**
25	61	6	64	11	0	98	9	**167**

This represents a 45% increase between 2018 and 2022. Additionally, 13 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 17 studies involving UCLouvain researchers performed at the CUSL and 26 studies performed only at the UCLouvain.

STATISTICAL SUPPORT

As of September 2022, 2.2FTE statisticians are dedicated to the exclusive support of the CUSL-sponsored studies.

54 projects are being monitored by the Statistical Support Unit, at the request of 9 different departments. Among these 54 projects, 43 (80%) include a REDCap activity, and 28 (52%) have a statistical consultancy component.

QUALITY AND ACCREDITATION

In 2022, the process for AAHRPP (Association for the Accreditation of Human Research Protection Programs) re-accreditation in 2023 was launched. The focus was also on the implementation of the European MDR, IVDR and CTR regulations. Support for academic drug and medical device research sponsored by CUSL was implemented in 2022. In order to keep users informed, the website is regularly updated (https://www.saintluc.be/en/research/index.php). The GCP training developed by the 7 Belgian academic hospitals (CHAB) and validated by Transcelerate was launched internally on December 14, 2022.

OPERATIONAL SUPPORT FOR THE STUDY COORDINATORS

The CTC is coordinating the financial aspect of the hiring and the training of the study coordinators. Thirty-one new study coordinators were hired in 2022. Among them, 16 have received a permanent contract.
Study coordinators at the CUSL on December 31, 2022: 84 employees: 70 FTE allocated to 39 medical services.

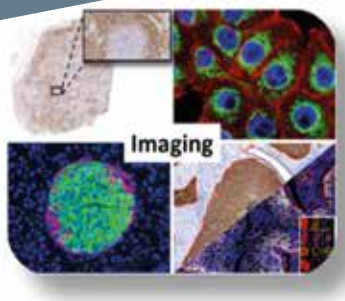
LEGAL SUPPORT

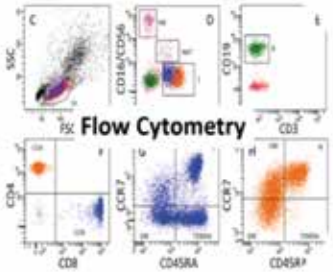
Since August 2018, a half-time legal officer from the legal department of the CUSL is dedicated to the CTC.

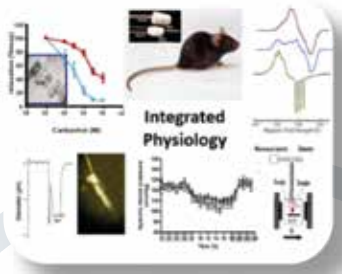
Together with other members of the legal department, she is involved in the legal review and advices for research contracts, consultancy agreements, master agreements, etc

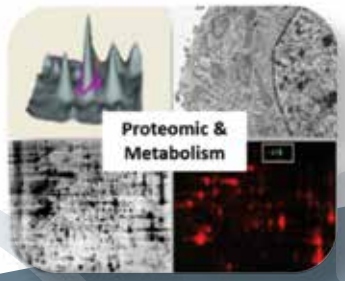
The legal officers provided support for 104 contracts, 16 legal advices and 15 support documents revision.

IREC TECHNOLOGICAL PLATFORMS









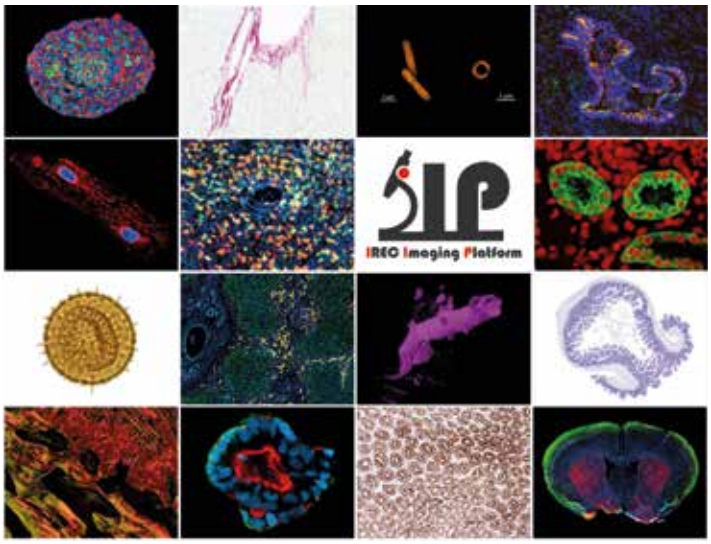
THE OBJECTIVES TARGETED BY OUR TECHNOLOGICAL PLATFORMS:

- 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 2022 AT A GLANCE

178	users
65	research groups
4003	bookings
8864	sections
2591	stainings
3152	immunostainings
4017	hours slide scanning
1998	hours fluorescence imaging
3558	hours image analysis
support	management & user committees account manager



PROPOSED SERVICES

Sample preparation services (service by 2IP or Histo-lab access):

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

New in 2022: CM1950 cryostat (Leica)
Bond RXm autostainer (Leica)

Image acquisition:

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

NEW in 2022: Pannoramic ScanII slide scanner (3DHistech)

Image analysis:

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

NEW in 2022: Imaris (Bitplane)

Contacts

Caroline Bouzin
caroline.bouzin@uclouvain.be
02/764.55.98

Michèle de Beukelaer
michele.debeukelaer@uclouvain.be
02/764.55.97

Aurélie Daumerie
a.daumerie@uclouvain.be
02/764.55.97

Université catholique de Louvain-IREC Imaging Platform

Avenue Hippocrate, 55 bte B1.55.20 - 1200 Bruxelles
https://uclouvain.be/en/research-institutes/irec/2ip

Through sustained collaborations, 2IP was also involved in the following projects published in 2022:

Santos-Ribeiro D, Lecocq M, De Beukelaer M, Verleden S, **Bouzin C**, **Ambroise J**, Dorfmuller P, Yakoub Y, Huaux F, Quarck R, Karmouty-Quintana H, Ghigna MR, Bignard J, Nadaud S, Soubrier F, Horman S, Perros F, Godinas L, Pilette C. Am J Respir Cell Mol Biol 2022 Dec 7. doi: 10.1165/rcmb.2021-0541OC. Disruption of GCN2 Pathway Aggravates Vascular and Parenchymal Remodeling During Pulmonary Fibrosis.

De Greef A, Choteau M, **Herman A**, Bouzin C, Marot L, Dachelet C, Lelotte J, Hoton D, Dumoutier L, Baeck M. Eur J Dermatol 2022 May 1;32(3):377-383. Chilblains observed during the COVID-19 pandemic cannot be distinguished from classic, cold-related chilblains.

Cury J, Smets H, **Bouzin C**, Doguet P, Vanhoestenberghe A, Delbeke J, Tahry RE, Nonclercq A, Gorza SP. **J Biophotonics**. 2022 Oct;15(10):e202200028. Optical birefringence changes in myelinated and unmyelinated nerves: A comparative study.

Renguet E, **De Loof M**, **Fourny N**, **Ginion A**, **Bouzin C**, Poüs C, **Horman S**, **Beauloye C**, **Bultot L**, **Bertrand L**. Am J Physiol Heart Circ Physiol. 2022 Jun 1;322(6):H1032-H1043. α-Tubulin acetylation on lysine 40 controls cardiac glucose uptake.

De Berdt P, Vanvarenberg K, Ucakar B, Bouzin C, Paquot A, Gratpain V, Loriot A, Payen V, **Bearzatto B**, Muccioli GG, Gatto L, Diogenes A, des Rieux A. Cell Mol Life Sci. 2022 Apr 21;79(5):252. The human dental apical papilla promotes spinal cord repair through a paracrine mechanism.

Pothen L, Verdoy R, De Mulder D, Esfahani H, Farah C, Michel LYM, Dei Zotti F, Bearzatto B, Ambroise J, Bouzin C, Dessy C, Balligand JL. Front Cardiovasc Med. 2022 Mar 14;9:854361. Sustained Downregulation of Vascular Smooth Muscle Acta2 After Transient Angiotensin II Infusion: A New Model of "Vascular Memory".

Farah C, Neveu MA, Yelek C, **Bouzin C**, Gallez B, **Baurain JF**, Mignion L, Jordan BF. Biomedicines. 2022 Mar 19;10(3):717. Combined HP 13C Pyruvate and 13C-Glucose Fluxomic as a Potential Marker of Response to Targeted Therapies in YUMM1.7 Melanoma Xenografts.

Capeloa T, **Krzystyniak J**, d'Hose D, **Canas Rodriguez A**, **Payen VL**, **Zampieri LX**, **Van de Velde JA**, **Benyahia Z**, **Pranzini E**, **Vazeille T**, Fransolet M, **Bouzin C**, **Brusa D**, Michiels C, Gallez B, Murphy MP, **Porporato PE**, **Sonveaux P**. Cancers (Basel). 2022 Mar 16;14(6):1516. MitoQ Inhibits Human Breast Cancer Cell Migration, Invasion and Clonogenicity.

Capeloa T, **Krzystyniak J**, R**odriguez AC**, **Payen VL**, **Zampieri LX**, Pranzini E, **Derouane F**, **Vazeille T**, **Bouzin C**, **Duhoux FP**, Murphy MP, Porporato PE, **Sonveaux P**. Cancers (Basel). 2022 Mar 15;14(6):1488. MitoQ Prevents Human Breast Cancer Recurrence and Lung Metastasis in Mice.

Yelek C, Mignion L, Paquot A, **Bouzin C**, **Corbet C**, Muccioli GG, Cani PD, Jordan BF. Cancers (Basel). 2022 Jan 23;14(3):562. Tumor Metabolism Is Affected by Obesity in Preclinical Models of Triple-Negative Breast Cancer.

Dechamps M, **De Poortere J**, Martin M, Gatto L, **Daumerie A**, **Bouzin C**, **Octave M**, **Ginion A**, **Robaux V**, **Pirotton L**, **Bodart J**, **Gerard L**, **Montiel V**, **Campion A**, Gruson D, Van Dievoet MA, Douxfils J, Haguet H, Morimont L, Derive M, Jolly L, **Bertrand L**, Dumoutier L, **Castanares-Zapatero D**, Laterre PF, **Horman S**, **Beauloye C**. Front Med (Lausanne). 2022 Jan 17;8:780750. Inflammation-Induced Coagulopathy Substantially Differs Between COVID-19 and Septic Shock: A Prospective Observational Study.

CTMA - Centre de technologies moléculaires appliquées

PROPOSED SERVICES

As technological platform of the IREC institute, CTMA offers technological support and expertise to IREC-researcher 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 integrates 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 biostatistics 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 / Targeted)
- CRISPR Validation
- mRNA sequencing (RNA-SEQ, miRNA-SEQ and scRNA-SEQ)
- Targeted RNA sequencing

In 2022, the CTMA also collaborated in monitoring the circulation of SARS-CoV-2 variants of concern in Belgium by joining the Belgian SARS-CoV-2 sequencing consortium. In this respect, 3500 SARS-CoV-2 genomes were sequenced in our premises. This allowed us to be associated with various studies and publications using the data generated on our platform.

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 long reads sequencer. During this year, CTMA has strengthened its third-generation sequencing capacity by acquiring two sequencers from Oxford Nanopore Technologies: a MinION Mk1C and a GridION. The main projects carried out on this technology concern:

- Resequencing of Bacterial, viral (e.g. SARS-COV2) and protist whole genome.
- RNA sequencing
- 16S Metagenomic analysis

CTMA has also developed specific activities and acquired solid expertise in developing immune assays and customized lateral flow assays. In fact, there are varying terminology to describe what lateral flow tests are. Common names include:

- Lateral Flow Assay (LFA)
- Lateral Flow Test (LFT)
- Lateral Flow device (LFD)
- Lateral Flow Immuno Assay (LFIA)
- Lateral Flow Immunochromatographic assays
- Dipstick, Express Test, Pen-Side test, Quick Test, Rapid Test and Test Strip.

These rapid screening tests are user-friendly and can be used as a diagnostic device to confirm the presence or absence of target analytes, such as pathogens or biomarkers in humans or in animals, or contaminants in water supplies, foodstuffs…etc. To make the picture clearer, think of the common known type of lateral flow rapid test strip which is the pregnancy test.

Our platform is endowed with SciFLEXArrayer S3, is an automated piezo driven, non-contact and 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:

- 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
- Development of nucleic acid lateral flow
- Amplicon preparation using isothermal amplification
- Probes spotting on the membranes with SciFLEXArrayer S3 robot
- Preparation of conjugate pad adapted for amplicon detection
- Functional validation

CTMA 2022 AT A GLANCE

8	Research groups
4170	NGS Libraries Preparation/analysis
	ILLUMINA: MiSeq/HiSeq/NovaSeq
80	- TRANSCRIPTOMIC (RNA-SEQ or scRNA-SEQ)
40	- GENOMIC (De NOVO / Resequencing)
45	- METAGENOMIC (Targeted – 16s)
80	- METAGENOMIC (Shotgun)
400	- CRISPR Validation
3500	- SARS-CoV-2 Whole genome sequencing
	OXFORD NANOPORE: MinION
20	- GENOMIC (De NOVO / Resequencing)
5	- METAGENOMIC (Shotgun)
550	GB of NGS DATA sequenced/analyzed

Contacts

Jean-Luc Gala
Jean-luc.gala@uclouvain.be
02/764.31.65

Bertrand Bearzatto
bertrand.bearzatto@uclouvain.be
02/764.31.96

Jérôme Ambroise
jerome.ambroise@uclouvain.be
02/764.31.96

Université catholique de Louvain-IREC

Centre de Technologies Moléculaires Appliquées
Avenue Hippocrate, 54 bte B1.54.01 - 1200 Bruxelles
https://uclouvain.be/fr/instituts-recherche/irec/ctma

REFERENCES 2022

CTMA has been involved in the following IREC collaborative project published in 2022 as well as other types of collaboration, e.g. with other institutes or institutions in Belgium or abroad. It is of note that the publications that only involve biostatistics/bioinformatics analyses are not listed here.

De Berdt P, Vanvarenberg K, Ucakar B, Bouzin C, Paquot A, Gratpain V, Loriot A, Payen V, **Bearzatto B**, Muccioli GG, Gatto L, Diogenes A, des Rieux A.
The Human Dental Apical Papilla promotes Spinal Cord Repair through a Paracrine Mechanism.
Cell Mol Life Sci 79: 252, 2022.

Pothen L, Verdoy R, De Mulder D, Esfahani H, Farah C, Michel L, Dei Zotti F, **Bearzatto B, Ambroise J**, Bouzin C, Dessy C, Balligand JL.
Sustained Downregulation of Vascular Smooth Muscle Acta2 After Transient Angiotensin II Infusion: A New Model of "Vascular Memory".
Front Cardiovasc Med 9: 854361, 2022.

Devresse A, Briol S, De Greef J, Lemaitre F, Boland L, Haufroid V, Scohy A, Kabamba B, Yombi JC, Belkhir L, Darius T, Buemi A, De Potter K, Mantegazza R, **Bearzatto B**, Goffin E, Kanaan N.
Safety, Efficacy, and Relapse of Nirmatrelvir-Ritonavir in Kidney Transplant Recipients Infected With SARS-CoV-2.
Kidney Int Rep 7 (11): 2356-2363, 2022.

Guilbert L, Dontaine J, Bultot L, Vertommen D, Gatto L, Martin M, Dumoutier L, **Bearzatto B, Ambroise J**, Balligand JL, Beauloye C, Horman S, Bertrand L.
On the road to discovering a new actor of cardiac pathological hypertrophy.
Arch Cardiovasc Dis Suppl 14 (2): 179-180, 2022.

Frère J, Chatzis O, Cremer K, Merckx J, De Keukeleire M, Renard F, Ribesse N, Minner F, Ruelle J, Kabamba B, Rodriguez-Villalobos H, **Bearzatto B**, Delforge ML, Henin C, Bureau F, Gillet L, Robert A, Van der Linden D.
SARS-CoV-2 Transmission in Belgian French-Speaking Primary Schools: An Epidemiological Pilot Study.
Viruses 14: 2199, 2022.

Santos-Ribeiro D, Lecocq, M, De Beukelaer M, Verleden S, Bouzin C, **Ambroise J**, Pilette C.
Disruption of GCN2 Pathway Aggravates Vascular and Parenchymal Remodeling During Pulmonary Fibrosis.
Am J Resp Cell Mol Biol, 2022.

Martin A, Bland MJ, Rodriguez-Villalobos H, **Gala JL**, Gabant P.
Promising Antimicrobial Activity and Synergy of Bacteriocins Against Mycobacterium tuberculosis.
Microb Drug Resist, 2022.

Renoz F, **Ambroise J, Bearzatto B**, Fakhour S, Parisot N, Ribeiro Lopes M, Gala JL, Calevro F, Hance T.
The Di-Symbiotic Systems in the Aphids Sipha maydis and Periphyllus lyropictus Provide a Contrasting Picture of Recent Co-Obligate Nutritional Endosymbiosis in Aphids.
Microorganisms 10 (7): 1360, 2022.

Bentahir M, Barry MD, Koulemou K, **Gala JL**.
Providing On-Site Laboratory and Biosafety Just-In-Time Training Inside a Box-Based Laboratory during the West Africa Ebola Outbreak: Supporting Better Preparedness for Future Health Emergencies.
Int J Environ Res Public Health 19 (18): 11566, 2022.

Merzouki, M, **Bentahir M**, Chigr F, Najimi M, **Gala JL**.
The Modelling of the Capacity of the Moroccan Healthcare System in the Context of COVID-19: The Relevance of the Logistic Approach. Handbook of Research on Pathophysiology and Strategies for the Management of COVID-19.
IGI Global: 17-26, 2022.

FLOW CYTOMETRY PLATFORM

CYTOFLUX 2022 AT A GLANCE

85	Users
34	Research groups
23	Trained people
696	Bookings
667	Flow cytometry hours
349	Cell Sorting hours

Contacts

Davide Brusa
davide.brusa@uclouvain.be
Tel: 02/764.55.63

UCLouvain - IREC Flow Cytometry Platform
Avenue Hippocrate, 55 +2 - 1200 Bruxelles
https://uclouvain.be/en/research-institutes/irec/cytometrie-de-flux.html

PROPOSED SERVICES

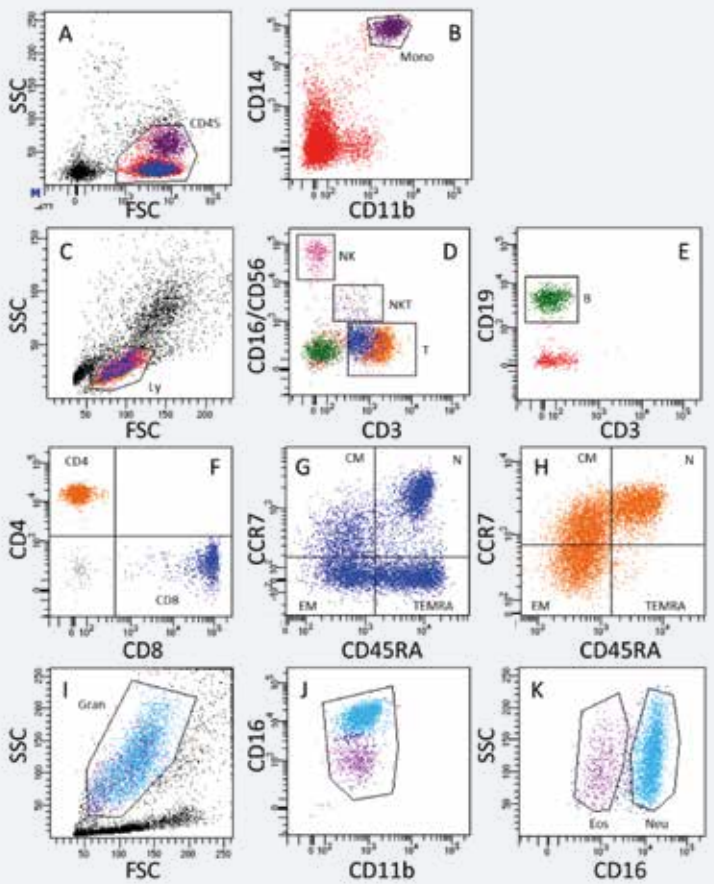
The platform logistician Davide Brusa welcomes you to the CytoFlux platform to discuss about projects involving the use of flow cytometry technology.

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:

- NovoCyte Quanteon, analyzer, 4 lasers, 25 fluorescences (new aquisition in 2022)
- 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, NovoExpress, FlowJo, FACSkin and R softwares.



REFERENCES 2022

Dadashzadeh A, Moghassemi S, Grubliauskaité M, Vlieghe H, Brusa D, Amorim CA. Medium supplementation can influence the human ovarian cells in vitro. J Ovarian Res. 2022 Dec 26;15(1):137.

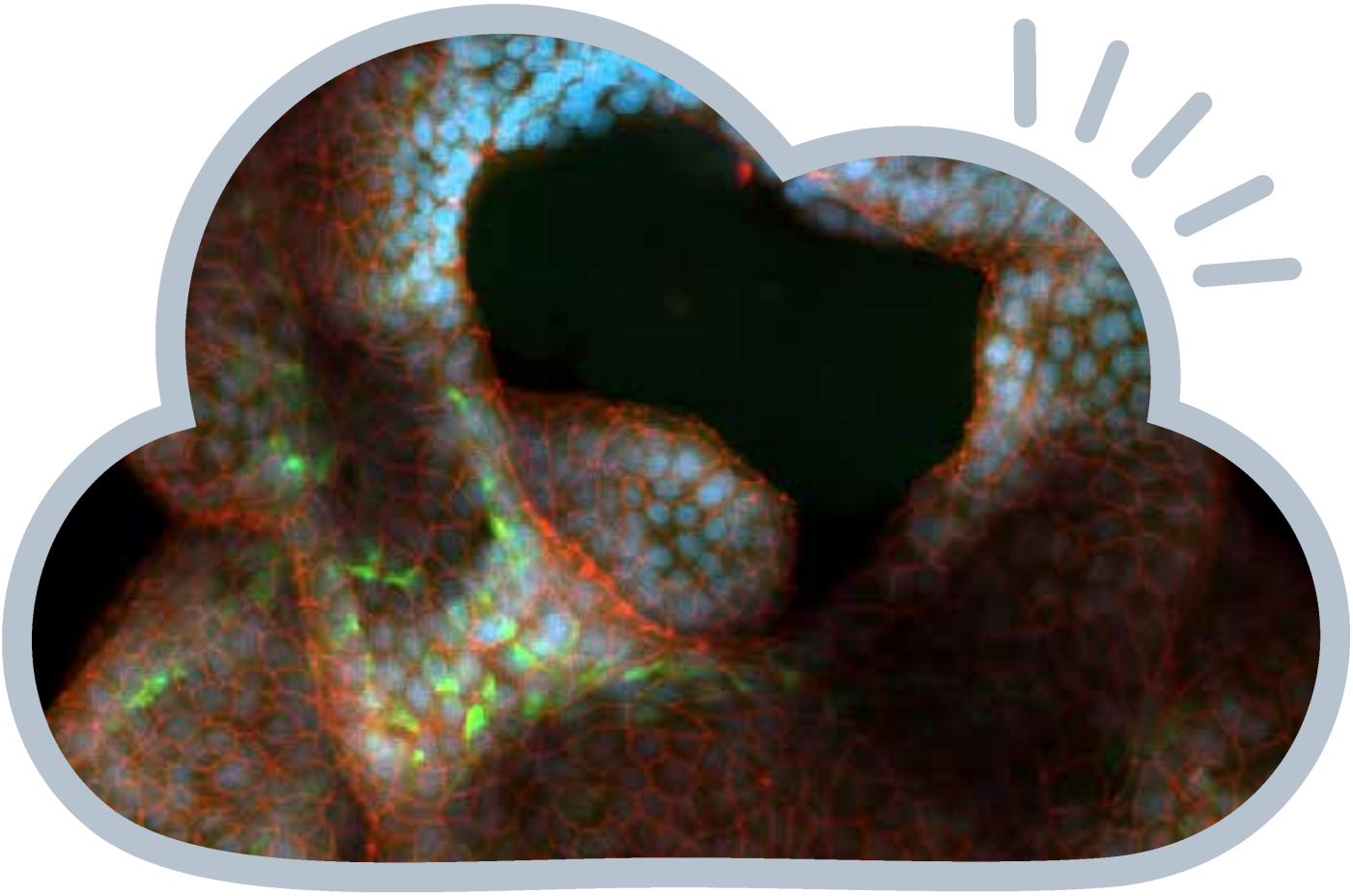
Capeloa T, Krzystyniak J, d'Hose D, Canas Rodriguez A, Payen VL, Zampieri LX, Van de Velde JA, Benyahia Z, Pranzini E, Vazeille T, Fransolet M, Bouzin C, Brusa D, Michiels C, Gallez B, Murphy MP, Porporato PE, Sonveaux P. MitoQ Inhibits Human Breast Cancer Cell Migration, Invasion and Clonogenicity. Cancers (Basel). 2022 Mar 16;14(6):1516. doi: 10.3390/cancers14061516.

van Dievoet MA, Brusa D, Octave M, Horman S, Stephenne X. Anti-GPVI (HY101) activates platelets in a multicolor flow cytometry panel. Platelets. 2022 Jan 17:1- 4.

d'Hose D, Isenborghs P, Brusa D, Jordan BF, Gallez B. The Short-Term Exposure to SDHI Fungicides Boscalid and Bixafen Induces a Mitochondrial Dysfunction in Selective Human Cell Lines. Molecules. 2021 Sep 26;26(19):5842.

Orsi M, Palmai-Pallag M, Yakoub Y, Ibouraadaten S, De Beukelaer M, Bouzin C, Bearzatto B, Ambroise J, Gala JL, Brusa D, Lison D, Huaux F. Monocytic Ontogeny of Regenerated Macrophages Characterizes the Mesotheliomagenic Responses to Carbon Nanotubes. Front Immunol. 2021 Jun 14;12:666107.

Piaggeschi G, Rolla S, Rossi N, Brusa D, Naccarati A, Couvreur S, Spector TD, Roederer M, Mangino M, Cordero F, Falchi M, Visconti A. Immune Trait Shifts in Association With Tobacco Smoking: A Study in Healthy Women. Front Immunol. 2021 Mar 9;12:637974.



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
- Advice and help regarding compliance to legal requirements

The platform is serviced with the following equipment:

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

The laboratories are 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 and activity cages
- Linné-like area: surgery, tumor induction, viral infection (L2 biosafety lab), metabolic cages
- SOPF area: surgery, cell therapy, tumor induction, inhalation cages

THE IREC ANIMAL FACILITY AT A GLANCE

3	Rodent confinement zones: Conventional, Linné-like and SOPF areas
1	BSL2 lab for virus injections, in the Linné-like area
1600	Mice IVC cages available (480 in the Conventional area, and 560 each in the Linné-like and SOPF areas)
420	Rat IVC cages available (140 in the Conventional area, and 105 each in the Linné-like and SOPF areas)
15	Research teams (PIs) using the Facility in 2022
146	Users trained to get access to the Facility since its opening in 2019

Contacts

Solveig Mouterde
solveig.mouterde@uclouvain.be
02/764.52.61
Office located on the IREC platforms floor, Harvey (55) level +2

Rachid El Kaddouri - Conventional area
rachid.elkaddouri@uclouvain.be
02/764.55.24
Office located at Laennec (57) level -1

Mihaly Palmai-Pallag - Linné-like area
mihaly.palmai@uclouvain.be
02/764.56.98
Office located at Laennec (57) level 0

Université catholique de Louvain

IREC Animal Facility
Avenue Hippocrate, 57 - bte B1.57.01
1200 Bruxelles

INTEGRATED PHYSIOLOGY

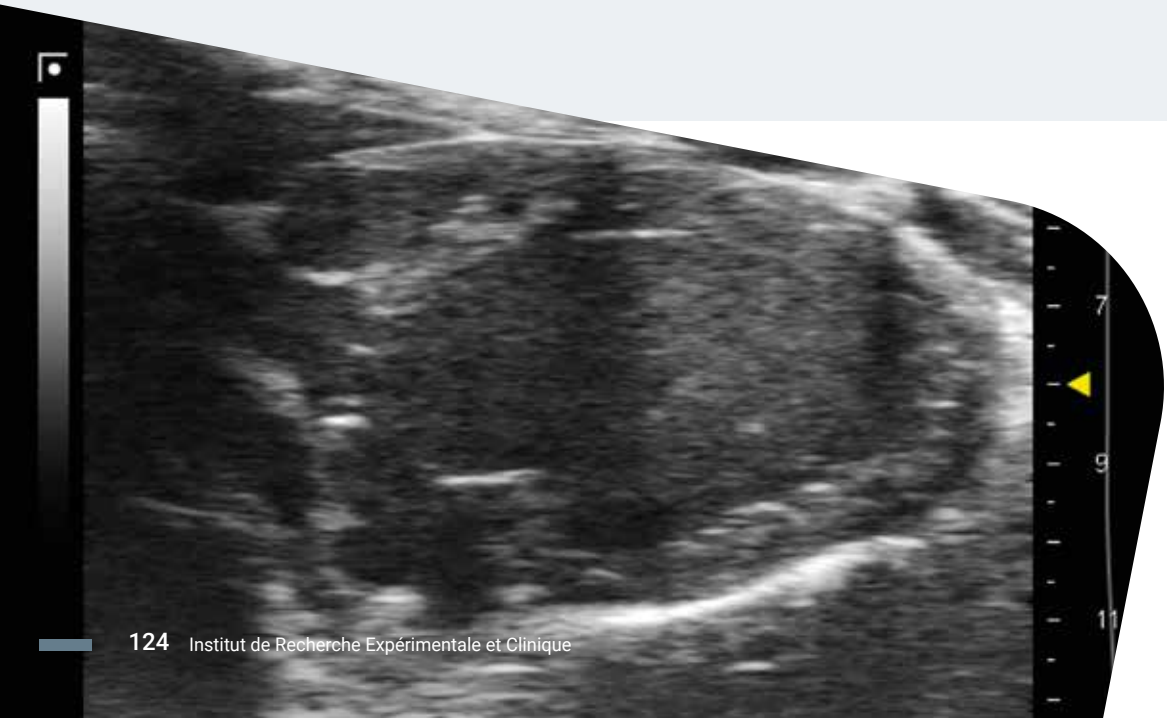
PROPOSED SERVICES

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

- **Vascular reactivity (55 +2):** Conductance and resistance artery reactivity, Calcium and contractility measurements, Tissue isolation. The platform proposes a full access to equipments, training of new users, help in setting experiment protocols and result analyses.
  Teaching and scientific support: C Dessy (FATH)
- **Telemetry (52 +5, transferred in the animal facility platform.):** Surgery, Haemodynamic profiling (HR/P), Variability evaluation, ECG.
  Technical support : H Esfahany (FATH)
  Scientific support : 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)

Contact

Chantal Dessy
chantal.dessy@uclouvain.be
Tel: 02/764.52.63
https://uclouvain.be/fr/instituts-recherche/irec/physiology-platform.html



REFERENCES

Vascular Endothelium-Dependent and Independent Actions of Oleanolic Acid and Its Synthetic Oleanane Derivatives as Possible Mechanisms for Hypotensive Effects.
Madlala HP, Metzinger T, van Heerden FR, Musabayane CT, Mubagwa K, Dessy C.
PLoS One. 2016 Jan 22;11(1):e0147395.

Nutritional depletion in n-3 PUFA in apoE knock-out mice: a new model of endothelial dysfunction associated with fatty liver disease.
Catry E, Neyrinck AM, Lobysheva I, Pachikian BD, Van Hul M, Cani PD, Dessy C, Delzenne NM.
Mol Nutr Food Res. 2016, 60(10):2198-2207.

Hyaluronidase 1 Deficiency Preserves Endothelial Function and Glycocalyx Integrity in Early Streptozotocin-Induced Diabetes.
Dogné S, Rath G, Jouret F, Caron N, Dessy C, Flamion B.
Diabetes. 2016 Sep;65(9):2742-53.

Effects of BM-573 on Endothelial Dependent Relaxation and Increased Blood Pressure at Early Stages of Atherosclerosis. Romero M, Leon-Gomez E, Lobysheva I, Rath G, Dogné JM, Feron O, Dessy C.
PLoS One. 2016 Mar 28;11(3):e0152579.
doi: 10.1371/journal.pone.0152579.

Heme-nitrosylated hemoglobin and oxidative stress in women consuming combined contraceptives. Clinical application of the EPR spectroscopy.
Lobysheva I. I., van Eeckhoudt S., Dei Zotti F., Rifahi A., Pothen L., Beauloye C., Balligand J.-L.
Free Radic Biol Med. 2017 Apr 7;108: 524-532.

Clinical and biochemical data on endothelial function in women consuming combined contraceptives.
Lobysheva I. I., van Eeckhoudt S., Dei Zotti F., Rifahi A., Pothen L., Beauloye C., Balligand J.-L.
DIB. 2017; 13: 46-52.

Targeting the gut microbiota with inulin-type fructans: preclinical demonstration of a novel approach in the management of endothelial dysfunction.
Catry E, Bindels LB, Tailleux A, Lestavel S, Neyrinck AM, Goossens JF, Lobysheva I, Plovier H, Essaghir A, Demoulin JB, Bouzin C, Pachikian BD, Cani PD, Staels B, Dessy C, Delzenne NM.
Gut. 2018 Feb;67(2):271-283

MicroRNA-199a-3p and MicroRNA-199a-5p Take Part to a Redundant Network of Regulation of the NOS (NO Synthase)/NO Pathway in the Endothelium.
Joris V, Gomez EL, Menchi L, Lobysheva I, Di Mauro V, Esfahani H, Condorelli G, Balligand JL, Catalucci D, Dessy C.
Arterioscler Thromb Vasc Biol. 2018 Oct;38(10):2345-2357.

Chitin-glucan and pomegranate polyphenols improve endothelial dysfunction.
Neyrinck AM, Catry E, Taminiau B, Cani PD, Bindels LB, Daube G, Dessy C, Delzenne NM.
Sci Rep. 2019 Oct 2;9(1):14150.

Extremely low frequency electromagnetic stimulation reduces ischemic stroke volume by improving cerebral collateral blood flow.
Kemps H, Dessy C, Dumas L, Sonveaux P, Alders L, Van Broeckhoven J, Font LP, Lambrichts S, Foulquier S, Hendrix S, Brône B, Lemmens R, Bronckaers A.J Cereb Blood Flow Metab. 2022 Feb 25:271678X221084410.
doi: 10.1177/0271678X221084410.

Endothelial dysfunction induced by hydroxyl radicals - the hidden face of biodegradable Fe-based materials for coronary stents.
Scarcello E, Lobysheva I, Bouzin C, Jacques PJ, Lison D, Dessy C.Mater Sci Eng C Mater Biol Appl. 2020 Jul;112:110938. doi: 10.1016/j.msec.2020.110938. Epub 2020 Apr 7.

Diesel exhaust particles alter the profile and function of the gut microbiota upon subchronic oral administration in mice.
van den Brule S, Rappe M, Ambroise J, Bouzin C, Dessy C, Paquot A, Muccioli GG, Lison D.Part Fibre Toxicol. 2021 Feb 9 ;18(1) :7. doi : 10.1186/s12989-021-00400-7.

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 :

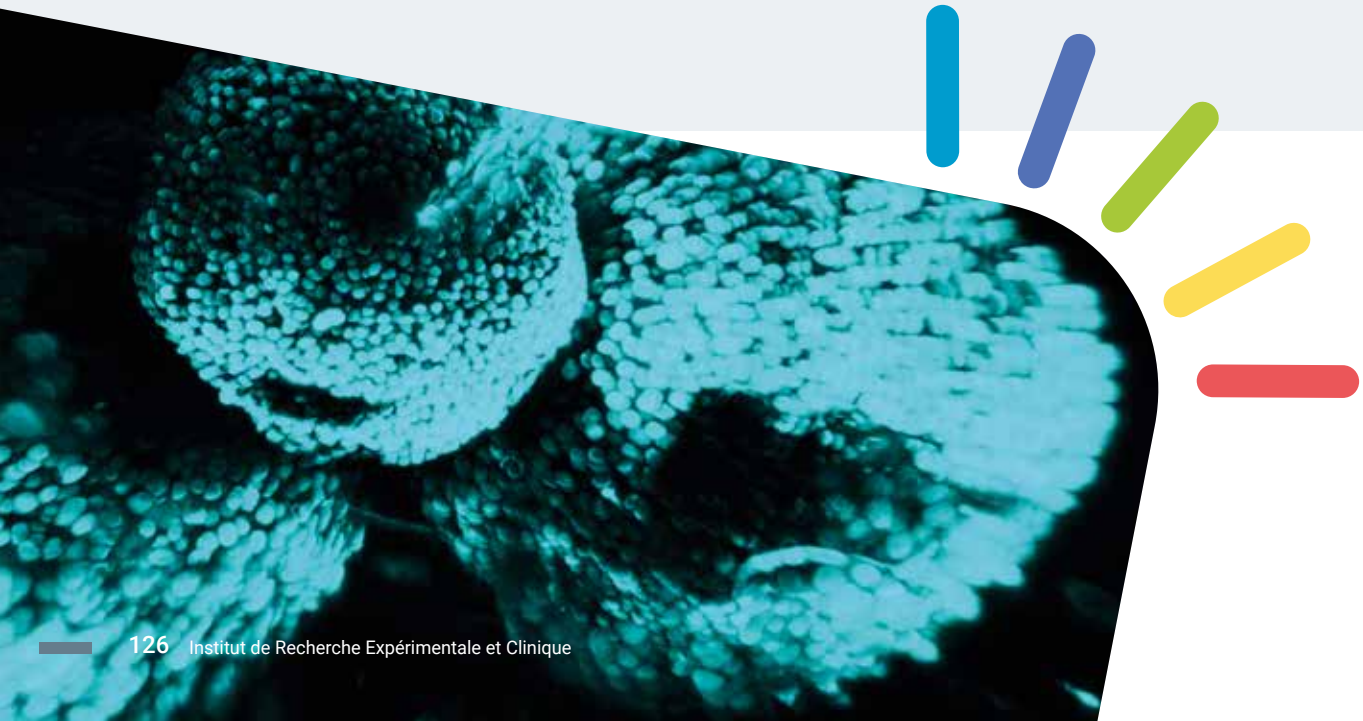
- Hypoxia worstation (Don Whitley H35) [cell culture at 0.1-21% O2]
- Seahorse XF96 Bioenergetic analyzer (Agilent)
  - real-time measurements of oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) for adherent and non-adherent cells
  - assessment of the specific activity of electron 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.

Contact

Olivier Feron
olivier.feron@uclouvain.be
Tel: 02/764.52.64

https://uclouvain.be/fr/instituts-recherche/irec/proteomics-and-metabolomics.html



REFERENCES

Corbet C, Bastien E, Santiago de Jesus JP, Dierge E, Martherus R, Vander Linden C, Doix B, Degavre C, Guilbaud C, Petit L, Michiels C, Dessy C, Larondelle Y, Feron O. TGFβ2-induced formation of lipid droplets supports acidosis-driven EMT and the metastatic spreading of cancer cells. Nat Commun. 2020 Jan 23;11(1):454.

Schoonjans CA, Joudiou N, Brusa D, Corbet C, Feron O, Gallez B. Acidosis-induced metabolic reprogramming in tumor cells enhances the anti-proliferative activity of the PDK inhibitor dichloroacetate. Cancer Lett. 2020 Feb 1;470:18-28. doi: 10.1016/j.canlet.2019.12.003.

Choumessi AT, Johanns M, Beaufay C, Herent MF, Stroobant V, Vertommen D, Corbet C, Jacobs R, Herinckx G, Steinberg GR, Feron O, Quetin-Leclercq J, Rider MH. Two isoprenylated flavonoids from Dorstenia psilurus activate AMPK, stimulate glucose uptake, inhibit glucose production and lower glycemia. Biochem J. 2019 Dec 19;476(24):3687-3704.

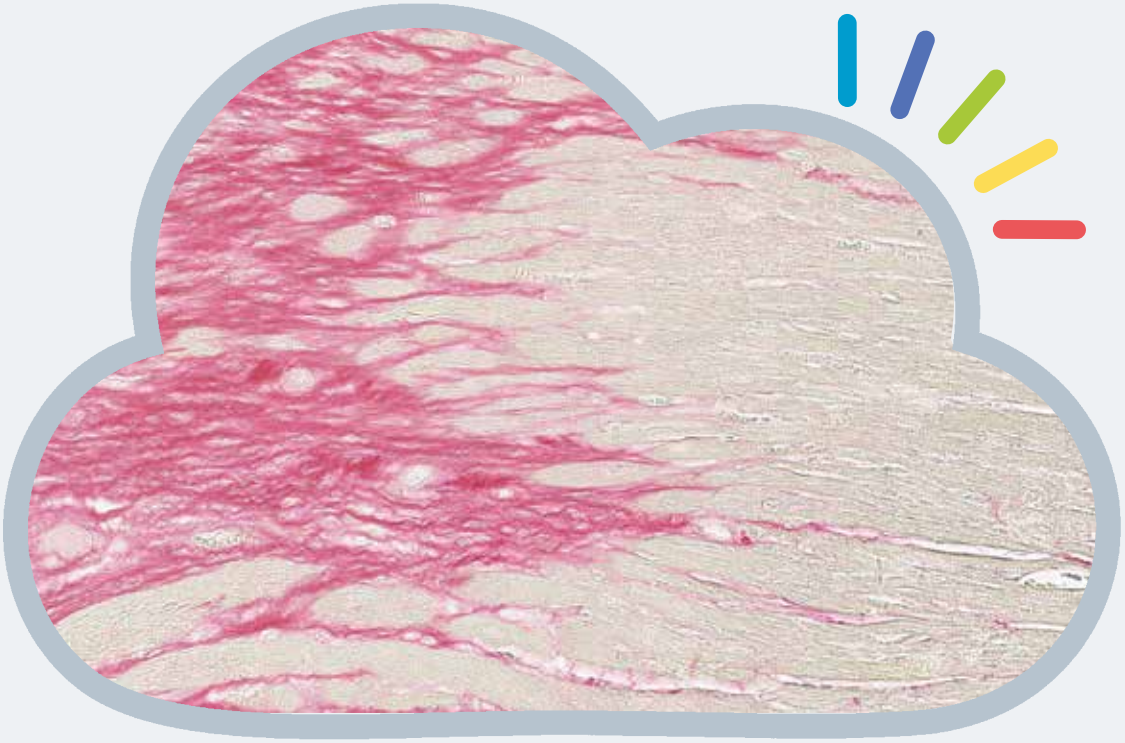
Strickaert A, Corbet C, Spinette SA, Craciun L, Dom G, Andry G, Larsimont D, Wattiez R, Dumont JE, Feron O, Maenhaut C. Reprogramming of Energy Metabolism: Increased Expression and Roles of Pyruvate Carboxylase in Papillary Thyroid Cancer. Thyroid. 2019 Jun;29(6):845-857

de Mey S, Jiang H, Corbet C, Wang H, Dufait I, Law K, Bastien E, Verovski V, Gevaert T, Feron O, De Ridder M. Antidiabetic Biguanides Radiosensitize Hypoxic Colorectal Cancer Cells Through a Decrease in Oxygen Consumption. Front Pharmacol. 2018 Oct 3;9:1073. doi: 10.3389/fphar.2018.01073.

Corbet C, Bastien E, Draoui N, Doix B, Mignion L, Jordan BF, Marchand A, Vanherck JC, Chaltin P, Schakman O, Becker HM, Riant O, Feron O. Interruption of lactate uptake by inhibiting mitochondrial pyruvate transport unravels direct antitumor and radiosensitizing effects. Nat Commun. 2018 Mar 23;9(1):1208.

Milosevic TV, Vertenoeil G, Payen VL, Sonveaux P, Tulkens PM, Constantinescu SN, Van Bambeke F. Prolonged inhibition and incomplete recovery of mitochondrial function in oxazolidinone-treated megakaryoblastic cell lines. Int J Antimicrob Agents. 2019 Nov;54(5):661-667.

Ippolito L, Morandi A, Taddei ML, Parri M, Comito G, Iscaro A, Raspollini MR, Magherini F, Rapizzi E, Masquelier J, Muccioli GG, Sonveaux P, Chiarugi P, Giannoni E. Cancer-associated fibroblasts promote prostate cancer malignancy via metabolic rewiring and mitochondrial transfer. Oncogene. 2019 Jul;38(27):5339-5355.



CTMA - Centre de technologies moléculaires appliquées

The "Centre de Technologies Moléculaires Appliquées (CTMA - Center for Applied Molecular Technologies)" is a mixed clinical-military biotechnological platform mutualizing the resources of two partners:

UCLouvain/IREC (Université catholique de Louvain/Institut de Recherche Expérimentale et Clinique). CTMA is the IREC-reference biotechnological platform (genetics and molecular genetics); therefore directly supporting IREC-related research activities and teams. CTMA actively develops its own proprietary research in the field of technology and security, following the Russian dolls strategy, which integrates research applied sciences activities at Belgian regional and federal European and international level.

- CTMA is conducting research to better control the biological risks related to the CBRN (Chemical, Bacteriological, Radiological and Nuclear threats spectrum).
- As GOARN /WHO member, CTMA develops and pilots the B-LiFE laboratory which is deployed during major crisis at the request of the National authorities, ERCC, GOARN/WHO, or in the context of a bilateral partnership.
- For the Cliniques Universitaires Saint-Luc (CUSL), CTMA carries out clinical research in the field of genetics and molecular genetics to support the medical activity of the academic hospital CUSL.
- Inside its CTMA-Myco premises, CTMA is actively developing service activity for industry by producing fungal biomass for the preparation of vaccines.

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

Jean-Luc Gala, MD, PhD, Director

Post-Doc:

Jerôme Ambroise, Ir, PhD

Bertrand Bearzatto, PhD

Mostafa Bentahir, PhD

Léonid Irenge Mwana Wa Bene, MD, PhD

Omar Nyabi, PhD

Pierre Vandenberghe, PhD

Olga Vybornova, PhD

Contact Person

Jean-Luc Gala
jean-luc.gala@uclouvain.be

•Director

Gala Jean-Luc,
MD, PhD, Director CTMA, CUSL

Staff

Demaret Christelle,
Director Assistant, IREC

Dillembourg Marc,
Technical Manager, IREC

Elmjouzi Maimouna,
Account Manager, IREC

Researchers

Durant Jean-François, IREC
Vybornov Aleksandr, IREC

PhD student

Bonjean, Maxime, IREC

Post-Docs

Ambroise Jérôme, Research Logistician, IREC
Bearzatto Bertrand, IREC
Bentahir Mostafa, UCLouvain collaborator
Hurel Julie, IREC
Irenge Mwana Wa Bene Leonid, MD, UCLouvain collaborator
Nyabi Omar, IREC
Vandenberghe Pierre, IREC
Vybornova Olga, IREC

Technicians

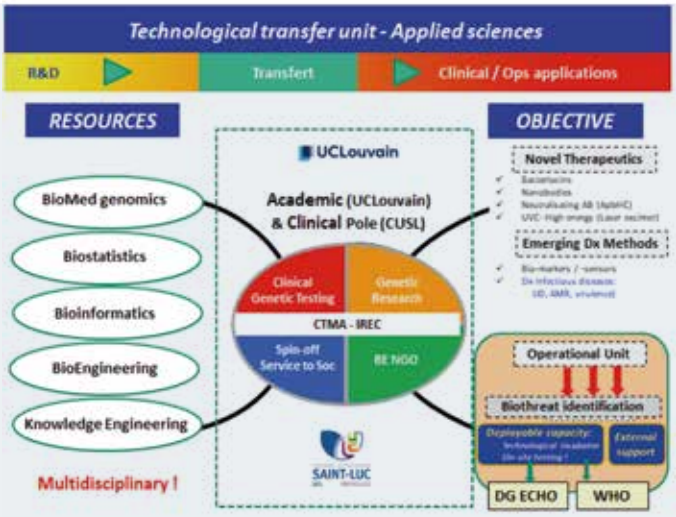
Chibani Nawfal, IREC
Cruz Mitjans Dennys, IREC
Cruz Mitjans Olga, IREC
Smits Benjamin, IREC

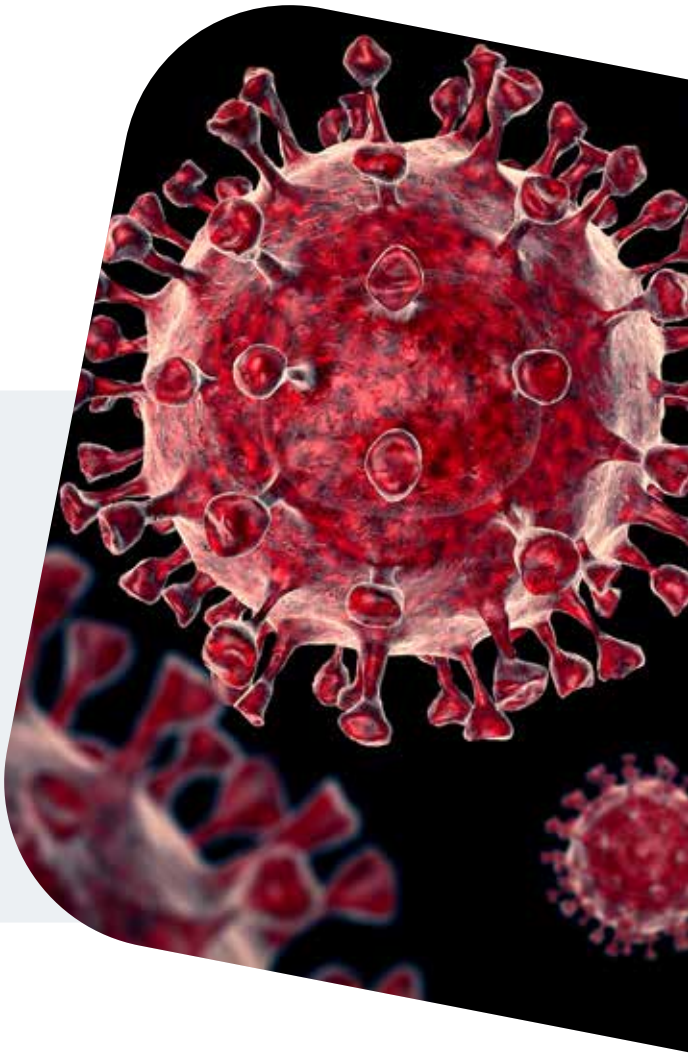
** CUSL: Cliniques universitaires Saint-Luc ** MOD: Ministry of Defense*

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.

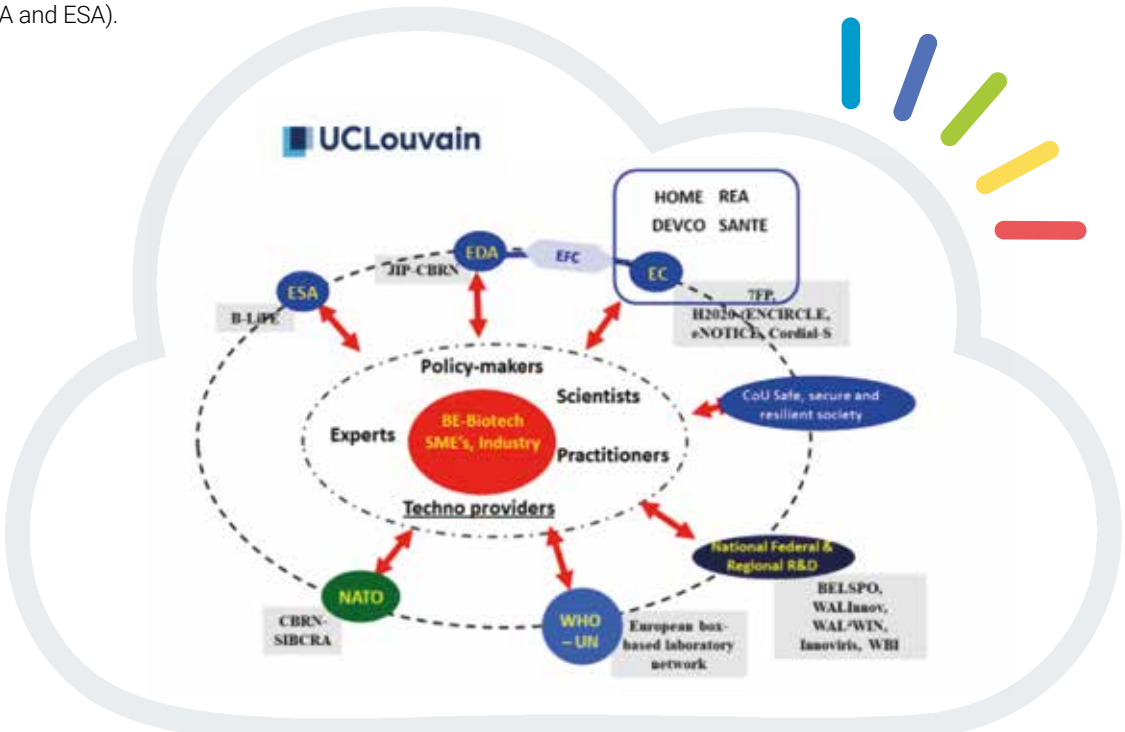
All these tools are designed to meet the constraints of use in the EU-certified deployable box-based laboratory B-LiFE (Biological Light Fieldable Laboratory for Emergencies) developed by CTMA for national and international missions justified by public health crisis. B-LiFE is part of the European box-based 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 Brussels (Innoviris, WBI) and Walloon (WALinnov and Win2 WAL) Regions, Federal (BELSPO, Food Chain Safety) and international institutions (EC, EDA and ESA).



SARS-COV-2 DETECTION

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.

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 a steady temperature, and allows it 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 realised.

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 showed a good sensitivity and specificity for simplex and multiplex detection of the genomic targets, on a large panel of 150 clinical samples

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

RT-LAMP detection of Vibrio cholerae is also being developed by the lab. LAMP primers sets have been designed, tested and selected for three virulence genes, ctxA, OmpW and tcpA. Simplex LAMP reactions have been performed on a large scale of V.cholerae DNA samples and controls and the data obtained have been compared to gold standard RT-qPCR method. Results showed concordant signals between the two methods. Development of a multiplex LAMP test is now ongoing in order to detect the three-virulence gene in one reaction.

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.

Scientific and logistical technical support of CTMA for the implementation of COVID-19 Federal platform (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 follow-up of the platform within the CTMA. Over the

last 24 months this scientific staff has also contributed to the management and validation of the qPCR results that have been transmitted to the Belgian federal and regional authorities.

Since the beginning of the pandemic the CTMA has also collaborated with the Morphology pole of the IREC in order to organise the qPCR-SARS-CoV-2 testing of all body donations made to the UCLouvain before the bodies are dedicated to the practical dissection work.

CTMA has also been implicated in the SARS-CoV-2 genomic surveillance and has developed a complete SARS-CoV-2 high throughput-sequencing pipeline. CTMA is involved in the follow up of the transmission of the results to the Belgian federal authorities for almost one year.

Participation in the WHO network of Rapid Response Mobile Laboratories

Jean-Luc GALA, Olga VYBORNOVA, Aleksandr VYBORNOV, Bertrand BEARZATTO, Omar NYABI, Pierre VANDEN BERGHE, Jean-François DURANT, Nawfal CHIBANI, Benjamin SMITS

CTMA is an active member of the part of the network of Rapid Response Mobile Laboratories (RRMLs) led by WHO and the Global Outbreak Alert and Response Network (GOARN). To strengthen the capacities and coordination of RRML in Europe and globally, in 2021 a simulation exercise (SimEx) programme for Rapid Response Mobile Laboratories (RRMLs) was established to test newly developed minimum standards for RRMLs and to support future RRML workforce development. The programme consists of a series of table-top and functional exercises as well as technical drills and a full-scale field exercise. All exercises are based on a common outbreak scenario and provide an interface to link in exercise activities from other institutions and partners. Over the course of 2021, two simulation exercises were implemented with participation of CTMA: a virtual table-top exercise (V-TTX, 31 August to 02 September 2021) and a virtual functional exercise (V-FX, 05 to 07 October 2021).

The CTMA mobile laboratory staff took part in the international field exercise of mobile rapid response laboratories, which took place on 11.10.2021-15.10.2021 in Kazan, Russian Federation. The mission objective was to expand and strengthen cooperation in the field of response to emergency situations of a sanitary and epidemiological nature, exchange experience of such response and acquire the skills of joint work of rapid response teams from different countries using mobile laboratories.

The List of Participating Institutions (alphabetical order) present in Kazan:

- Bernhard-Nocht Institute for Tropical Medicine (BNITM), Germany
- Biodefense Laboratory, Biomedical Engineering Centre, Institute of Optoelectronics, Poland
- Bundeswehr, Institute of Microbiology, Germany
- Centre de Technologies Moléculaires Appliquées (CTMA), UCLouvain, Belgium
- Directorate-General for European Civil Protection and Humanitarian Aid Operations (DG ECHO),
- European Commission
- Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing of the
- Russian Federation (Rospotrebnadzor), Russian Federation
- Global Outbreak Alert and Response Network (GOARN)
- Institut Pasteur Paris (IP), France
- Médecins Sans Frontières (MSF), Spain
- Robert Koch Institute (RKI), Germany
- UK Public Health Rapid Support Team (UK-PHRST), United Kingdom
- WHO:
  - WHO Regional Office for Europe
  - WHO Regional Office for Africa
  - WHO Headquarters

RRML training in Moldova: filed diagnostic in RRML with focus on PCR, Fluorescence Microscopy, Biosafety and biosecurity

Jean-Luc GALA, Olga VYBORNOVA, Jean-François DURANT, Omar NYABI, Pierre VANDENBERGHE

The Republic of Moldova maintains a Rapid Response Mobile Laboratory (RRML) at the National Agency of Public Health (NAPH) and has requested additional assistance from the WHO Country Office (WHO CO MDA) in order to operationalize the RRML. This RRML type IV (as per Guidance on RRLM Classification) is intended to support health care services for newly arrived refugees in Chisinau,

Illustration of the JiTT in Chisinau From mission preparation in Belgium to on-site lab set up, teaching and training.

the capital of Moldova, and possibly in border regions. The capacity was not operational due to lack of maintenance and lack of use (water leaks, electricity breakdown affecting sensitive part of the mobile laboratory). At the request of WHO and following a recent scoping mission, a CTMA team of technical experts from the Global Outbreak Alert and Response Network (GOARN) RRML was deployed from the 19th to 24th September 2022 to strengthen emergency preparedness and response by providing training to build national diagnostic and emergency capacity to deal with an emerging crisis, including a peak refugee crisis following the current crisis between Ukraine and the Russian Federation.

The CTMA prepared and delivered a training programme on specific mobile laboratory practices (PCR, inverted fluorescence microscopy, reception and decontamination of potentially hazardous human, animal or environmental samples, basic biosafety and biosecurity; dressing and undressing procedure for personal protective clothing, including a protective mask). Ten trainees followed a customised JITT (Just In Time Training) programme, focusing on topics selected by the Moldovan National Institute of Public Health to meet their specific needs in terms of mobile diagnostic capacity.

EC H2020 CORDIAL-S Portable and fast surface plasmon resonance Point-of-Care test for COVID-19 (2020 – 2022)

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 saliva 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 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. The rapid COVID-19 diagnostic test is deployable in the field of mobile laboratories like our B-LIFE deployable lab.

EU H2020 eNOTICE: European Network Of CBRN Tralning Centers - Funding: (2017-2023)

Olga VYBORNOVA

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 organises 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.

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

Olga VYBORNOVA, Aleksandr VYBORNOV, Omar NYABI

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

ENCIRCLE uses an innovative approach to 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 141 registered organisations in the Technological community and 94 practitioner organisations. There are 279 tools and 39 finished and running projects, listed in the ENCIRCLE dynamic catalogue.

EC PANDEM-2 : Pandemic Preparedness and Response – Funding EU (2021-2023)

Julie HUREL, Olga VYBORNOVA, Jérôme Ambroise, Maxime BONJEAN, Pierre VANDENBERGHE

PANDEM-2 implements and demonstrates the most important novel concepts and IT systems to improve the capacity of European pandemic planning and response. Following the PANDEM project (with the same coordinator and many shared partners) and extensive subsequent stakeholder engagement, research and prioritisation, PANDEM-2 meets the real-world needs of public health agencies responsible for pandemics ('pandemic managers') and first responders across Europe.

PANDEM-2 will enable and demonstrate the capture and integration of pandemic-relevant data from international systems (Go.Data outputs, EWRS, TESSy, etc.), participative surveillance (Influenzanet, Studybugs, etc.), from laboratory (next generation sequencing) systems and from social media (Twitter, Reddit). This data will be accessible and can be analysed via an online dashboard, designed and built to support the specific needs of pandemic managers. Additional high-priority tools for pandemic spread prediction, visual analytics and resources management, including workforce capacity mapping, will improve preparedness and planning, and enable pandemic managers to be as well positioned as possible for a pandemic when it comes.

In order to test the system, while also networking and building relationships across borders and organisations, pandemic managers and first responders from multiple Member States will work together in EU-wise demonstrations, planning and responding to several pandemic scenarios, from Ebola to SARS/MERS CoV, to pandemic influenza. Pandemic communications, highlighted as a key capability gap, will be addressed by resource creation, training and evaluation.

CTMA 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. - Funding: EU H2020 (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 organisations, expert laboratories, industrial partners and end-users. Training courses at basic and advanced levels will be developed and attended by the EuroBioTox network partners, followed by a series of proficiency tests which, through these "outer circle" associates, will disseminate best practice methods across Europe. The outcomes are a pan-European network of competence, certified reference materials, standard operating procedures and a common way of handling biotoxin incidents

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

Omar NYABI, Mostafa BENTAHIR, Jamal BADIR, , Nawfal CHIBANI, Pierre VANDENBERGHE

Arboviruses (Arthropod-Borne Diseases) are a 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 shortens 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 (LAMP) 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 a good path by bringing into focal, isothermal amplification, LAMP, towards detection of the pane flavivirus (Zika, Dengue and Yellow fever viruses).

Walloon Region Win2Wal COVIMMUN : Coronavirus (SARS-Cov1, MERS-Cov, and SARS+Cov2), influenza virus and RSV antigen and genetic detection of based on Lateral Flow Assay (2021 – 2024)

Omar NYABI, Benjamin SMITS, Nawfal CHIBANI

The study of the epidemiology of respiratory viral infections, the understanding of their interaction with the human body and the improvement of knowledge on the progression of the disease require the development of new tools to contain their spread.

Therefore, it seems necessary to develop means to improve the quality and acuity of diagnosis by proposing, among other things, a rapid diagnostic system for respiratory viral infections caused mainly by respiratory syncytial virus, influenza and coronavirus.

In 2009, we were faced with the H1N1/09 pandemic. Today, we are overwhelmed with the SARS-CoV-2 pandemic, the most problematic global health crisis for our societies and still one of the greatest challenges we have been facing since World War II. The high virulence of this pathogen and its sometimes-lethal consequences are prompting the scientific community to develop global response strategies in all areas of human activities based on innovation, collaboration and commitment. Strategies that will provide the necessary guidelines to create adapted and sustainable responses in the event of the emergence of mutant forms of the virus that could compromise efforts to develop vaccines and antibody treatment to combat COVID-19.

The CTMA (UCL) and the CRPP-HISTO (ULIEGE), in partnership with their industrial sponsor ZenTech, which is particularly visible and active both in Belgium and internationally, will therefore focus their efforts on developing

1- An MPX/MPM lateral flow test allowing the concomitant detection of the 5 most prevalent and/or problematic viruses in respiratory distress (influenza virus, RSV, SARS-CoV, MERS-CoV and SARS-CoV-2).

2- A multiplex diagnostic test for "Mass Screening" based on the combination of LAMP-seq and MinION techniques (Oxford Nanopore Technologies). This technology will be transportable to the field.

This partnership between, on the one hand, an innovative academic development (university type research) and, on the other hand, the mastery of the lateral flow test, industrial partner ZenTech is an added value for monitoring the disease and will give the industrial partner an undeniable competitive advantage on the world market.

The strong points of this collaboration coordinated by CTMA will assure

(a) The positioning of the CTMA and the CRPP as Covid-19 analysis laboratories;

(b) Long-standing clinical expertise in the validation of new diagnostic tests;

(c) Internationally recognized expertise, both in the development of new technologies and in their application at different levels (the CTMA coordinates numerous regional, federal, European and international projects);

(d) The integration of these Walloon technologies in the deployable B-LIFE laboratory (owned by the CTMA) during its deployments under the agencies of the European Union (EC, DG ECHO, EUCPM mechanism) and international operations (WHO, GOARN mechanism) ensures a prominent international showcase for Walloon technologies.

In several respects, the CTMA-ZenTech partnership assisted by the CRPP represents a consortium of extremely complementary partners.

Walloon Region POC/(THERACOV)/Single Domain antibodies as therapeutics for SARS-CoV-2 disease

Omar NYABI, Benjamin SMITS, Nawfal CHIBANI

The COVID-19 global pandemic caused by the SARS-CoV-2 coronavirus has had serious consequences in terms of mortality, morbidity, and socioeconomic impact. The rapid loss of seroneutralization capability of natural and post-vaccine anti-SARS-CoV-2 antibodies was exacerbated by a vaccine escape effect associated with the virus's rapid genetic evolution and the appearance of variants with changes in the spike and receptor binding domain (RBD).

Camelid-antibodies or single-domain antibodies (VHH, nanobodies) are an alternative or complement to conventional vaccinations and monoclonal antibodies due to their low complexity, small size, and unique epitope recognition.

We developed several VHH antibodies that bind specifically and strongly to the spike protein and RBD of several SARS-CoV-2 variants of concern (Alpha B1.1.7, DeltaB.1.617.2.1 and Omicron B.1.1.529) using bioinformatic modelling tools for proteomic prediction pattern combined with surface plasmon resonance (SPR) and Biolayer interferometry (BLI).

Next, we are planning preclinical studies on mice models using SARS-CoV-2 VHH. This is crucial for protecting the huge number of immunocompromised people, who remain at risk of severe COVID-19 disease despite the current vaccines availability.

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 – 2025)

(RDC) - CTMA

Léonid IRENGE MWANA WA BENE

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 students 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.

Adaptation of an NGS kit for pharmacogenetic targets in ALL to new sequencing chemistries and optimisation of accuracy and cost per sample

Bertrand BEARZATTO

The survival rate of patients with acute lymphoblastic leukaemia (ALL) has improved over the last decades and this is mainly due to an improvement in therapeutic responses due to a better understanding of the mechanisms involved in relapse, treatment resistance and the mechanisms leading to the development of drug toxicity. Differences in therapeutic responses (toxicity and treatment efficacy) between patients can, at least in part, be explained by genetic predispositions associated with genetic polymorphisms. Numerous ongoing genetic association studies suggest new associations between genetic variants and therapeutic outcomes (drug toxicity, resistance and relapse). In childhood ALL, the complexity of these studies is increased by the number of cytotoxic agents used. Some treatment protocols such as EORTC 58081 (CLG Treatment guidelines for Acute Lymphoblastic Leukaemia) combine 6 different molecules including glucocorticoids (prednisone, dexamethasone), L-asparaginase, anthracyclines (daunorubicin, doxorubicin), methotrexate, vincristine and 6-mercaptopurine.

In a preliminary study funded by the Salus Sanguinis Foundation in 2016-2017, the CTMA developed a first version of a high-throughput sequencing kit (custom kit) to sequence 37 genes potentially involved in the relapse, toxicity or loss of efficacy of a series of cytotoxic agents used in the therapeutic protocol of the time of the Cliniques Universitaires St-Luc, the EORTC 58081 protocol.

Recently the Salus Sanguinis Foundation decided to finance the continuation of this project. The objective of this new project is therefore twofold, since it aims on the one hand to continue the development of the kit by adapting it to the new multiplex PCR enrichment chemistry proposed by Illumina. On the other hand, we will be able to adapt the panel of sequenced genes on the basis of the evolution of the therapeutic protocol used at the CUSL and the evolution of the literature over the last two years.

A second funding obtained from the Saint Luc Foundation will also make it possible to finance the development of the same NGS kit based on the principle of capture by probe. A comparison of the two methods (multiplex PCR versus probe capture) and validation of the new kit will be carried out on a limited number of samples (n=~ 40). This will allow us to compare the two technologies in terms of homogeneity of coverage, proportion of off-target sequencing, possibilities of pooled analysis of clinical samples within the same NGS run.

The combination of the means provided by these two sources of financing should allow us to produce and validate a second-generation kit with a view to its transfer to the clinic. The integration of this new tool into a future multicenter study strategy piloted by the paediatric department (Prof B. Brichard, MD, PhD; Prof M. de Ville de Goyet, MD, PhD; Prof A Van Damme MD, PhD; Dr C Boulanger, MD; Dr M. Le Roux MD) will also be evaluated during this project.

Rheumatoid arthritis and interstitial lung disease: contribution of a variant gain-of-function of the MUC5B gene's promoter ?

Bertrand BEARZATTO, Jean-François DURANT

Prof. Antoine Froidure (Pneumology, CUSL) and Prof. Patrick Durez (Rheumatology, CUSL) are studying factors that can predict the development of pulmonary fibrosis in patients with recently diagnosed rheumatoid arthritis. There is a potential link between pulmonary fibrosis and a variant gain-of-function of the MUC5B gene's promoter, which codes for mucin (a protein that makes up the mucus in the lungs). CTMA is now characterised by high throughput sequencing of this variant among patients included in the study.

BESecured PSS - Funding ESA 4S (Secure Satcom for Safety & Security) (2022)

Aleksandr VYBORNOV

The major focus of this Project is to develop a multi-mission, multi-user Nomadic Rapidly Deployable Telecommunication Node for Emergencies (or Telecommunication Emergencies Node - TEN). This solution is presented in "All-In-One" (AIO) form-factor/conception, defined as a fully integrated stand-alone solution, which provides all types of required telecommunication services including terrestrial (TETRA, LTE, 5G, Wi-Fi) and SatCom communications for PPDR end-users/stakeholders irrespective of the type and location of the crisis. This tactical telecommunication bubble provides a coverage for the TETRA users ~10km,

for the LTE ~1km, for Wi-Fi and 5G ~0.2km, depending on landscape, on deployment scale (small/medium/large), the corresponding potential number of users supported by TEN will be ~25/50/100. Satellite communications are integrated with terrestrial telecommunication to form a multimodal telecommunication system independent from any communication network which could be rapidly overstressed by an exceptional mobilisation of many emergency and security services. So, all relevant information is delivered timely and securely to them by an autonomous and robust communication, command and control system.

GenoPredict (2022 – 2024)

Maxime BONJEAN, Jérôme AMBROISE, Jean-Luc GALA

The project aims at using data mining and Machine Learning (ML) approaches on dedicated genome-based databases in order to assist key research question strengthening the phylogenetic scale: is it possible to reliably predict the transmission mode, including candidate vectors, the host group and the tissue tropism from the genome sequence of newly discovered and uncharacterized viruses? Such improvement of the phylogenetic scale of risk analysis will complete and facilitate the evaluation of spatial, temporal and socio-economic scales in order to identify, prevent or contain future damaging viral outbreaks for humans, other animals and plants.

HORIZON-EIC MOBVEC: Mobile Bio-Lab to support first response in Arbovirus outbreaks – Funding EU (2023-2027)

Léonid IRENGE, Aleksandr VYBORNOV

The WHO estimates that vector-borne diseases (VBD) account for more than 17% of all infectious diseases. Every year, more than 2.5 billion people are at risk of contracting dengue alone, and VBDs cause almost 1 million deaths. In the last decades several species of invasive disease carrying mosquitoes have invaded the northern hemisphere of the planet through the transport of goods, increasing international travel and climate change. In 2018 a West Nile fever outbreak transmitted by mosquitoes occurred in the EU. For this disease there are no vaccines or medications. There were 1503 cases reported in 11 countries, and 181 deaths. VBD Mobile Bio-Labs could have assisted health authorities in containing this outbreak, reducing cases and preventing deaths. Unfortunately such a system does not exist. MOBVEC will be the first VBD Mobile Bio-Lab, providing:

1- Automatic information about vector populations, obtained in real-time by smart-traps, powered by machine-learning and edge computing: insect species, sex, age, and viral infection.
2- GEOSS compliant vector risk maps of adult insects and eggs/larvae, built on field + Copernicus data;
3- GEOSS compliant disease transmission models in mosquito populations, fusing data from Copernicus, clinical and diagnostic data of reference labs, and vector risk maps;
4- GEOSS compliant citizen-science platform to reinforce the surveillance of mosquitoes using citizens as observation nodes.
5- VBD mobile bio-lab with the capacities of points 1, 2, 3 and 4 + VBD Epidemiological maps and forecast models, to be rapidly operational in the heart of outbreaks to assist first-responders.
This technology will be the first line of defence against disease vectors worldwide, help prevent and fight devastating disease outbreaks, and will save lives while saving millions of euros in healthcare and lost working-hours. This has never been done before, and our consortium has the interdisciplinary research capacities to make it a reality.

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.

Stallergènes (2013 –)

Marc DILLEMBOURG, Olga Maria CRUZ-MITJANS, Dennys CRUZ-MITJANS, Jean-François DURANT

The project aims at producing freeze dried, gamma inactivated, fungal raw material for use in allergy research & treatment, starting from pure cultures & inert substrates.

A service type contract has recently been signed with a biopharmaceutical industry leader specialised in the treatment of severe respiratory allergies.

Consequently, selected strains have been deposited at Mycothèque de l'Université catholique de Louvain (BCCM/MUCL).

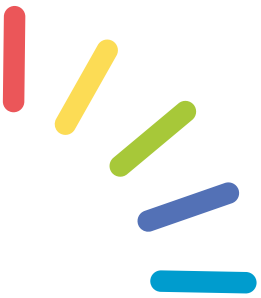
The production of biomasses can be adjusted to the specificities of any customer (scientific community or industrial sector) in order to guarantee the quality of allergen extracts made using our products.

In 2020, CTMA/MYCO has moved from Louvain-la-Neuve to Woluwé-Saint-Lambert UCLouvain Campus. So now all CTMA activities are grouped on the same site.

CTMA/MYCO meets strict quality & safety standards, in compliance with European regulatory requirements (origin, processing, identification & purity).

It has the equipment & expertise allowing detection, identification & monitoring of microbial contaminants of indoor & outdoor air. Detection & monitoring is based on surface & air sampling methods. Identification of airborne particles is achieved by standard light microscopy, culture, SDS-PAGE profiling & DNA signature sequences.

Another goal of the project is to perform research on the quantification and analysis of proteins for test and control purposes and in the context of allergy test.



REFERENCES 2022

Martin A, Bland MJ, Rodriguez-Villalobos H, **Gala JL**, Gabant P.
Promising Antimicrobial Activity and Synergy of Bacteriocins Against Mycobacterium tuberculosis.
Microb Drug Resist, 2022.

Renoz F, **Ambroise J**, **Bearzatto B**, Fakhour S, Parisot N, Ribeiro Lopes M, **Gala JL**, Calevro F, Hance T.
The Di-Symbiotic Systems in the Aphids Sipha maydis and Periphyllus lyropictus Provide a Contrasting Picture of Recent Co-Obligate Nutritional Endosymbiosis in Aphids.
Microorganisms 10 (7) : 1360, 2022.

Bentahir M, Barry MD, Koulemou K, **Gala JL**.
Providing On-Site Laboratory and Biosafety Just-In-Time Training Inside a Box-Based Laboratory during the West Africa Ebola Outbreak: Supporting Better Preparedness for Future Health Emergencies.
Int J Environ Res Public Health 19 (18) : 11566, 2022.

Cosentino G, Bernard M, **Ambroise J**, Giannoli JM, Guedj J, Débarre F, Blanquart F.
SARS-CoV-2 viral dynamics in infections with Alpha and Beta variants of concern in the French community.
J Infect 84 (1) : 94-118, 2022.

Santos-Ribeiro D, Lecocq M, De Beukelaer M, Verleden S, Bouzin C, **Ambroise J**, Dorfmuller P, Yakoub Y, Huaux F, Quarck R, Karmouty-Quintana H, Ghigna MR, Bignard J, Nadaud S, Soubrier F, Horman S, Perros F, Godinas L, Pilette C.
Disruption of GCN2 Pathway Aggravates Vascular and Parenchymal Remodeling During Pulmonary Fibrosis.
Am J Respir Cell Mol Biol, 2022.

Pothen L, Verdoy R, De Mulder D, Esfahani H, Farah C, Michel LYM, Dei Zotti F, **Bearzatto B**, **Ambroise J**, Bouzin C, Dessy C, Balligand JL.
Sustained Downregulation of Vascular Smooth Muscle Acta2 After Transient Angiotensin II Infusion: A New Model of "Vascular Memory".
Front Cardiovasc Med 9 : 854361, 2022.

Beyaert S, Delahaut G, **Ambroise J**, Lawson G, Bachy V, Hassid S, Delacroix L, Remacle M, Van der Vorst S.
Transoral radiofrequency of the terminal branches of the recurrent nerve in the treatment of adductor spasmodic dysphonia: our experience over 11 patients.
Eur Arch Otorhinolaryngol 279(9) : 4465-4472, 2022.

Cuypers L, Dellicour S, Hong SL, Potter BI, Verhasselt B, Vereecke N, Lambrechts L, Durkin K, Bours V, Klamer S, Bayon-Vicente G, Vael C, Ariën KK, De Mendonca R, Soetens O, Michel C, **Bearzatto B**, Naesens R, Gras J, Vankeerberghen A, Matheeussen V, Martens G, Obbels D, Lemmens A, Van den Poel B, Van Even E, De Rauw K, Waumans L, Reynders M, Degosserie J; COVID-19 Genomics Belgium Consortium; Maes P, André E, Baele G.
Two Years of Genomic Surveillance in Belgium during the SARS-CoV-2 Pandemic to Attain Country-Wide Coverage and Monitor the Introduction and Spread of Emerging Variants. Viruses 14(10) : 2301, 2022.

Frère J, Chatzis O, Cremer K, Merckx J, De Keukeleire M, Renard F, Ribesse N, Minner F, Ruelle J, Kabamba B, Rodriguez-Villalobos H, **Bearzatto B**, Delforge ML, Henin C, Bureau F, Gillet L, Robert A, Van der Linden D.
SARS-CoV-2 Transmission in Belgian French-Speaking Primary Schools: An Epidemiological Pilot Study.
Viruses 14(10) : 2199, 2022.

Cuypers L, Bode J, Beuselinck K, Laenen L, Dewaele K, Janssen R, Capron A, Lafort Y, Paridaens H, Bearzatto B, Cauchie M, Huwart A, Degosserie J, Fagnart O, Overmeire Y, Rouffiange A, Vandecandelaere I, Deffontaine M, Pilate T, Yin N, Micalessi I, Roisin S, Moons V, Reynders M, Steyaert S, Henin C, Lazarova E, Obbels D, Dufrasne FE, Pirenne H, Schepers R, Collin A, Verhasselt B, Gillet L, Jonckheere S, Van Lint P, Van den Poel B, Van der Beken Y, Stojkovic V, Garrino MG, Segers H, Vos K, Godefroid M, Pede V, Nollet F, Claes V, Verschraegen I, Bogaerts P, Van Gysel M, Leurs J, Saegeman V, Soetens O, Vanhee M, Schiettekatte G, Huyghe E, Martens S, Lemmens A, Nailis H, Laffineur K, Steensels D, Vanlaere E, Gras J, Roussel G, Gijbels K, Boudewijns M, Sion C, Achtergael W, Maurissen W, Iliano L, Chantrenne M, Vanheule G, Flies R, Hougardy N, Berth M, Verbeke V, Morent R, Vankeerberghen A, Bontems S, Kehoe K, Schallier A, Ho G, Bafort K, Raymaekers M, Pypen Y, Heinrichs A, Schuermans W, Cuigniez D, Lali SE, Drieghe S, Ory D, Le Mercier M, Van Laethem K, Thoelen I, Vandamme S, Mansoor I, Vael C, De Sloovere M, Declerck K, Dequeker E, Desmet S, Maes P, Lagrou K, André E.
Nationwide Harmonization Effort for Semi-Quantitative Reporting of SARS-CoV-2 PCR Test Results in Belgium.
Viruses 4(6) : 1294, 2022.

De Berdt P, Vanvarenberg K, Ucakar B, Bouzin C, Paquot A, Gratpain V, Loriot A, Payen V, **Bearzatto B**, Muccioli GG, Gatto L, Diogenes A, des Rieux A.
The human dental apical papilla promotes spinal cord repair through a paracrine mechanism. Cell Mol Life Sci 79(5) : 252, 2022.

Devresse A, Sébastien Briol, De Greef J, Lemaitre F, Boland L, Haufroid V, Scohy A, Kabamba B, Yombi JC, Belkhir L, Darius T, Buemi A, De Potter K, Mantegazza R, **Bearzatto B**, Goffin E, Kanaan N.
Safety, Efficacy, and Relapse of Nirmatrelvir-Ritonavir in Kidney Transplant Recipients Infected With SARS-CoV-2.
Kidney Int Rep 7(11) : 2356-2363, 2022.

Merzouki, M, **Bentahir M**, Chigr F, Najimi M, **Gala JL**.
The Modelling of the Capacity of the Moroccan Healthcare System in the Context of COVID-19: The Relevance of the Logistic Approach.
Handbook of Research on Pathophysiology and Strategies for the Management of COVID-19. IGI Global : 17-26, 2022.

PHD THESES

Date: 06/01/2022 Name: **PIRAUX Elise** **Lab: PNEU**
Thesis: Exercise as a part of treatment in cancer:
Specific focus on the pretreatment and treatment phases
Promotor: REYCHLER Grégory Copromotor: CATY Gilles (CHWAPI)

Date: 13/01/2022 Name: **ZAMPIERI Luca** **Lab: FATH**
Thesis: Targeting mitophagy to overcome chemoresistance in ovarian and brain cancer
Promotor: SONVEAUX Pierre

Date: 14/01/2022 Name: **PRIEUR Guillaume** **Lab: GHRV et GRKR/PNEU**
Thesis: Strategies to reduce exertional dyspnea and increase functional capacity
in patients with COPD
Promotor: REYCHLER Grégory Copromotor: LAMIA Bouchra (CHU Rouen)

Date: 26/01/2022 Name: **VAN GOETHEM Ninae** **Lab: EPID**
Thesis: Towards genomic-informed pathogen surveillance and control in Belgium. Integration of genomic information for the surveillance and control of infectious diseases within the national public health institute in Belgium
Promotor: ROBERT Annie Copromotor: VAN OYEN Herman (Sciensano)

Date: 07/02/2022 Name: **VANDER LINDEN Catherine** **Lab: FATH**
Thesis: Towards a more rational use of metabolism-targeting drugs as anticancer treatments
Promotor: FERON Olivier Copromotor: CORBET Cyril

Date: 11/02/2022 Name: **DEL VENTO Federico** **Lab: GYNE pôle andrologie**
Thesis: Fertility restoration using immature testicular tissue cryopreserved before gonadotoxic treatment: optimization of the transplantation technique
Promotor: WYNS Christine

Date: 24/02/2022 Name: **ZANGO Serge Henri** **Lab: EPID**
Thesis: Co-infections of malaria and curable sexually transmitted infections in pregnant women in rural Burkina Faso
Promotor: ROBERT Annie

Date: 24/02/2022 Name: **NGUYEN THI YEN Thu** **Lab: GYNE**
Thesis: Feasibility of frozen-thawed ovarian tissue transplantation in patients with central nervous system tumors and Turner syndrome
Promotor: DOLMANS Marie-Madeleine

Date: 01/03/2022 Name: **SINGH Bilal** **Lab: EDIN**
Thesis: Rôle des changements de [Ca2+]c dans le contrôle de la sécrétion de glucagon par le glucose et les modulateurs des canaux KATP
Promotor: GILON Patrick

Date: 29/04/2022 Name: **CACCIOTTOLA Luciana** **Lab: GYNE**
Thesis: Improving ovarian tissue transplantation using adipose tissue-derived stem cells
Promotor: DOLMANS Marie-Madeleinek

Date: 02/05/2022 Name: **COHILIS Marie** **Lab: MIRO**
Thesis: Clinical integration and applications of fast Monte Carlo simulations in proton therapy
Promotor: LEE John Copromotor: STERPIN Edmond

Date: 01/06/2022 Name: **BALDIN Pamela** **Lab: MIRO**
Thesis: Characterisation of clinico-pathological features and tumour immune-microenvironment of colorectal liver metastases
Promotor: VAN DEN EYNDE Marc Copromotor: MOURIN Anne

Date: 02/06/2022 Name: **D'ABADIE Philippe** **Lab: CUSL & MIRO**
Thesis: Liver radioembolization: from dosimetry to clinical effects
Promotor: JAMAR François Copromotor: LHOMMEL Renau

Date: 03/06/2022 Name: **PREVOST Julien** **Lab: CMFA**
Thesis: Towards the discovery and the synthesis of new Arginase 1 inhibitors
Promotor: FRÉDÉRICK Raphaël

Date: 13/06/2022 Name: **HEMPTINNE Coralie** **Lab: IONS**
Thesis: Is amblyopia only bad vision ?
Promotor: YUKSEL Demet Copromotor: ROSSION Bruno

Date: 30/06/2022 Name: **MACCIONI Luca** **Lab: GAEN**
Thesis: Gut barrier dysfunctions and alcohol-associated liver disease in humans: old partners in crime
Promotor: STARKEL Petert Copromotor: ROSSION Bruno

Date: 18/07/2022 Name: **COUTTENIER Alexandra** **Lab: EPID**
Thesis: Prognostic value of statins and beta-blockers in ovarian cancer
Promotor: ROBERT Annie

Date: 19/07/2022 Name: **ROJAS MATTOS Marcelo** **Lab: EPID**
Thesis: Spatial distribution of tuberculosis in Cochabamba, socioeconomic determinants and catastrophic costs for households
Promotor: ROBERT Annie

Date: 23/08/2022 Name: **DONTAINE Justine** **Lab: CARD**
Thesis: AMP-activated protein kinase and O-GlcNAcylation: A new paradigm to protect the failing heart
Promotor: BERTRAND Luc Copromotor: BEAULOYE Christophe

Date: 25/08/2022 Name: **OCTAVE Marie** **Lab: CARD**
Thesis: Linking platelet lipid metabolism and thrombosis: role of acetyl-CoA carboxylase
Promotor: HORMAN Sandrine Copromotor: BEAULOYE Christophe

Date: 31/06/2022 Name: **POTHEN Lucie** **Lab: FATH**
Thesis: Vascular memory, from old concepts to a new model: Sustained down-regulation of alpha-Smooth Muscle Actin induced by Angiotensin II
Promotor: BALLIGAND Jean Luc

Date: 05/09/2022 Name: **IESARI Samuele** **Lab: CHEX**
Thesis: Pharmacological advances in liver transplantation and resection
Promotor: GIANELLO Pierre Copromotor: BONACCORSI RIANI Eliano

Date: 21/09/2022 Name: **EVERARD Gauthier** **Lab: NMSK**
Thesis: Virtual reality to improve assessment and rehabilitation in stroke rehabilitation
Promotor: LEJEUNE Thierry Copromotor: EDWARDS Martin

Date: 11/10/2022 Name: **BUTI Gregory** **Lab: MIRO**
Thesis: Robust treatment planning for proton therapy: computational methods to deal with geometric and target volume uncertainties
Promotor: STERPIN Edmond Copromotor: LEE John

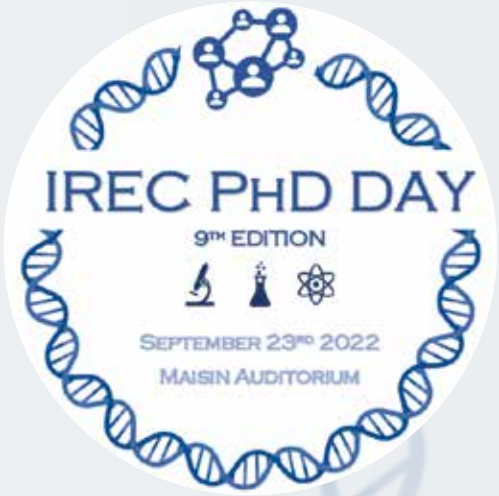
Date: 20/10/2022 Name: **HOSSAY Camille** **Lab: GYNE**
Thesis: Follicle outcomes in cryopreserved ovarian tissue: effect of (re)freezing, in vitro culture and grafting
Promotor: DOLMANS Marie-Madeleine

Date: 03/11/2022 Name: **TRIAILLE Clément** **Lab: RUMA**
Thesis: Deciphering transcriptomic heterogeneity in Rheumatoid Arthritis Synovium
Promotor: LIMAYE Nisha Copromotor: LAUWERYS Bernard

Date: 07/12/2022 Name: **SANTOS RIBEIRO Diana** **Lab: PNEU**
Thesis: Study of the pulmonary vasculature in chronic lung disease: role of GCN2
Promotor: PILETTE Charles Copromotor: GODINAS Laurent (UZ Leuven)

Date: 21/12/2022 Name: **LEJEUNE Sibille** **Lab: CARD**
Thesis: Heart failure with preserved ejection fraction: from comorbidities to endothelial dysfunction, exploring the road through inflammation and oxidative stress
Promotor: POULEUR Anne-Catherine Copromotor: GERBER Bernhard

9th IREC PHD DAY
23/09/2022



THE 9th IREC PHD DAY ORGANIZING COMMITEE

- Alba Sánchez (PNEU) alba.sanchez@uclouvain.be
- Justine Van de Velde (FATH) justine.vandevelde@uclouvain.be
- Louise Declerck (NMSK) louise.declerck@uclouvain.be
- Hanne Vieghe (REPR) hanne.vlieghe@uclouvain.be
- Kelly Crémer (EPID) kelly.cremer@uclouvain.be
- Thai Che Hoang (EPID) hoang.che@uclouvain.be

THANK YOU TO THE AWARD COMMITTEE

Oral presentations jury

Julien Vandamme	IMAG
Luciana Cacciottola	GYNE
Laura Orioli	EDIN
Marine Blackman	FATH
Justine Gillard	GAEN
Evelyne Harkemanne	HEMATOLOGY
Isabelle Massart	EDIN
Louise Declercq	NMSK

Poster presentations jury

Léo Aubert	FATH
Camille Selvais	EDIN
Sébastien Ibanez	FATH
Elena Borderias	MIRO
Marc Kanbar	ANDRO

AWARDS

One award for the best oral presentation
One award for the best poster presentation
One prize for the public choice for the best oral presentation
One prize for the public choice for the best poster presentation

PROGRAM

8h30 – 9h Registration and poster installation

9h – 10h15 First session

Moderators:
Julien Vandamme (IMAG), Luciana Cacciottola (GYNE)

Welcoming words

Alba Sáchez Montalvo (GYNE) - ***Staphylococcus aureus is capable of inducing a neutrophilic inflammation in a surgical mouse model of CRS, in a more prominent way than Pseudomonas aeruginosa or Streptococcus pneumoniae.***

Brieuc Van Nieuwenhuyse (PEDI) – ***TBD***

Loïc Vander Veken (MIRO) - ***Implementation and validation in radiation oncology of mechanically-assisted and non-invasive ventilation (MANIV).***

Françoise Derouane (MIRO) - ***TBD***

10h15 – 10h45 Coffee Break and poster session

10h45 – 12h Second session

Moderators:
Laura Orioli (EDIN), Marine Blackman (FATH)

Ines costa (NEFR) - ***TBD***

Welcoming word - Isabelle Leclercq and/or Jean-Luc Balligand

Christina Anna Stratopoulou (GYNE) - ***Investigation of the role of M2 macrophages in endometrial epithelial and stromal cell invasiveness in adenomyosis.***

Maxime De Rudder (GAEN) - ***TBD***

Davide Brusa – CytoFlux platform

12h – 14h Lunch and poster session

14h – 15h15 Third session

Moderators:
Louise Declercq (NMSK), Justine Gillard (GAEN)

Hasnae Boughaleb (FATH) - ***Bacopaside II, a specific inhibitor of AQP1 could improve the vascular oxidative stress in healthy volunteers.***

Valentin Van den Bossche (FATH) - ***TBD***

Melanie Dechamps (CARD) - ***TBD***

Simon Beyaert (MIRO) – ***Translational investigations of biological modifications induced by afatinib, a TKI inhibitor, administered prior to surgery in patients with primary squamous cell carcinoma of the head and neck (HNSCC) in a window-of-opportunity (WOO) study.***

Julie Vanacker – Clinical Trial Center

15h15 – 15h30 Coffee Break

15h30 – 17h30 Fourth session

Moderators:
Evelyne Harkemanne (Hematology), Isabelle Massart (EDIN)

Natasha Honoré (MIRO) - ***Circulating tumor DNA (ctDNA) to detect minimal residual disease (MRD) in squamous cell carcinoma of the head and neck (SCCHN).***

Finoula Maestre Osorio (MIRO) - ***TBD***

Sebastian Bott (GAEN) - ***Foz/foz mice with non-alcoholic steatohepatitis (NASH) feature pathological cardiac hypertrophy and endothelial dysfunction.***

Camille Pichon (GAEN) - ***Deletion of Hepatic Glutamine Synthetase Promotes NASH and NASH Associated HCC.***

Speaker TBD - CTMA platform

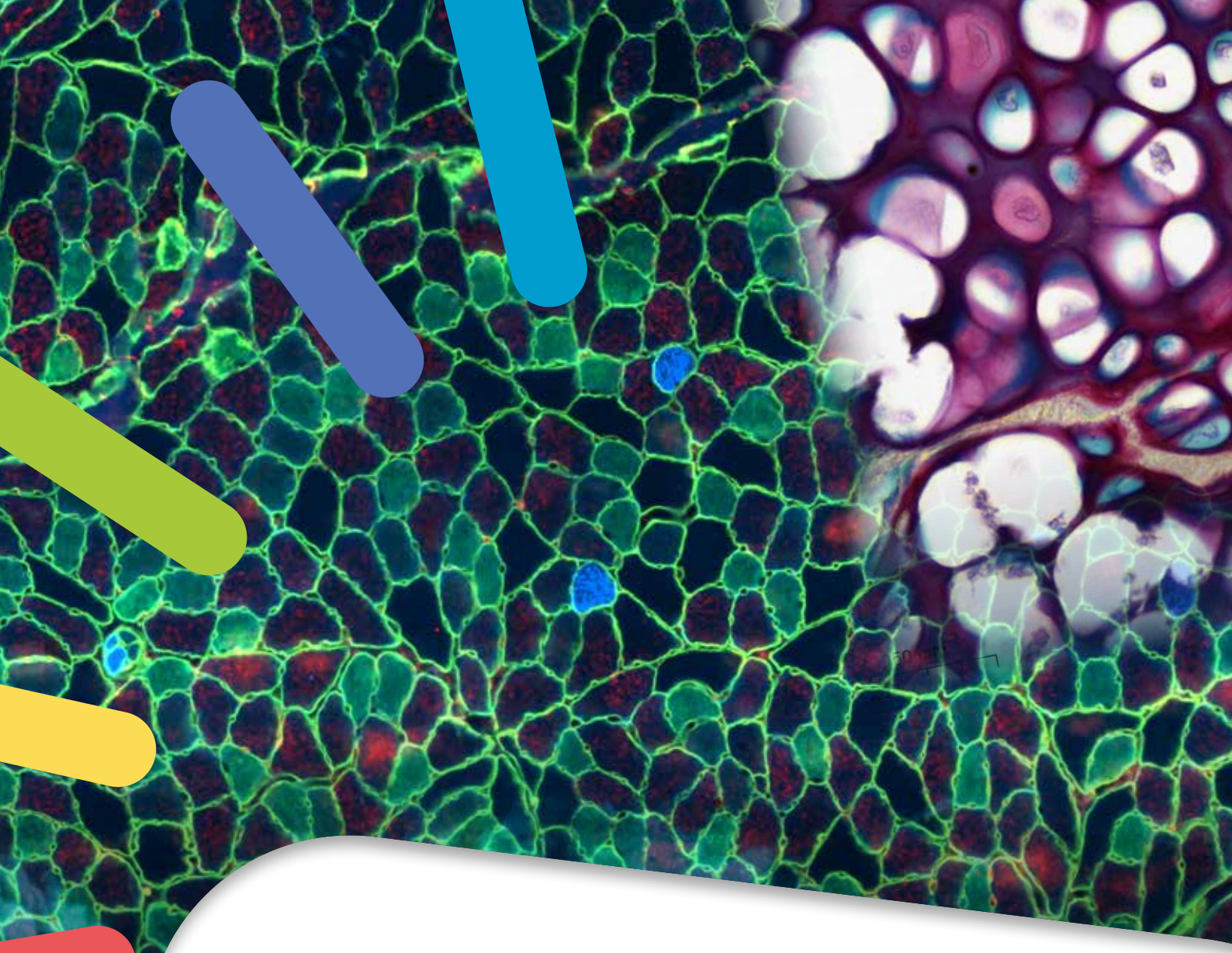
Best poster and best presentation awards

POSTERS

Name	Abstract title	Poster
Manjitha Parambath	Glucose inhibits glucagon secretion of mice with α-cell-specific deletion of KATP channels.	1
Chiara Longo	Exposure to silica: what does biomonitoring tell us?	2
Camille Draguet	Automated clinical decision support system with deep learning dose prediction and NTCP models to evaluate treatment complications in patients with esophageal cancer	3
Ananya Ajith	TDB	4
Justine Van de Velde	Is there a metabolic control of invasion and tissue-specific metastasis in human PDAC?	5
Antoine Chretien	Biomechanical, Microstructural and Material Properties of Tendon in the Young oim Mice Model of Osteogenesis Imperfecta.	6
Marine De Loof	Interplay between cytoskeleton and cardiac metabolism : the role of α-tubulin acetylation on Lys40 in glucose transport.	7
Katarzyna Glowacka	The acidic tumor compartment, phenotypic characterisation and role in drug tolerance.	8
Charline Degavre	TBD	9
Arthur de Schaetzen	Sox9, a gearbox for ductular reaction?	10
Hanne Vlieghe	Characterization of human theca cells differenciated from postmenopausal ovarian stromal cells	11
Léa Hiéronimus	TBD	12
Laeticia Perez	Poorly soluble low toxicity (PSLT) particles modulate genes related to inflammation and cancer development to a greater extent in rat than mouse macrophages.	13
Laura Guilbert	The discovery of a key actor of cardiac pathological hypertrophy.	14
Evelien Krumb	Barriers to haemophilia carrier identification, screening and counseling – an interim analysis of the PROCARRIERS1 study.	15
Kelly Cremer	SARS-CoV-2 antibody seroprevalence in children and workers from Belgian French-speaking primary schools.	16
Alexandre Luc	Do the kinematics and sensorimotor control of people with chronic non-specific neck pain differ from those of healthy individuals when assessed in an immersive virtual reality environment? A systematic review.	17
Julien De Greef	TBD	18
Claire Baufays	Impact of SGLT2 inhibitors on cardiac fibroblasts properties.	19
Miguel Vega Prieto	Engineered CRISPR/Cas9 System For Preventing Immunogenicity During HA Treatment.	20
Benjamin Roberfroid	Towards validation of Ethos® AI-based adaptive radiation therapy : automated planning evaluation.	21
Elena Richiardone	Targeting microenvironment-driven tumor metabolic preferences to thwart tumor aggressiveness in colorectal cancers.	22
Charlotte de Fays	Expression of pIgR by club cells in human small airways in COPD.	23
Alexandre Englebert	TBD	24
Marchand Dorothée	TBD	25
Nicolas Lambricht	Could we use a smartphone video to assess the body dynamics in the sagittal plane during single leg hops?	26
Danah Pross	TBD	27
Laurence Pirotton	TBD	28
Justin Rondeau	Genetic and metabolic control of radiotherapy-induced breast cancer metastasis.	29
Dhoha Kourta	TBD	30

IREC SEMINARS 2022

DATE	SPEAKER	INSTITUTION	TITLE/THEME
17.01.2022	Agne Velthut-Meikas	Tallinn University of Technology	"Intercellular communication in the ovarian follicle revealed by transcriptomic"
31.01.2022	Rita Manco	UCLouvain	Clump together: when neighbours can help in decipher spatial information and more!
21.02.2022	Maikel Colli	ULB	An integrated multi-omics approach to identify the landscape of interferon-α-mediated responses of human pancreatic beta cells
24.03.2022	Peter W. de Leeuw	Maastricht University	Is Renal Artery Stenosis truly a hypertensive disorder ?
26.04.2022	Patrik Rorsman	University of Oxford	Let there be light' – interrogating beta-cell electrical activity by optical methods
02.05.2022	Giovanni Sorrentino	University of Trieste	Liver organoids for regenerative medicine and disease modeling
09.05.2022	Olivier Feron	UCLouvain	Tumor acidosis : from the passenger to the driver's seat
16.05.2022	Ricardo Azevedo	University of Brasília	Nanotechnology and photodynamic therapy for cancer therapy
24.05.2022	Sebastian Mueller	University of Heidelberg	Long-term follow-up and mortality in heavy drinkers: Is alcoholic liver disease primarily a disease of the red blood cell ?
13.06.2022	Andreas Moor	ETH Zurich	Spatial biology in intestinal homeostasis and cancer
27.06.2022	Philipp Koch	Universität Mannheim	Hepatic Angiodiversity Controls Organ Function and Disease
04.10.2022	Emeric Deruy	Agilent	Does the innovation must always lead to change my habits? Let's discuss multiple flow applications and discover the NovoCyte –eon series
25.10.2022	Benjamin Marty	Institut de Myologie, Paris	Le muscle squelettique en recherche clinique et fondamentale : nouveautés en 2022
14.11.2022	Gabriele Chiattarella	Max Delbrück Center for Molecular Medicine	Mechanistic Underpinnings of Cardiometabolic HFpEF



The 2022 activity report of the Institut de Recherche Expérimentale et Clinique is a publication from IREC

Project supervisor: Caroline Dutry et Veronica Curto

Responsible Editor: Isabelle Leclercq

Published: October 2023

Institut de Recherche Expérimentale et Clinique

Avenue Hippocrate, 55 bte B1.55.02

1200 Woluwé-Saint-Lambert

SCAN TO WATCH IREC VIDEO:

IREC Institut de Recherche Expérimentale et Clinique

UCLouvain

EXPERTISE DISCOVERY INNOVATION

Design: www.acg-bxl.be