2021

ACTIVITY REPORT

IREC

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

Albert Szent-Gyorgyi,
1937 Nobel Prize for Medicine

INTRODUCTION BY THE PRESIDENT

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

In June 2016, our Scientific Advisory Board composed of prominent international scientists visited the Institute on-site, heard presentations from the PI's and researchers from all the research Poles and elaborated a report with recommendations on our prospective research strategy. Since then, several steps were taken to implement this strategic reorientation. The research Poles of the Institute were re-organized in Thematic groups, for improved collaborations within a critical mass of gathered expertise, better visibility and integration with clinical departments of excellence in the Cliniques Universitaires Saint-Luc. In 2018, the new research building ("Tour Laënnec") was officially inaugurated, offering top-of-the-line research facilities, including dedicated space for animal experimentation fulfilling all latest regulatory requirements.

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

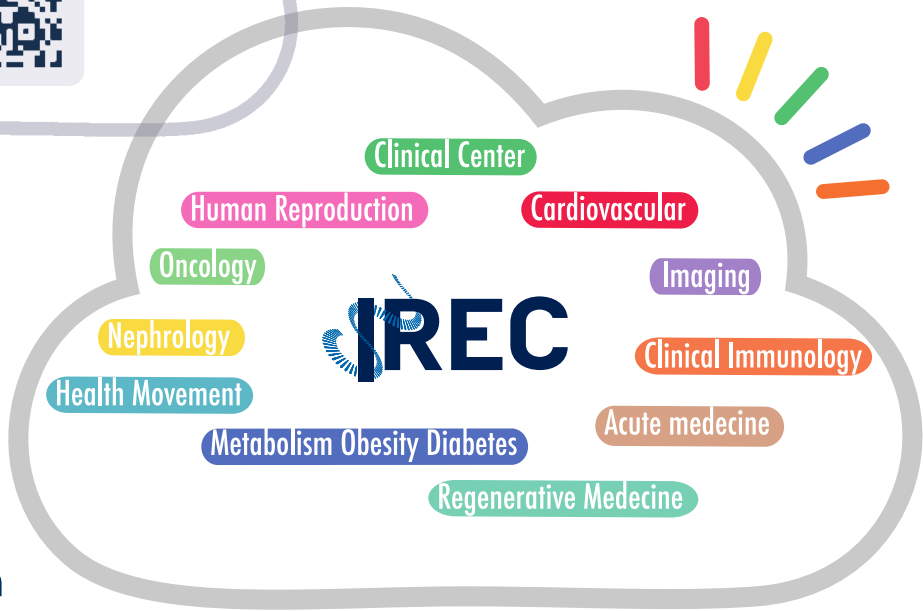
As in past years, and despite the COVID-19 pandemic, we enjoyed the (mostly virtual) visits of prominent national and international scientists at our monthly Seminars (now held in the new "G. Cori" Auditorium in the Laënnec building), and held highly praised networking events, such as the "IREC lunch"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

Through this year 2021, 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.

Jean-Luc Balligand

IREC President

SCAN TO WATCH IREC VIDEO:



UCLouvain

ADMINISTRATIVE STRUCTURE

The Institute of Experimental and Clinical Research is a Translational Research Institute. It conducts research in all areas of clinical and experimental medicine aiming a better understanding of the mechanisms underlying diseases as well as a discovery and development of new therapeutics.
The Institute gathers multidisciplinary researchers (clinicians, fundamentalists), technological platforms and a Clinical Trial Center, in close collaboration with the « Cliniques Universitaires Saint-Luc », thereby constituting a critical mass of expertise that meets the challenges of the medicine of tomorrow.

President : *Professor Jean-Luc Balligand*

ADMINISTRATIVE COORDINATOR:

Veronica Curto / Caroline Dutry

SCIENTIFIC COORDINATOR:

Nancy Van Overstraeten

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

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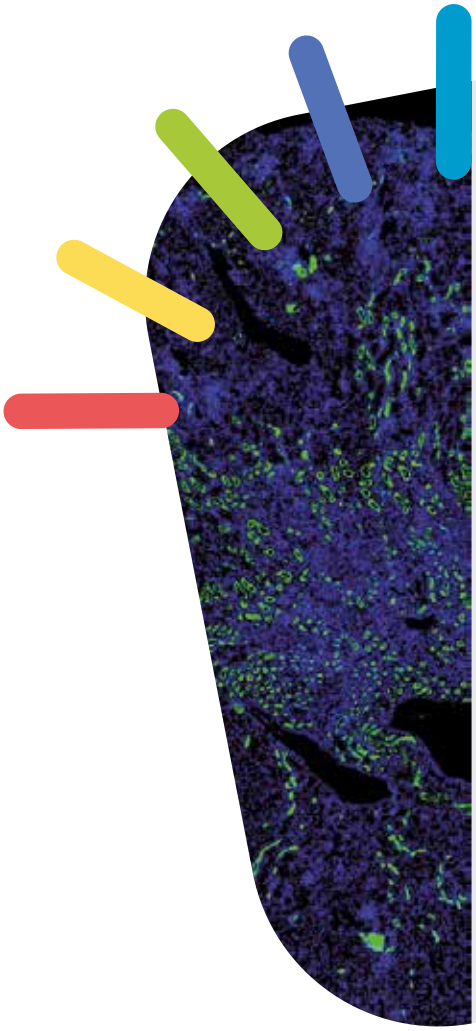
SCIENTIFIC ADVISORY BOARD

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

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



Prof. B. Vanhaesebroek,
Professor at University College of London
London, UK

Prof. B. Wouters,
Executive Vice-President,
Science and Research at University Health Network,
Toronto, Canada

Prof. H. Vidal,
Professor at Claude Bernard University,
Lyon, France

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

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

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

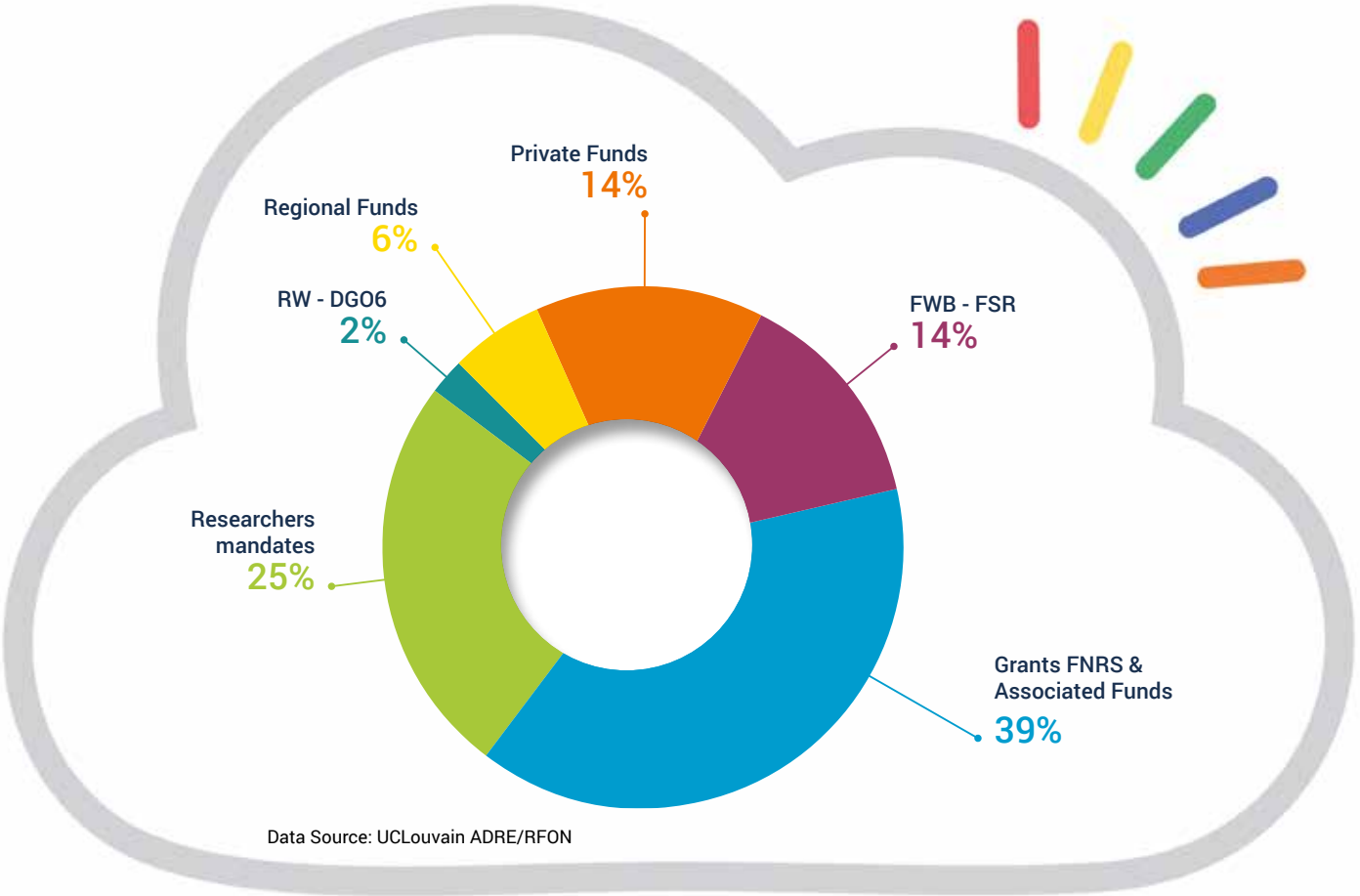
The SAB will regularly visit the Institute to monitor the progress and update the evaluation.

The next visit will take place in Fall 2022.

NEW RESEARCH AGREEMENTS AND CONTRACTS CONCLUDED IN 2021

Funding Sources	N. of agreements	Funding Amount
Regional Funds	8	€ 909 823
Private Funds	17	€ 2 066 864
FWB - FSR	17	€ 813 700
Grants FNRS & Associated Funds	48	€ 6 552 816
Researchers mandates	31	€ 65 000
RW - DGO6	2	€ 1 710 784
Total	**123**	**€ 12 118 987**

SIGNED FUNDING AGREEMENTS PER FUNDING SOURCE (%) 2021



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:

Marine Angé, MD, PhD student
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
Mélanie Dechamps, MD, PhD student
Julien De Poortere, PhD student
Justine Dontaine, PhD student
Cécile Dufeys, Postdoctoral Fellow
Natacha Fourny, Postdoctoral fellow
Anais Gauthey, MD, PhD student
Coralie Georges, PhD student
Audrey Ginion, Research Scientist
Laura Guilbert, PhD student
Vincent Hanet, MD, PhD student
Pauline Krug, MD, PhD Student
Sibille Lejeune, MD, PhD student
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

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POLE OF PHARMACOLOGY AND THERAPEUTICS (FATH)

Chantal Dessy, PhD

Jean-Luc Balligand, MD, PhD

Members:

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
Nancy Vanoverstraten, Postdoctoral Fellow
Roxane Verdoy, Technician
Deborah Morrens, Grants and Contracts Administrator

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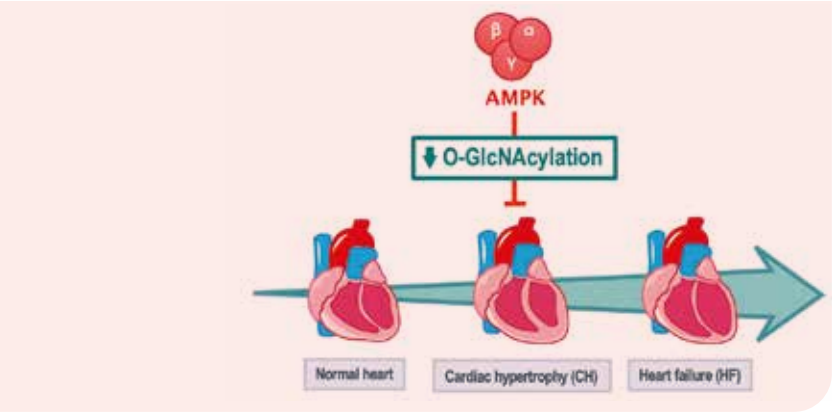
CARDIAC HYPERTROPHY

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

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

AMPK was known to inhibit cardiac hypertrophy. However, the precise molecular mechanism involved in this action was unknown. Our previous study reveals that AMPK activation blocks cardiac hypertrophy by reducing a particular post-translational modification called O-GlcNAcylation. Using several models of cardiac hypertrophy, we more recently showed that AMPK activation can also reverse cardiac hypertrophy once already developed. This reversibility protects the heart improving systolic function., We also established an unbiased mass spectrometry approach, identifying more than 1400 different O-GlcNAcylated proteins in the hypertrophic heart, several of them being 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, 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 will be tested in a RCT in patients with structural cardiac disease presenting with heart failure with preserved ejection fraction (HFpEF), for which there is, as yet, no treatment with proven efficacy. 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.

Mechanisms for the "memory" of cardiovascular risk factors

L. Pothen, R. Verdoy, JL 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 remod-

eling. 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.).

MiR-199a and the NOS/NO pathway.

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

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

From gut to the endothelium

V Joris, L Dumas, C Dessy

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

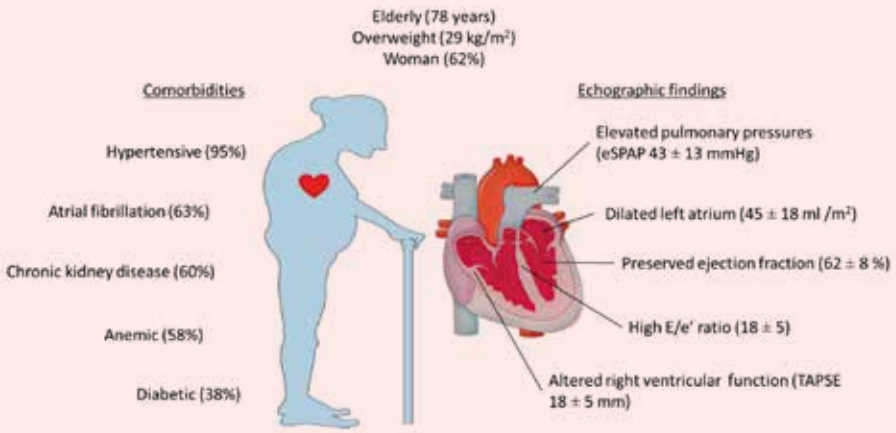
HEART FAILURE WITH PRESERVED EJECTION FRACTION

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

S. Lejeune, 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.

Clinical and echographic charactersitics of our HFpEF population



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 tocharacterize the expression/phosphorylation of key regulatory proteins mediating cardiac myocyte relaxation, as well as EC coupling and myofilament calcium sensitivity (skinned myocytes; collab. w/J. van der Velden, NL), as well as their putative regulation by beta3AR.

Future treatments, translational perspectives

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

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

DIABETIC CARDIOMYOPATHY

The increased O-GlcNAcylation level found in the diabetic heart, a main actor of cardiac diabetic dysfunction

Natacha Fourny, L. Bultot, S. Horman, C. Beauloye, L. Bertrand

We found that O-GlcNAcylation is increased in the diabetic heart. By comparing different mouse model of diabetic cardiomyopathy, we also showed that the increase in protein O-GlcNAcylation nicely correlates with the level of cardiac dysfunction. Via an unbiased mass spectrometry approach, we recently map the O-GlcNAcylated proteins potentially involved in the development of the disease.

CARDIAC FIBROSIS

Cardiac fibrosis/oxidant stress

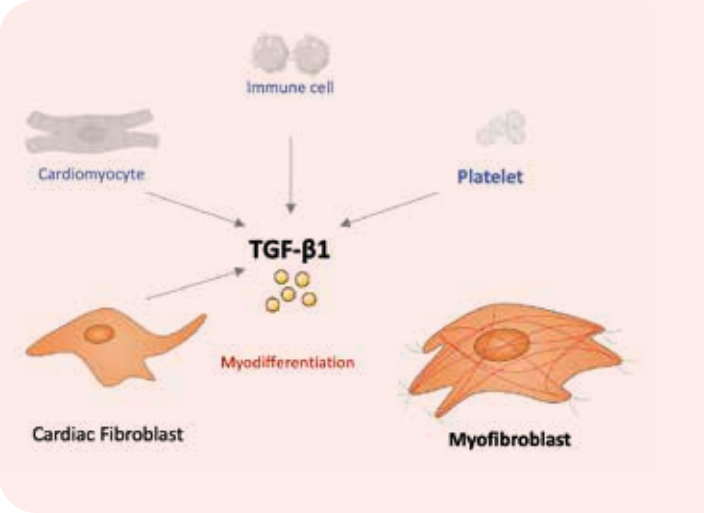
N. Hermida, H. Esfahani, J.-L. Balligand

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 fibroblast myodifferentiation and fibrosis after myocardial infarction.



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

J. Cumps, A. Marino, S. Battault, 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 myodifferentiation processes. We are currently investigating the underlying mechanisms, as well as the significance of these observations in in vivo models of cardiac fibrosis.

CARDIAC REGENERATION

Cardiac progenitor cells

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

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

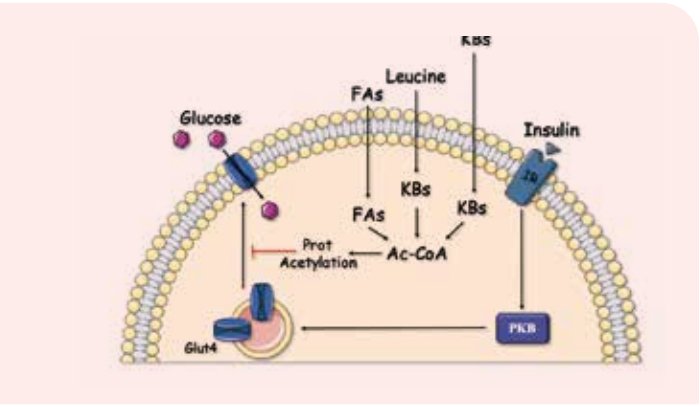
In collaboration with L. Bertrand, CARD, we also identified critical shifts in metabolic substrate utilization in CPC during their differentiation to cardiac myocytes, with concurrent regulation of mitochondrial content and oxidative metabolism (André et al.)

CONTROL OF CARDIAC METABOLISM

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

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

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



Connection between beta3-AR and glucose uptake

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)

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

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

Although sodium glucose cotransporter 1 (SGLT1) has been identified as one of the major SGLT isoforms expressed in the heart, its exact role remains elusive. Evidence using phlorizin, the most common inhibitor of SGLTs, has suggested its role in glucose transport. However, phlorizin could also affect classical facilitated diffusion via glucose transporters (GLUTs), bringing into question the relevance of SGLT1 in overall cardiac glucose uptake. Accordingly, we assessed the contribution of SGLT1 in cardiac glucose uptake using the SGLT1 knockout mouse model, which lacks exon 1. Glucose uptake was similar in cardiomyocytes isolated from SGLT1-knockout (Δex1KO) and control littermate (WT) mice either under basal state, insulin, or hyperglycemia. Interestingly, we discovered that mouse and human hearts expressed a shorter slc5a1 transcript, leading to SGLT1 protein lacking transmembrane domains and residues involved in glucose and sodium bindings. The inhibitory effect of phlorizin on cardiac glucose uptake is SGLT1-independent and can be explained by GLUT transporter inhibition. These data open new perspectives in understanding the role of SGLT1 in the heart.

Evaluation of pregnancy outcomes in patients with congenital heart diseases

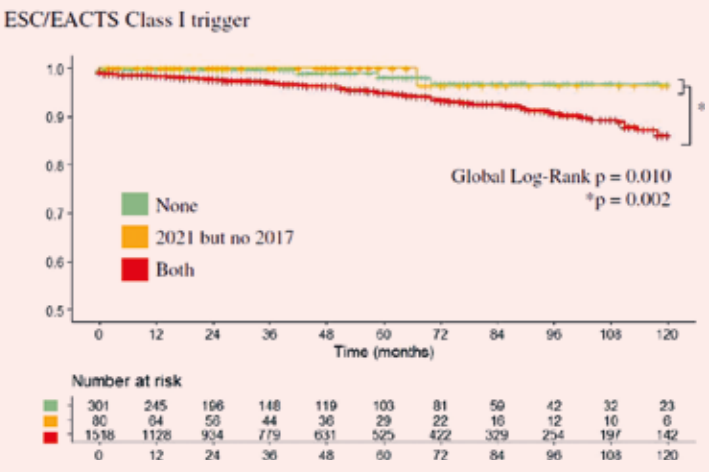
N. Rahnama, S. Pierard

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

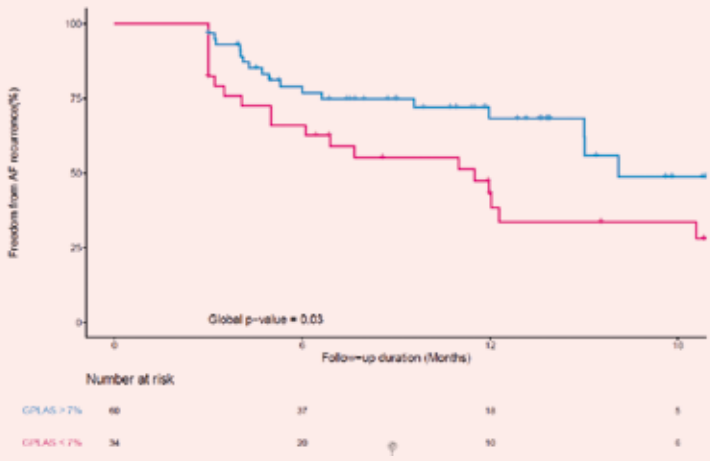
P. Krug, A.-C. Pouleur, B. Gerber

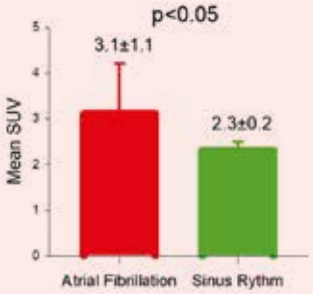
We evaluated the consequences of radiation exposure during radiotherapy for breast cancer on the heart on development of coronary artery disease, valvular heart disease and myocardial fibrosis in 80 patients with breast cancer10 years after treatment. We also started work in patients undergoing acute 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

Ongoing research consists 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.

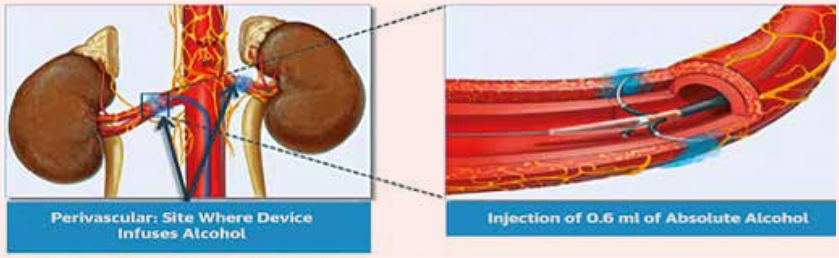




Resistant Hypertension, Fibromuscular Dysplasia and Spontaneous Coronary Artery Dissection

ML. Lopez-Sublet, D. Adlam, A. Persu

Resistant hypertension: research consisted in evaluating the safety and blood-pressure lowering effects of ultrasound- (1) and alcohol infusion-based (2-4) renal denervation. The contribution of the group is further highlighted by participation to the European Society of Hypertension (ESH) position paper on renal denervation (5).

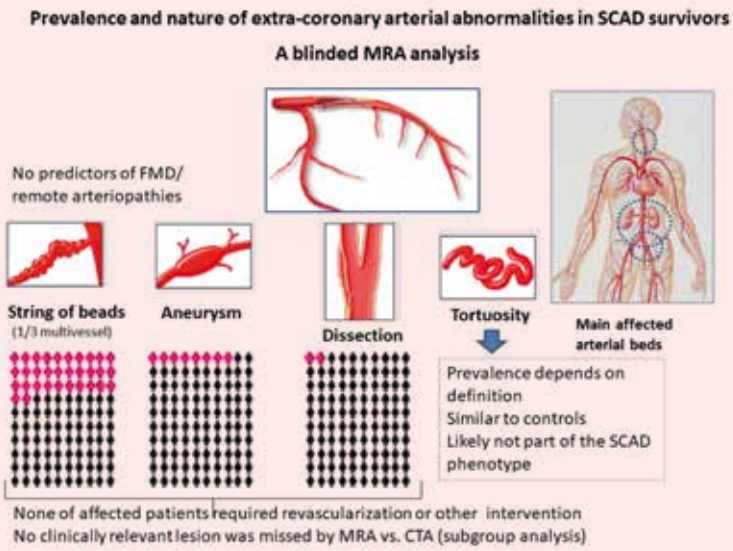


Mahfoud, F. et al. J Am Coll Cardiol Intv. 2020;13(4):471–84.

(A) 6-month follow-up of change in 24-h ambulatory and office blood pressure. Data are mean ± SD with 95% confidence intervals. (B) Site of infusion of 0.6 ml alcohol in the perivascular space of the renal arteries using the Peregrine Catheter. ABP = ambulatory blood pressure; BP = blood pressure; CI = confidence interv

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,T. Metzinger, C. Dessy

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

From gut to the endothelium

L. Dumas, V. Joris, C. Dessy

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

Clinical assessment of endothelial (dys) function

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

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

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

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

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 (PaO2/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)

Control of endothelial barrier/Canagliflozin/ AMPK signalling

M. Angé, J. De Poortere, M. Dechamps, C. Dufeys, A. Ginion,, C. Beauloye, S. Horman

Sepsis capillary leak syndrome (SCLS) is an independent prognostic factor for poor sepsis outcome. We previously demonstrated that α1AMP-activated protein kinase (α1AMPK) prevents sepsis-induced vascular hyperpermeability by mechanisms involving VE-cadherin (VE-Cad) stabilization and activation of p38 mitogen activated protein kinase/heat shock protein of 27 kDa (p38MAPK/HSP27) pathway. Canagliflozin, a sodium-glucose co-transporter 2 inhibitor, has recently been proven to activate AMPK in endothelial cells. Therefore, we hypothesized that canagliflozin could be of therapeutic potential in patients suffering from SCLS. We herein report that canagliflozin, used at clinically relevant concentrations, counteracts lipopolysaccharide-induced vascular hyperpermeability and albumin leakage in wild-type, but not in endothelial-specific α1AMPK-knockout mice. In vitro, canagliflozin was demonstrated to activate α1AMPK/p38MAPK/HSP27 pathway and to preserve VE-Cad's integrity in human endothelial cells exposed to human septic plasma. In conclusion, our data demonstrate that canagliflozin protects against SCLS via an α1AMPK-dependent pathway, and lead us to consider novel therapeutic perspectives for this drug in SCLS.

Vascular dysfunction and haemostatic disorders during sepsis/AMPK signalling

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

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

Head-to-head comparison between COVID-19 and Septic Shock: A Prospective Observational Study

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

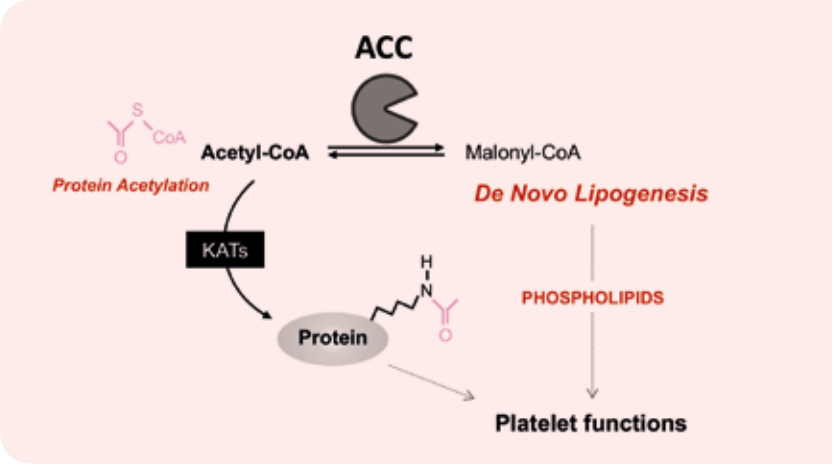
Critical COVID-19, like septic shock, is related to a dysregulated systemic inflammatory reaction and is associated with a high incidence of thrombosis and microthrombosis. Improving the understanding of the underlying pathophysiology of critical COVID-19 could help in finding new therapeutic targets already explored in the treatment of septic shock. The current study prospectively compared 48 patients with septic shock and 22 patients with critical COVID-19 regarding their clinical characteristics and outcomes, as well as key plasmatic soluble biomarkers of inflammation, coagulation, endothelial activation, platelet activation, and NETosis. Forty-eight patients with matched age, gender, and co-morbidities were used as controls. Critical COVID-19 patients exhibited less organ failure but a prolonged ICU length-of-stay due to a prolonged respiratory failure. Inflammatory reaction of critical COVID-19 was distinguished by very high levels of interleukin (IL)-1β and T lymphocyte activation (including IL-7 and CD40L), whereas septic shock displays higher levels of IL-6, IL-8, and a more significant elevation of myeloid response biomarkers, including Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) and IL-1ra. Subsequent inflammation-induced coagulopathy of COVID-19 also differed from sepsis-induced coagulopathy (SIC) and was characterized by a marked increase in soluble tissue factor (TF) but less platelets, antithrombin, and fibrinogen consumption, and less fibrinolysis alteration. In conclusion, COVID-19 inflammation-induced coagulopathy substantially differs from SIC. Modulating TF release and activity should be evaluated in critical COVID-19 patients.

PLATELETS AND THROMBOSIS

Linking platelet lipid metabolism and platelet functions

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

Platelets contain thousands of distinct lipid species. They are either incorporated from circulating plasma low density lipoproteins, generated following phospholipid cleavage by phospholipases, or actively synthesized by platelets via de novo lipogenesis. Lipids are essential components of platelet structure, intracellular signaling and energy store. Given their key roles in platelet function, it is imperative to understand the molecular basis of their regulation during platelet activation. Acetyl-coA carboxylase (ACC) is a key enzyme regulating lipid metabolism. It catalyzes the carboxylation of acetyl-CoA into malonyl-CoA, the rate-limiting substrate for de novo lipogenesis. Thanks to the use of a transgenic mouse model of active ACC, we have demonstrated that a stimulation of endogenous lipogenesis in platelets can promote their activation and subsequent thrombus formation. Based on these results, it was logical to speculate that targeting ACC would limit platelet lipogenesis, which could be an efficient strategy to limit platelet activation and thrombosis. To test this hypothesis, we have generated megakaryocyte (MK)/platelet-specific Knock-out mice where ACC can be selectively invalidated. This experimental model is being used in our laboratory to determine how de novo lipogenesis and ACC can influence platelet reactivity and thrombosis in various physiological and pathological conditions.



Metabolic signalling and protein acetylation

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

ACC inhibition decreases lipogenesis and, in parallel, increases the acetyl-CoA content, which serves as a substrate for protein acetylation. Several findings support a role for acetylation signaling in coordinating signaling systems that drive platelet cytoskeletal changes and aggregation. Therefore, we investigated the impact of ACC inhibition on tubulin acetylation and platelet functions. Human platelets were incubated with CP640.186, a pharmacological ACC inhibitor, prior to thrombin stimulation. We have herein demonstrated that CP640.186 treatment does not affect overall platelet lipid content, yet it is associated with increased tubulin acetylation levels, both at the basal state and after thrombin stimulation. This resulted in impaired platelet aggregation. The mechanism involves a downregulation of the Rac1/PAK2 pathway and of ROS production but is independent of actin cytoskeleton.

α-tubulin acetylation in platelets from coronary artery disease patients

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

Despite dual antiplatelet therapy (DAPT) combining aspirin and a P2Y12 receptor inhibitor, high platelet reactivity persists in some patients due to poor response to treatment and is associated with ischemic risk. It remains unknown if circulating platelets in high-risk patients have different morphological characteristics which could participate in their pro-thrombotic potential. In this study, we postulate that α-tubulin acetylation, a cytoskeletal modification known to regulate platelet shape change, could reflect circulating platelet reactivity and impact their morphology. We collected arterial blood samples from 187 patients admitted for coronary angiography. Platelet reactivity was assessed in whole blood using multiplate analysis. Platelets were then isolated to evaluate α-tubulin acetylation level by western blotting. We reveal high platelet α-tubulin acetylation as a potential marker of efficient platelet inhibition by dual antiplatelet therapy. Since α-tubulin acetylation is a hallmark of stable microtubules, we postulate that its increase could contribute to maintaining resting morphology of circulating platelets.

REFERENCES 2021

MAJOR REFERENCES

Angé M, De Poortere J, Ginion A, Battault S, Dechamps M, Muccioli GG, Roumain M, Morelle J, Druart S, Mathivet T, Bertrand L, Castanares-Zapatero D, Horman S, Beauloye C. Canagliflozin protects against sepsis capillary leak syndrome by activating endothelial α1AMPK. Sci Rep. 2021 Jul 1;11(1):13700. doi: 10.1038/s41598-021-93156-1. PMID: 34211080.

Arnaud C, Boulanger M, Lorthioir A, Amar L, Azarine A, Boyer L, Chatellier G, Di Monaco S, Jeunemaitre X, Kastler A, Mousseaux E, Oppenheim C, Thony F, Persu A, Olin JW, Azizi M, Touzé E; ARCADIA Co-investigators. Male Sex Is Associated With Cervical Artery Dissection in Patients With Fibromuscular Dysplasia. J Am Heart Assoc. 2021;10:e018311.

Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, Rump LC, Persu A, Basile J, Bloch MJ, Daemen J, Lobo MD, Mahfoud F, Schmieder RE, Sharp ASP, Weber MA, Sapoval M, Fong P, Pathak A, Lantelme P, Hsi D, Bangalore S, Witkowski A, Weil J, Kably B, Barman NC, Reeve-Stoffer H, Coleman L, McClure CK, Kirtane AJ; RADIANCE-HTN investigators. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet. 2021; 397(10293):2476-2486.

Bertrand L, De Loof M, Beauloye C, Horman S, Bultot L. A new degree of complexi(n)ty in the regulation of GLUT4 trafficking. Biochem J. 2021 Apr 16;478(7):1315-1319. doi: 10.1042/BCJ20210008. PMID: 33821970.

Boulif J, Slimani A, Lazam S, de Meester C, Piérard S, Pasquet A, Pouleur AC, Vancraeynest D, El Khoury G, de Kerchove L, Gerber BL, Vanoverschelde JL. Diagnostic and Prognostic Accuracy of Aortic Valve Calcium Scoring in Patients With Moderate-to-Severe Aortic Stenosis. Front Cardiovasc Med. 2021 May 17;8:673519. doi: 10.3389/fcvm.2021.673519. eCollection 2021.

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 (Lausanne). 2022 Jan 17;8:780750. doi: 10.3389/fmed.2021.780750. eCollection 2021. PMID: 35111777.

Dufeys C, Daskalopoulos EP, Castanares-Zapatero D, Conway SJ, Ginion A, Bouzin C, Ambroise J, Bearzatto B, Gala JL, Heymans S, Papageorgiou AP, Vinckier S, Cumps J, Balligand JL, Vanhaverbeke M, Sinnaeve P, Janssens S, Bertrand L, Beauloye C, Horman S. AMPKα1 deletion in myofibroblasts exacerbates post-myocardial infarction fibrosis by a connexin 43 mechanism. Basic Res Cardiol. 2021 Feb 9;116(1):10. doi: 10.1007/s00395-021-00846-y. PMID: 33564961.

Ferté L, Marino A, Battault S, Bultot L, Van Steenbergen A, Bol A, Cumps J, Ginion A, Koepsell H, Dumoutier L, Hue L, Horman S, Bertrand L, Beauloye C. New insight in understanding the contribution of SGLT1 in cardiac glucose uptake: evidence for a truncated form in mice and humans. Am J Physiol Heart Circ Physiol. 2021 Feb 1;320(2):H838-H853. doi: 10.1152/ajpheart.00736.2019. Epub 2021 Jan 8. PMID: 33416451.

Fourny N, Beauloye C, Bernard M, Horman S, Desrois M, Bertrand L. Sex Differences of the Diabetic Heart. Front Physiol. 2021 May 27;12:661297. doi: 10.3389/fphys.2021.661297. eCollection 2021. PMID: 34122133.

Georges A, Yang ML, Berrandou TE, Bakker MK, Dikilitas O, Kiando SR, Ma L, Satterfield BA, Sengupta S, Yu M, Deleuze JF, Dupré D, Hunker KL, Kyryachenko S, Liu L, Sayoud-Sadeg I, Amar L, Brummett CM, Coleman DM, d'Escamard V, de Leeuw P, Fendrikova-Mahlay N, Kadian-Dodov D, Li JZ, Lorthioir A, Pappaccogli M, Prejbisz A, Smigielski W, Stanley JC, Zawistowski M, Zhou X, Zöllner S; FEIRI investigators; International Stroke Genetics Consortium (ISGC) Intracranial Aneurysm Working Group; MEGASTROKE, Amouyel P, De Buyzere ML, Debette S, Dobrowolski P, Drygas W, Gornik HL, Olin JW, Piwonski J, Rietzschel ER, Ruigrok YM, Vikkula M, Warchol Celinska E, Januszewicz A, Kullo IJ, Azizi M, Jeunemaitre X, Persu A, Kovacic JC, Ganesh SK, Bouatia-Naji N. Genetic investigation of fibromuscular dysplasia identifies risk loci and shared genetics with common cardiovascular diseases. Nat Commun. 2021;12:6031.

Kwak S, Everett RJ, Treibel TA, Yang S, Hwang D, Ko T, Williams MC, Bing R, Singh T, Joshi S, Lee H, Lee W, Kim YJ, Chin CWL, Fukui M, Al Musa T, Rigolli M, Singh A, Tastet L, Dobson LE, Wiesemann S, Ferreira VM, Captur G, Lee S, Schulz-Menger J, Schelbert EB, Clavel MA, Park SJ, Rheude T, Hadamitzky M, Gerber BL, Newby DE, Myerson SG, Pibarot P, Cavalcante JL, McCann GP, Greenwood JP, Moon JC, Dweck MR, Lee SP. Markers of Myocardial Damage Predict Mortality in Patients With Aortic Stenosis. J Am Coll Cardiol. 2021 Aug 10;78(6):545-558. doi: 10.1016/j.jacc.2021.05.047.

Lejeune S, Roy C, Slimani A, Pasquet A, Vancraeynest D, Vanoverschelde JL, Gerber BL, Beauloye C, Pouleur AC. Diabetic phenotype and prognosis of patients with heart failure and preserved ejection fraction in a real-life cohort. Cardiovasc Diabetol. 2021 Feb 19;20(1):48. doi: 10.1186/s12933-021-01242-5. PMID: 3360800

Mahfoud F, Bertog S, Lauder L, Böhm M, Schmid A, Wojakowski W, Parise H, Fischell TA, Kandzari DE, Pathak A, Persu A, Sievert H. Blood pressure lowering with alcohol-mediated renal denervation using the Peregrine infusion Catheter is independent of injection site location. Catheter Cardiovasc Interv. 2021;98:E832-E838.

Mahfoud F, Sievert H, Bertog S, Lauder L, Ewen S, Lengelé JP, Wojakowski W, Schmieder R, van der Giet M, Weber MA, Kandzari DE, Parise H, Fischell TA, Pathak A, Persu A. Long-Term Results up to 12 Months After Catheter-Based Alcohol-Mediated Renal Denervation for Treatment of Resistant Hypertension.Circ C ardiovasc Interv. 2021;14:e010075.

Mahfoud F, Weber M, Schmieder RE, Lobo MD, Blankestijn PJ, Persu A, Fischell TA, Parise H, Pathak A, Kandzari DE. Catheter-based alcohol-mediated renal denervation for the treatment of uncontrolled hypertension: design of two sham-controlled, randomized, blinded trials in the absence (TARGET BP OFF-MED) and presence (TARGET BP I) of antihypertensive medications. Am Heart J. 2021;239:90-99.

Marino A, Hausenloy DJ, Andreadou I, Horman S, Bertrand L, Beauloye C. AMP-activated protein kinase: A remarkable contributor to preserve a healthy heart against ROS injury. Free Radic Biol Med. 2021 Apr;166:238-254. doi: 10.1016/j.freeradbiomed.2021.02.047. Epub 2021 Mar 4. PMID: 33675956 Review.

Militaru, S. Panovsky R. Hanet V., Amzulescu MS, Langet H, Pisciotti MM, Pouleur AC, Vanoverschelde JL, Gerber BL Multivendor Comparison of Global and Regional 2D CMR Feature Tracking Strains vs Tissue Tagging at 3T. JCMR 2021 May 13;23(1):54

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.

Morelle J, Marechal C, Yu Z, Debaix H, Corre T, Lambie M, Verduijn M, 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.

N Engl J Med. 2021 Oct 21;385(17):1570-1580.

Ngo Njembe MT, Pachikian B, Lobysheva I, Van Overstraeten N, Dejonghe L, Verstraelen E, Buchet M, Rasse C, Gardin C, Mignolet E, Balligand JL, Larondelle Y. A Three-Month Consumption of Eggs Enriched with ω-3, ω-5 and ω-7 Polyunsaturated Fatty Acids Significantly Decreases the Waist Circumference of Subjects at Risk of Developing Metabolic Syndrome: A Double-Blind Randomized Controlled Trial.

Nutrients. 2021 Feb 18;13(2):663. doi: 10.3390/nu13020663.

Octave M, Pirotton L, Ginion A, Robaux V, Lepropre S, Ambroise J, Bouzin C, Guigas B, Giera M, Foretz M, Bertrand L, Beauloye C, Horman S. Acetyl-CoA Carboxylase Inhibitor CP640.186 Increases Tubulin Acetylation and Impairs Thrombin-Induced Platelet Aggregation. Int J Mol Sci. 2021 Dec 4;22(23):13129. doi: 10.3390/ijms222313129. PMID: 34884932.

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.

PLoS One. 2021 Aug 4;16(8):e0255335

Pothen L, Balligand JL. Legacy in Cardiovascular Risk Factors Control: From Theory to Future Therapeutic Strategies? Antioxidants (Basel). 2021 Nov 22;10(11):1849

Ricke-Hoch M, Stelling E, Lasswitz L, Gunesch AP, Kasten M, Zapatero-Belinchón FJ, Brogden G, Gerold G, Pietschmann T, Montiel V, Balligand JL, Facciotti F, Hirsch E, Gausepohl T, Elbahesh H, Rimmelzwaan GF, Höfer A, Kühnel MP, Jonigk D, Eigendorf J, Tegtbur U, Mink L, Scherr M, Illig T, Schambach A, Pfeffer TJ, Hilfiker A, Haverich A, Hilfiker-Kleiner D. Impaired immune response mediated by prostaglandin E2 promotes severe COVID-19 disease.

Schmieder RE, Mahfoud F, Mancia G, Azizi M, Böhm M, Dimitriadis K, Kario K, Kroon AA, D Lobo M, Ott C, Pathak A, Persu A, Scalise F, Schlaich M, Kreutz R, Tsioufis C; members of the ESH Working Group on Device-Based Treatment of Hypertension. European Society of Hypertension position paper on renal denervation 2021. J Hypertens. 2021;39:1733-1741.

Structural and Functional Correlates of Gradient-Area Patterns in Severe Aortic Stenosis and Normal Ejection Fraction. Slimani A, Roy C, de Meester C, Bouzin C, Pasquet A, Pouleur AC, Vancraeynest D, Noirhomme P, El Khoury G, Gerber BL, Vanoverschelde JL. JACC Cardiovasc Imaging. 2021 Mar;14(3):525-536. doi: 10.1016/j.jcmg.2020.09.031. Epub 2020 Nov 18.

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

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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

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

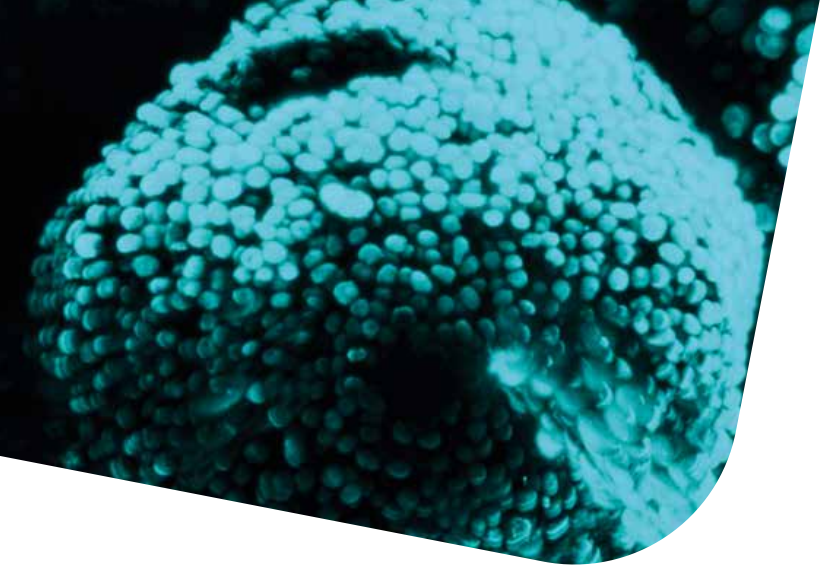
Two cases of optic neuropathy due to superficial siderosis (SS) are reported in two patients, aged 29 and 38 years, operated for intracranial neoplasms, the first one with a desmoplasic infantile ganglioglioma excised in 1991, and the other one with a pilocytic astrocytoma, operated on in 1997, 1998 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

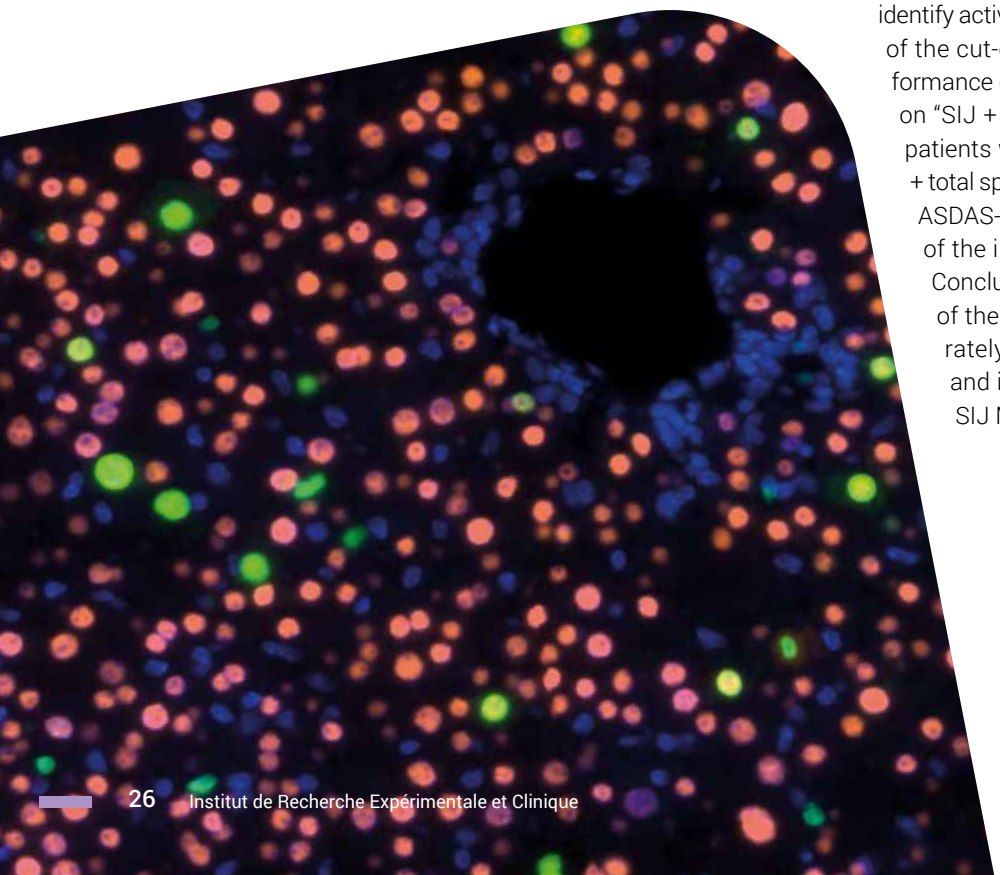
Purpose: To compare tomographic (TUS) with radiographic (RUS) union scores in nailed shaft fractures during normal healing and in non-unions. Methods: Two radiologists blinded to fracture age separately determined RUS and TUS in nailed femoral or tibial shaft fractures by analyzing the radiographic and 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

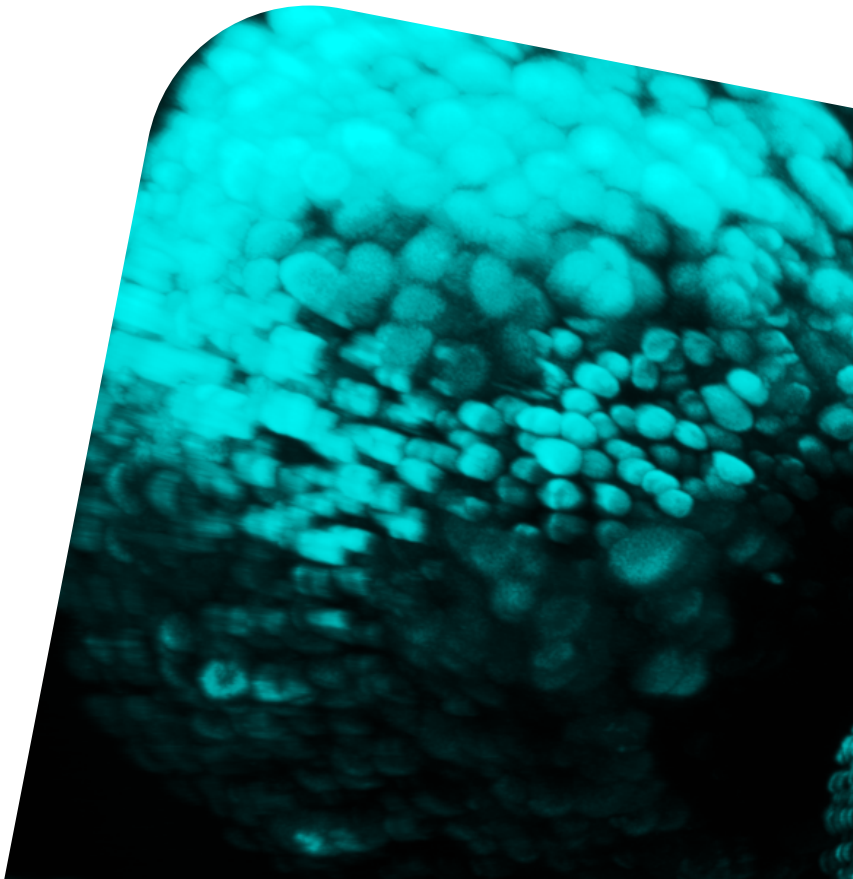
Multicenter oncology trials increasingly include MRI examinations with apparent diffusion coefficient (ADC) quantification for lesion characterization and follow-up. However, the repeatability and reproducibility (R&R) limits above which a true change in ADC can be considered relevant are poorly defined. 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

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https://www.scopus.com/inward/record.uri?eid=2-s2.0-85103726086&doi=10.1016%2fj.neuchi.2021.03.001&partnerID=40&md5=25df1570aa09f9696485eb21ff555196

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https://www.scopus.com/inward/record.uri?eid=2-s2.0-85103714264&doi=10.1016%2fj.rmed.2021.106383&partnerID=40&md5=9912253cf32fbbdf4221b0ad59b19e65

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85106613304&doi=10.1016%2fj.diii.2021.03.005&partnerID=40&md5=11a8a18ae40deb4be7d674bf45587199

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=bdcc81079f0b43836306bc18ba807ac7

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

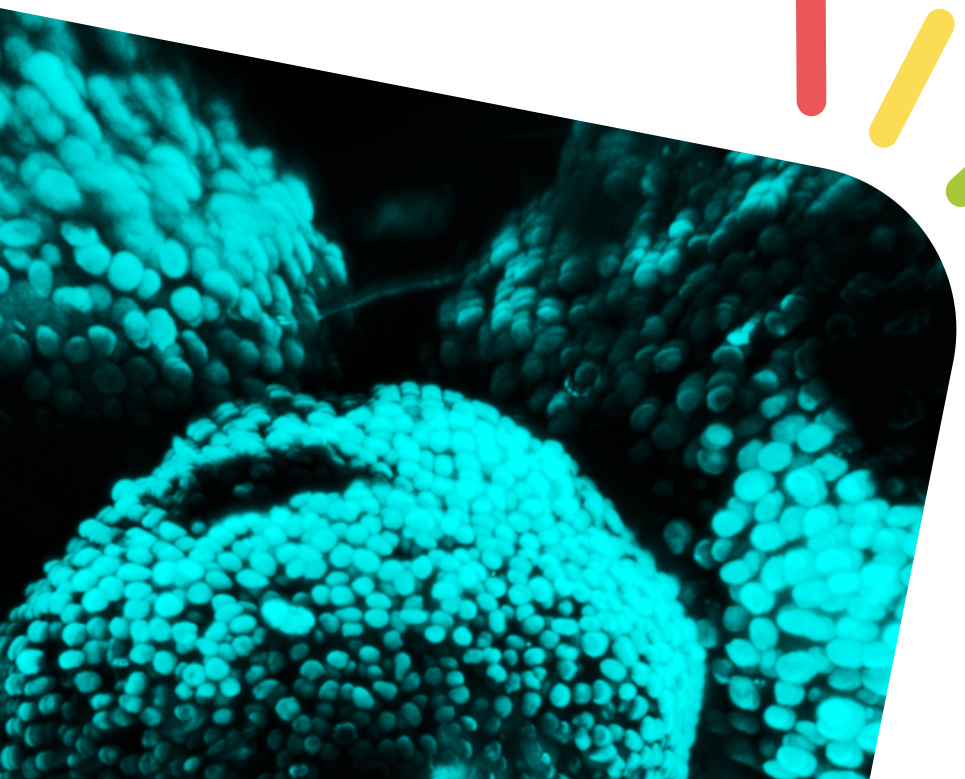
https://www.scopus.com/inward/record.uri?eid=2-s2.0-85096167115&doi=10.1016%2fj.ejrad.2020.109412&partnerID=40&md5=8f528bcadaa240ee24d44565ab4bc3fc

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=56e2a6ab198942925172a5e300f54cc7

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85099032937&doi=10.1007%2fs00330-020-07522-0&partnerID=40&md5=138f5f98362e21606f74cb48e0438343

https://www.scopus.com/inward/record.uri?eid=2-s2.0-85116160126&doi=10.1055%2fs-0041-1730401&partnerID=40&md5=ce569a59d7f5d4c30630a0e5c86c668b



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.

Research Poles

POLE OF RHEUMATOLOGY RESEARCH (RUMA)

Patrick Durez, MD

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Samantha Genten, Laboratory assistant
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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 clininical, 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.

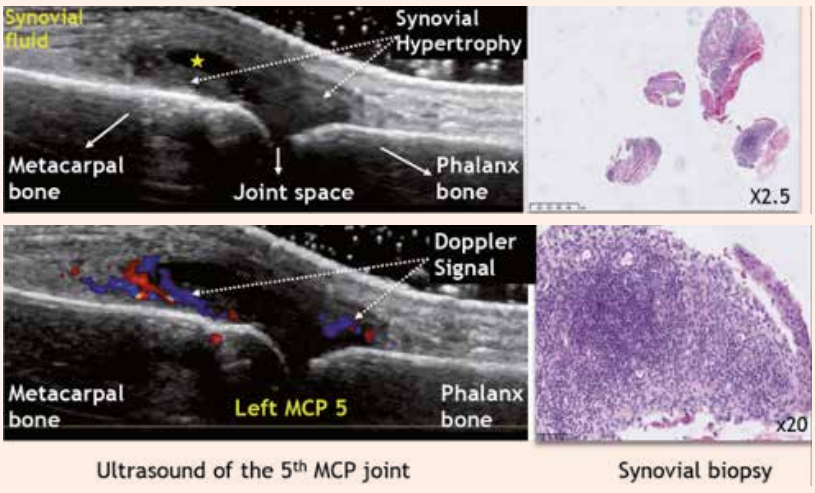

Figure 1: Ultrasound-guided synovial biopsies deliver material for a better stratification of RA patients based on the identification of specific molecular profiles in the tissue.

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.

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Research Projects

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

Immune suppression during particle-induced diseases

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

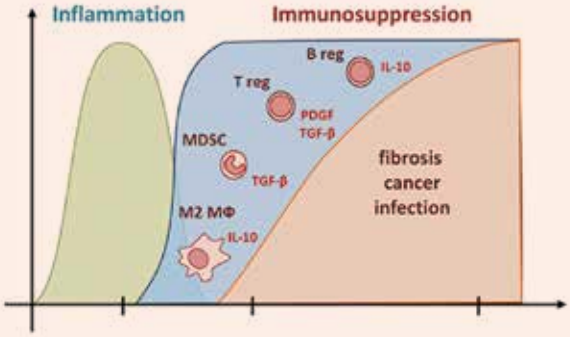

Figure 1: ***Pathological functions of persistent immunosuppressive cells and mediators during long-term responses to particles.*** Unresolved Immunosuppression (in blue) represents an alternative event during the responses to particles. According to this new pathological pathway, fibrogenesis, and carcinogenesis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

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

The sensing arsenal of phagocytes capable of recognizing inhaled particles

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

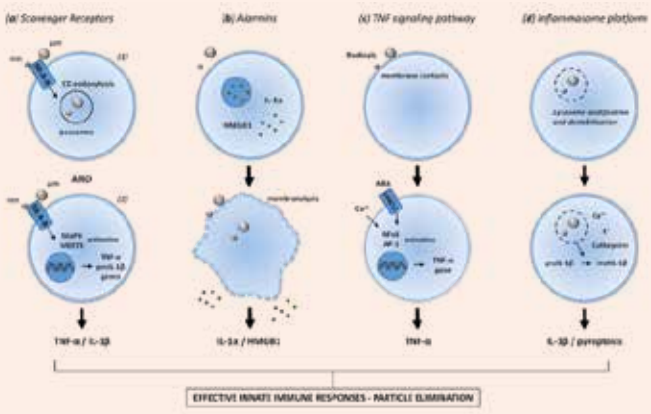

Figure 2: ***Early sensing and alerting processes are combined and mutually linked in response to inhaled particles.*** (a1) Micrometric (μm) and nanometric (nm) particles are internalized by phagocytes through the scavenger receptors (SR) A and B and clathrin-dependent (CD) endocytosis. (a2) Particle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

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)

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Research Projects

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

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

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

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

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

Each phenotype is a potential therapeutic target. Impairment in pharyngeal dilator muscle control and function during sleep could be treated by Electro-stimulation of the hypoglossal nerve or has been assessed in our center (IMTHERA III). Currently a Phase III trial is ongoing. Specif-

ic training of oropharyngeal muscles on OSA syndrome has also been evaluated, and results show a significant improvement in a majority of patients unfortunately compliance to these exercises was poor of compliance to specific measures in postural OSA. We are also studying a prosthetic device allowing a muscles tongue training in order to counteract the bad compliance to the exercises.

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

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

Physiology of exercise and airway deposition.

The research projects of the group « Exercise, aerosol and physiotherapy » were based on the deposition of nebulized particles in the lung and in the nasal area. New tools for functional exercise capacity and for comorbidities related to lung diseases evaluation were also investigated. Studies were mainly performed in neuromuscular patients and in children to validate these new tools. The dysphagia was one of the main topics this last year. Exercise training programs and telemedicine were tested in new indications (cancer, congenital heart disease, sleep apnea, Ehlers-Danlos). Rehabilitation in cancer and exercise during radiotherapy were investigated. The place of exercise and rehabilitation in patients with lung cancer was largely investigated. Physiological effects of airway clearance techniques were also studied by the group including original tools of evaluations (electrical impedance tomography, lung clearance index). Their effect on the physical properties of sputum was quantified by the use of rheology. Moreover, the oxygen delivery was recently included in the thematic of the group with studies about high flow and way of delivery. In the particular context of the COVID-19 pandemic, the field of interest of the group was mainly focused on the consequences of the virus on oxygen need and functional exercise capacity.

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

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

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

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

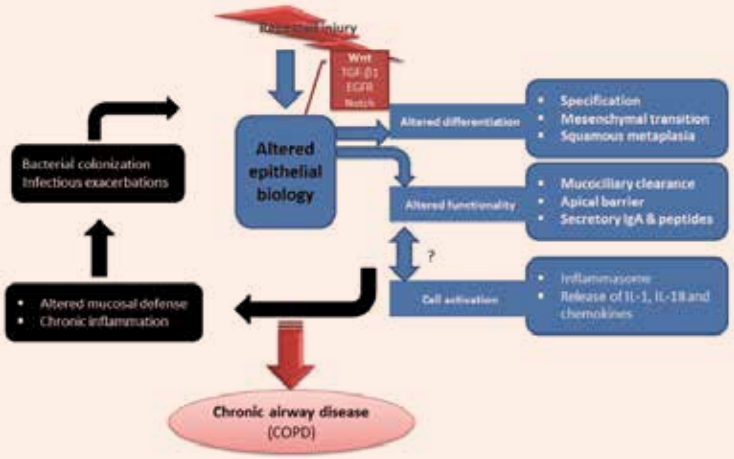


Figure 1. Hypothesis of airway epithelial cell dysregulation in COPD. The epithelium, repeatedly activated by cigarette smoke may become persistently dysregulated through aberrant signalling, with altered differentiation and functionality. This leads to impaired frontline defense against pathogens, further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

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

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

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

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

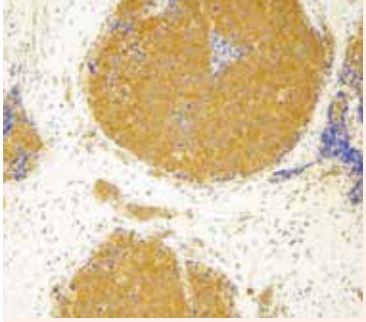


Figure 2. ***Total FAK expression in a small-cell lung cancer tissue.*** Two tissue microarrays consisting of SCLC tissues coming from 85 patients were incubated with an antibody against total FAK (A-17). In this figure is displayed a representative image of SCLC tumor with moderate total FAK expression.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

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

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

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

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

PUBLICATIONS 2021 (SELECTION)

PHYSIOLOGY AND SLEEP MEDECINE

Audag N, Liistro G, Goubau C, Vandervelde L, **Poncin W**, Toussaint M, et al. Screening for oropharyngeal dysphagia in adult patients with neuromuscular diseases using the Sydney Swallow Questionnaire. Muscle Nerve 2021;64(3):277-84.

Derasse M, Lefebvre S, **Liistro G, Reychler G**. Chest Expansion and Lung Function for Healthy Subjects and Individuals With Pulmonary Disease. Respir Care 2021;66(4):661-8.

Ribeiro Baptista B, Faure M, **Mwenge GB**, Morelot-Panzini C, Straus C, Similowski T. Feasibility of a Hypoxic Challenge Test Under Noninvasive Ventilation Versus Oxygen in Neuromuscular Patients with Chronic Respiratory Insufficiency. High Alt Med Bio 2021 Sep;22(3):346-350.

EXERCISE AND AEROSOL MEDICINE

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. 2021 Dec 8:1-8. doi: 10.1007/s10877-021-00784-z. Online ahead of print. PMID: 34877626

Prieur G, Beaumont M, Delorme M, **Combret Y,** Medrinal C, Hilfiker R, Bonnevie T, Gravier FE, Smondack P, Lamia B, **Reychler G**. Short-term effects of menthol on walking dyspnoea in patients with COPD: a randomised, single blinded, cross-over study, ERJ Open Res. 2021 Oct 25;7(4):00450-2021. doi: 10.1183/23120541.00450-2021. eCollection 2021 Oct. PMID: 34708112

Latiers F, Vandenabeele M, **Poncin W, Reychler G**.

Prevalence and risk factors of musculoskeletal pain in patients with chronic obstructive pulmonary disease: A systematic review, Clin Respir J. 2021 Dec;15(12):1286-1301. doi: 10.1111/crj.13443. Epub 2021 Sep 9. PMID: 34459145

Reychler G, Straeten CV, Schalkwijk A, **Poncin W**. Effects of surgical and cloth facemasks during a submaximal exercise test in healthy adults, Respir Med. 2021 Sep;186:106530. doi: 10.1016/j.rmed.2021.106530. Epub 2021 Jul 6. PMID: 34273733

Iturain Barrón A, Quintana Riera S, **Reychler G**. The 3 Minute Step Test is a validated field test to evaluate the functional exercise capacity in children aged 6 to 12, Respir Med Res. 2021 Nov;80:100833. doi: 10.1016/j.resmer.2021.100833. Epub 2021 Jun 4. PMID: 34147867

Reychler G, De Backer MM, **Piraux E, Poncin W**, Caty G. Physical therapy treatment of hypermobile Ehlers-Danlos syndrome: A systematic review, Am J Med Genet A. 2021 Oct;185(10):2986-2994. doi: 10.1002/ajmg.a.62393. Epub 2021 Jun 19. PMID: 34145717

Martin I, Braem F, Baudet L, **Poncin W**, Fizaine S, **Aboubakar F, Froidure A, Pilette C, Liistro G**, De Greef J, Yildiz H, Pothen L, Yombi JC, Belkhir L, **Reychler G**. Follow-up of functional exercise capacity in patients with COVID-19: It is improved by telerehabilitation, Respir Med. 2021 Jul;183:106438. doi: 10.1016/j.rmed.2021.106438. Epub 2021 Apr 30. PMID: 33964817

Combret Y, Boujibar F, Gennari C, Medrinal C, Sicinski S, Bonnevie T, Gravier FE, Laurans M, Marguet C, Le Roux P, Lamia B, **Prieur G, Reychler G**. Measurement properties of the one-minute sit-to-stand test in children and adolescents with cystic fibrosis: A multicenter randomized cross-over trial, PLoS One. 2021 Feb 12;16(2):e0246781. doi: 10.1371/journal.pone.0246781. eCollection 2021. PMID: 33577586

Combret Y, Prieur G, Hilfiker R, Gravier FE, Smondack P, Contal O, Lamia B, Bonnevie T, Medrinal C. The relationship between maximal expiratory pressure values and critical outcomes in mechanically ventilated patients: a post hoc analysis of an observational study, Ann Intensive Care. 2021 Jan 13;11(1):8. doi: 10.1186/s13613-020-00791-4. PMID: 33438092 Free PMC article.

Reychler G, Cabillic M, **Morales Mestre N, Poncin W, Audag N**, Caty G. Predictive model for the 1-minute sit-to-stand test in healthy children aged 6 to 12 years, Ann Phys Rehabil Med. 2021 Mar;64(2):101410. doi: 10.1016/j.rehab.2020.05.013. Epub 2020 Jul 16. PMID: 32590075

MUCOSAL IMMUNOLOGY AND EPITHELIAL BIOLOGY IN INFLAMMATORY OR FIBROTIC DISEASES:

Plante-Bordeneuve T, Pilette C, Froidure A. the epithelial-immune crosstalks in pulmonary fibrosis. Frontiers Immunol 2021 Jun 24;12:691227. IF 6.429

Carlier FM, de Fays C, Pilette C. Epithelial barrier dysfunction in chronic respiratory diseases. Frontiers Physiol 2021 Jun 24;12:691227. IF 4.134

De Greef J, Scohy A, Zech F, **Aboubakar F, Pilette C, Gerard L**, Pothen L, Yildiz H, Belkhir L, Yombi JC. Determinants of IgG antibodies kinetics after severe and critical COVID-19. J Med Virol. 2021 Sep;93(9):5416-5424.

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 JC, Ghaye B. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respir Med. 2021 May;181:106383.

Gerard L, Marylene Lecocq; Caroline Bouzin, Delphine Hoton, Gregory Schmidt, Joao Pinto Pereira, Virginie Montiel, **Thomas Plante-Bordeneuve**, Pierre-François Laterre, **Charles Pilette**. Expression of Angiotensin-Converting Enzyme and Angiotensin-Converting Enzyme 2 in COVID-19 and in COVID-unrelated Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2021; 204(9):1024-103 (accepted on 28 July). IF (2020): 21.405

Porsbjerg C, Anke H. Maitland-van der Zee, Guy Brusselle, Giorgio Walter Canonica, Alvar Agusti, Rosa Faner, Claus F. Vogelmeier, Martijn Nawijn, Maarten van denBerge, Franca Rusconi, **Charles Pilette**, Valeria Ramiconi, Courtney Coleman, Rekha Chaudhuri, Kian Fan Chung, Jadwiga Wedzicha, Sejla Saglani, Marc P. Van der Schee, Liam Heaney, Arnaud Bourdin, Graham Roberts, Ratko Djukanovic, Piotr Kuna, Maceij Kupczyk, Judith Axmann, Heribert Staudinger, Graham W. Clarke, Sven Erik Dahlen, Chris Brightling. 3TR: a pan-European cross-disease research consortium aimed at improving personalised biological treatment of asthma and COPD. European Respiratory Journal 2021; Oct 21;58(4):2102168.

Collin AM, Lecocq M, Detry B, Carlier FM, Bouzin C, de Sany P, Hoton D, Verleden S, **Froidure A, Pilette C**, **Gohy S**. Loss of ciliated cells and altered airway epithelial integrity in cystic fibrosis. J Cyst Fibros 2021 Oct 14:S1569-1993(21)01424-7.

Gohy S, Moeremans A, **Pilette C, Collin A**. Immunoglobulin A Mucosal Immunity and Altered Respiratory Epithelium in Cystic Fibrosis. Cells 2021 Dec 20;10(12):3603. IF: 6.600

Vlastos I, Mullol J, **Hox V**, Doulaptsi M, Seys S, Hellings P, Prokopakis E. Multidisciplinary Care for Severe or Uncontrolled Chronic Upper Airway Diseases. Curr Allergy Asthma Rep. 2021 Apr 1;21(4):27. doi: 10.1007/s11882-021-01004-z.

Klimek L, Jutel M, Bousquet J, Agache I, Akdis CA, **Hox V**, Gevaert P, Tomazic PV, Rondon C, Cingi C, Toppila-Salmi S, Karavelia A, Bozkurt B, Förster-Ruhrmann U, Becker S, Chaker AM, Wollenberg B, Mösges R, Huppertz T, Hagemann J, Bachert C, Fokkens W. Management of patients with chronic rhinosinusitis during the COVID-19 pandemic-An EAACI position paper. Allergy. 2021 Mar;76(3):677-688. doi: 10.1111/all.14629.

Addison AB, Wong B, Ahmed T, Macchi A, Konstantinidis I, Huart C, Frasnelli J, Fjaeldstad AW, Ramakrishnan VR, **Rombaux P**, Whitcroft KL, Holbrook EH, Poletti SC, Hsieh

JW, Landis BN, Boardman J, Welge-Lüssen A, Maru D, Hummel T, Philpott CM. Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. J Allergy Clin Immunol. 2021 May;147(5):1704-1719. doi: 10.1016/j.jaci.2020.12.641.

Wiszniewska M, Dellis P, van Kampen V, Suojalehto H, Munoz X, Walusiak-Skorupa J, Lindstrom I, Merget R, Romero-Mesones C, Sastre J, Quirce S, Mason P, Rifflart C, Godet J, de Blay F, **Vandenplas O**, on behalf of the European network for the PHenotyping of OCcupational ASthma. Characterization of occupational eosinophilic bronchitis in a multicenter cohort of subjects with work-related asthma symptoms. J Allergy Clinical Immunol Pract 2021;9:937-44 e4. doi: 10.1016/j.jaip.2020.08.056. (IF 2019: 7.550)

Migueres N, Debaille C, Walusiak-Skorupa J, Lipińska-Ojrzanowska A, Munoz X, van Kampen V, Suojalehto H, Suuronen K, Seed M, Lee S, Rifflart C, Godet J, de Blay F, **Vandenplas O**, on behalf of the European network for the PHenotyping of OCcupational ASthma (E-PHOCAS). Occupational asthma caused by quaternary ammonium compounds: A multicenter cohort study. J Allergy Clinical Immunol Pract 2021;9:3387-3395. doi: 10.1016/j.jaip.2021.04.041. (IF 2019: 7.550)

Bousquet J, Pfaar O, Agache I, Bedbrook A, Akdis CA, Canonica GW, ... **Vandenplas O**, ... ARIA-EAACI care pathways for allergen immunotherapy in respiratory allergy. Clinical and Translational Allergy 2021;11(4):e12014. doi: 10.1002/clt2.12014. (IF 2019: 4.232)

Bousquet J, Anto JM, Bachert C, Haahtela T, Zuberbier T, Czarlewski W,. ..... Vandenplas O, ...

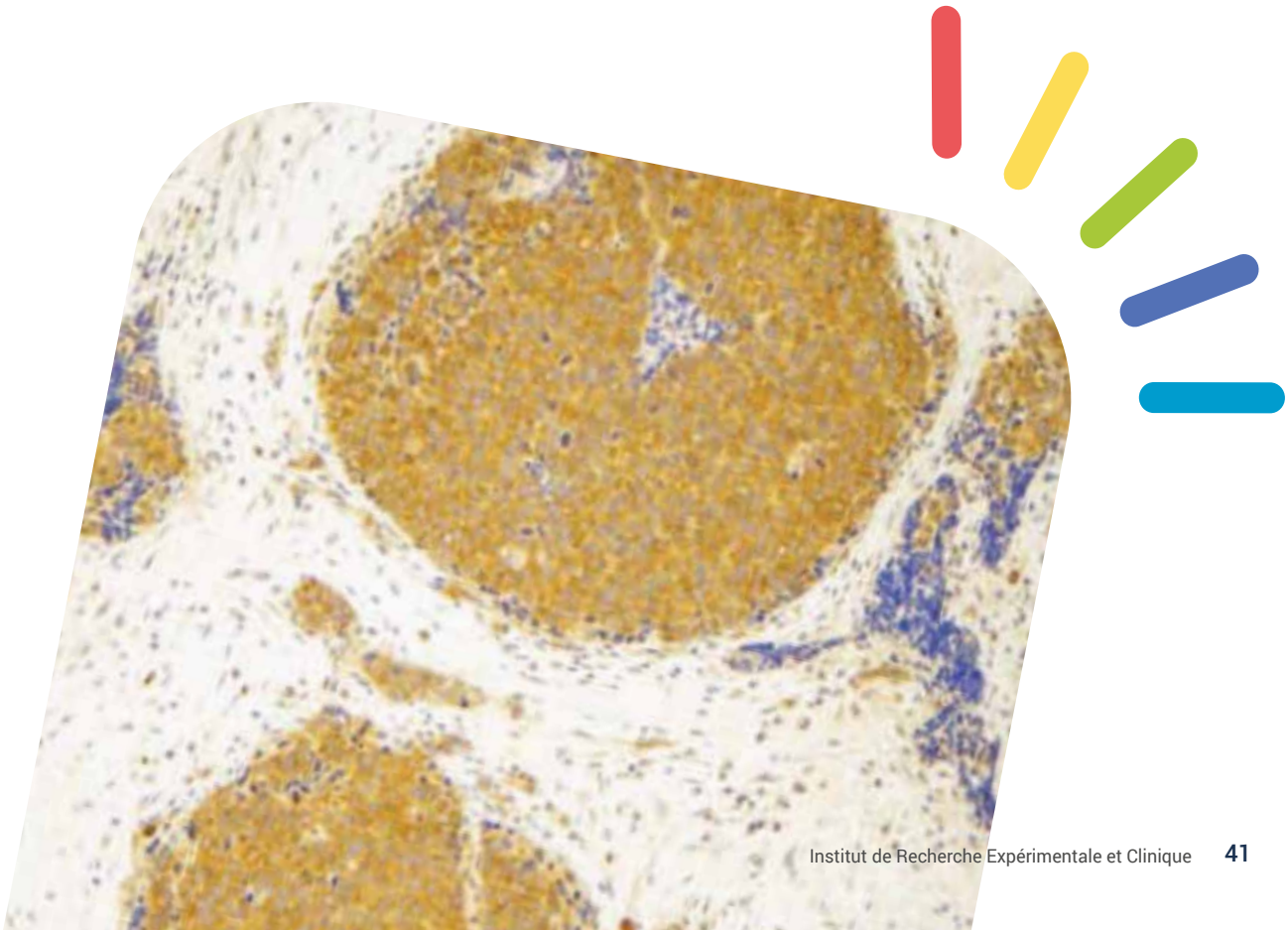
ARIA digital anamorphosis: Digital transformation of health and care in airway diseases from research to practice. Allergy 2021;76(1):168-90. Doi: 10.1111/all.14422. (IF 2019: 6.771)

EPITHELIAL BIOLOGY IN CANCER:

Van Damme H, Dombrecht B, Kiss M, Roose H, Allen E, Van Overmeire E, Martens L, Murgaski A, Bardet PMR, Kancheva D, Bolli E, Schmoetten M, Elkrim Y, Dooley J, Schwarze JK, Tacke F, Movahedi K, Vandamme N, Neyns B, **Ocak S**, Scheyltjens I, **Aboubakar Nana F**, Merchiers P, Laoui D and Van Ginderachter JA. Therapeutic depletion of CCR8+ tumor-infiltrating regulatory T cells elicits antitumor immunity and synergizes with anti-PD-1 therapy. J Immunother Cancer 2021 Feb;9(2):e001749. doi: 10.1136/jitc-2020-001749

Aboubakar Nana F, Ocak S. Targeting BRAF activation as acquired resistance mechanism to EGFR tyrosine kinase inhibitors in EGFR-mutant non-small-cell lung cancer. Pharmaceutics 2021 Sep 15;13(9):1478. doi: 10.3390.

Ocak S, Tournoy K, Berghmans T, Demedts I, Durieux R, Janssens A, Moretti L, Nackaerts K, **Pieters T**, Surmont V, Van Eycken L, Vrijens F, Weynand B, van Meerbeeck JP. Lung cancer in Belgium. J Thorac Oncol. 2021 Oct;16(10):1610-1621. doi: 10.1016/j.jtho.2021.07.022



ACUTE MEDICINE

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

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

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

This 2021 year was particularly demanding for clinicians working in acute medicine due to the Covid 19 infection. This report will focus attention on research paper devoted to severe coronavirus disease, concerning various themes like the challenge of ventilator-associated pneumonia, the place of antibiotics, the role of Interleukin 7 immunotherapy, and the management of thrombosis including pulmonary embolism.

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Geoffrey Horlait, MD
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Improvement of the understanding of sepsis

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

PF. Laterre co-authored a study devoted to selepressin, a selective vasopressin type 1a receptor agonist which increases arterial pressure and has the potential to reduce vascular leakage and pulmonary edema. This trial showed promising results for selepressin by rapidly replacing norepinephrine while maintaining adequate blood pressure, and by improving fluid balance and shortening the time of mechanical ventilation (1). PF. Laterre and X.Wittebolle coordinated a phase 2 clinical trial on the safety and efficacy of Nangibotide, which is a specific TREM-1 inhibitor that tempered deleterious host-pathogens interactions, restored vascular function, and improved survival, in animal septic shock models. The positive results in 49 randomized patients encourage further evaluation of Nangibotide and further exploration of plasma sTREM-1 concentrations as a predictive efficacy biomarker in septic shock.

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

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

Management of thrombosis in the COVID 19 area

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

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

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

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

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

Cardiopulmonary resuscitation and the role of cerebral saturation

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

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

Management of lung and respiratory parameters

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

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

A. Dive, P.Bulpa and X. Wittebole participated in a Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE). In secondary analysis, the study could demonstrate that: 1. hyperoxemia and excess oxygen use were both prevalent in early ARDS but were most often non-sustained. No relationship was found between hyperoxemia or excessive oxygen use and patient outcome;; 2. No evidence was found for benefit or harm with hypercapnia.

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

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

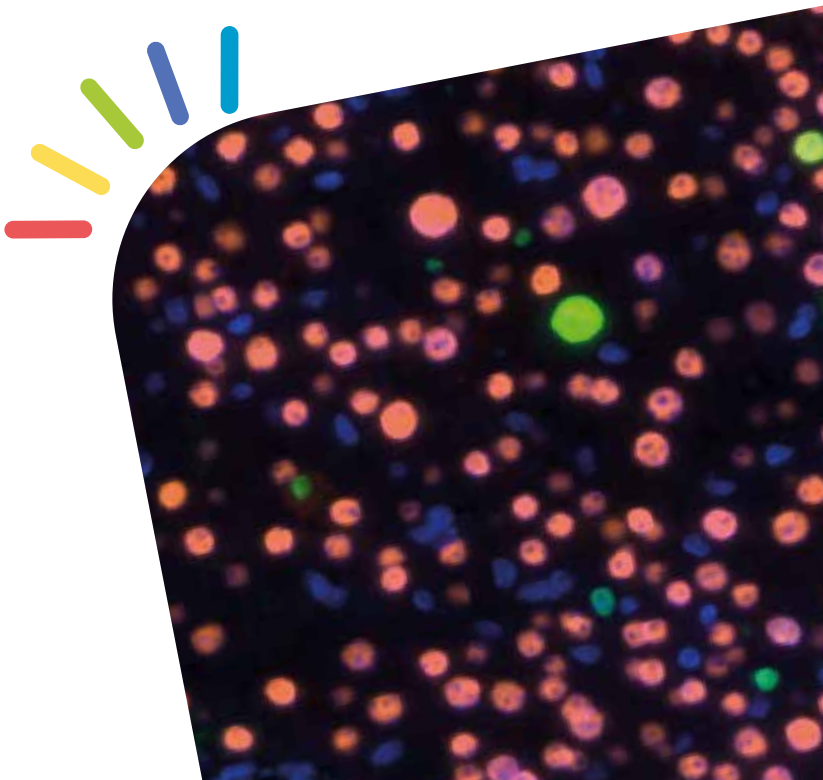
Patients suffering from COVID-19 infection may develop severe ARDS. In that context, G. Horlait contributed in the COVADIS study which observed a large and prolonged use of Neuromuscular blocking agent (NMBA). After adjustment, a prolonged course of NMBA was not associated with a lower rate of extubation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

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

Managing acute life-threatening poisoning

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

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



REFERENCES 2021

Angus DC, **Laterre PF**, Lewis RJ; SEPSIS-ACT Investigators. Selepressin for Patients With Septic Shock-Reply. JAMA. 2020 Feb 18;323(7):667-668. (I.F. 2019 : 45.540)

François B, **Wittebole X**, Ferrer R, Mira JP, Dugernier T, Gibot S, Derive M, Olivier A, Cuvier V, Witte S, Pickkers P, Vandenhende F, Garaud JJ, Sánchez M, Salcedo-Magguilli M, **Laterre PF**. Nangibotide in patients with septic shock: a Phase 2a randomized controlled clinical trial. Intensive Care Med. 2020 Jul;46(7):1425-1437

Lafon, Thomas Cazalis, Marie-Angélique Vallejo, Christine Tazarourte, Karim Blein, Sophie **Laterre PF Verschuren F** et al. TRIAGE study group. Prognostic performance of endothelial biomarkers to early predict clinical deterioration of patients with suspected bacterial infection and sepsis admitted to the emergency department. Ann Intensive Care. 2020 Aug 12;10(1):113

Pierre-François Laterre, et al. A phase Ib/IIa, randomised, double-blind, multicentre trial to assess the safety and efficacy of expanded Cx611 allogeneic adipose-derived stem cells (eASCs) for the treatment of patients with community-acquired bacterial pneumonia admitted to the intensive care unit. BMC Pulm Med. 2020; 20: 309. Published online 2020 Nov 25. doi: 10.1186/s12890-020-01324-2

Hardy M, Lecompte T, Douxfils J, **Lessire S**, Mullier F Management of the thrombotic risk associated with COVID-19: Guidance with the haemostasis laboratory. Thrombosis Journal (IF 2.57) volume 18, Article number: 17 (2020) . Septembre 2020

Hardy M, **Lessire S**, Kasikci S, Lecompte T, Mullier F Effects of Time-Interval since Blood Draw and of Anticoagulation on Platelet Testing (Count, Indices and Impedance Aggregometry) : A Systematic Study With Blood from Healthy Volunteers.. J Cin Med (IF 5,688). Aug 2020

Hardy M, **Michaux I**, **Lessire S**, Douxfils J, Dogné JM, Bareille M, Horlait G, **Bulpa P**, Chapelle C, Laporte S, Testa S, Jacqmin H, Lecompte T, **Dive A**, Mullier F.Prothrombotic disturbances of hemostasis of patients with severe COVID-19: A prospective longitudinal observational study. Thromb Res. 2020 Oct 24;197:20-23. doi: 10.1016/j.thromres.2020.10.025

Soumagne T, Lascarrou JB, Hraiech S, **Horlait G**, et al. Factors Associated With Pulmonary Embolism Among Coronavirus Disease 2019 Acute Respiratory Distress Syndrome: A Multicenter Study Among 375 Patients. Crit Care Explor. 2020 Jun 25;2(7):e0166

Lessire, S., **Dincq, A.-S.**, Siriez, R., Douxfils, J., Mullier, F. Assessment of low plasma concentrations of apixaban in the periprocedural setting. International Journal of Laboratory Hematology, 2020, 42(4), pp. 394–402

Xhaët, O., Deceuninck, O., Robaye, B., ...**Gourdin, M.**, Blommaert, D.A circular mapping catheter is not mandatory for isolating pulmonary veins during paroxysmal atrial fibrillation ablation with radiofrequency. Journal of Interventional Cardiac Electrophysiology, 2020

Dubois, V., Fostier, G., Dutrieux, M., Eloy, P., Dubois, P.E. Philips Intellivue NMT module: precision and performance improvements to meet the clinical requirements of neuromuscular block management Journal of Clinical Monitoring and Computing, 2020, 34(1), pp. 111–116

Genbrugge C, Eertmans W, Salcido DD. Monitor the quality of cardiopulmonary resuscitation in 2020. Curr Opin Crit Care. juni 2020;26(3):219–27

Genbrugge C, Jorissen E, Eertmans W, Jans F, Boer W, Dens J, e.a. Increase in regional cerebral saturation after elective electrical cardioversion of atrial fibrillation is only transient and without beneficial effects on neuropsychological functioning: cerebral saturation during electrical cardioversion. J Clin Monit Comput. februari 2021;35(1):165–73

Madotto, Fabiana Rezoagli, Emanuele Pham, Tài Schmidt, Marcello McNicholas, Bairbre **Bulpa, Pierre [UCL] Dive**, **Alain-Michel [UCL] Wittebole, Xavier**. LUNG SAFE Investigators and the ESICM Trials Group. Hyperoxemia and excess oxygen use in early acute respiratory distress syndrome: insights from the LUNG SAFE study. Crit Care. 2020 Mar 31;24(1):125

Ranieri VM, **Bulpa P**, **Dive A** INTEREST Study Group. Effect of Intravenous Interferon β-1a on Death and Days Free From Mechanical Ventilation Among Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA 2020 Feb 17. doi: 10.1001/jama.2019.22525. (IF 2019: 45.540)

François B, **Laterre PF**, Luyt CE, Chastre J. The challenge of ventilator-associated pneumonia diagnosis in COVID-19 patients. Crit Care. 2020 Jun 5;24(1):289

Scohy A, **Gérard L**, **Wittebole X**, **Collienne C**, **Laterre PF**. Co-infections in COVID-19 critically ill and antibiotic management: a prospective cohort analysis. Crit Care. 2020 Jul 9;24(1):410

Laterre PF, François B, **Collienne C**, **Hantson P**, Jeannet R, Remy KE, Hotchkiss RS. Association of Interkeukin 7 immunotherapy with Lumphocyte Counts Among Patients with severe Coronavirus Diesase 2019 (Covid 19). JAMA Netw Open. 2020 Jul 1;3(7)

Courcelle R, Gaudry S, Serck N, Blonz G, Lascarrou JB, Grimaldi D, **Horlait G** on behalf the COVADIS study group. Neuromuscular blocking agents (NMBA) for COVID-19 acute respiratory distress syndrome: a multicenter observational study. Critical care 2020: 24; 446. DOI : 10.1186/s13054-020-03164-2 (IF 2019 : 5.44)

Wiart A, Castanares-Zapatero D, **Wittebole X**, Maerckx G, David G, **Laterre PF**, **Gerard L**. Prone positioning in spontaneously breathing patients with moderate or severe ARDS under invasive mechanical ventilation: a monocentric retrospective study. Respir Care 2020

Warnant A, **Gerard L**, Haufroid V, **Hantson P.** Coma Reversal After Intravenous Lipid Emulsion Therapy in a Trazodone-Poisoned Patient. Clin Neuropharmacol. 2020 Jan/Feb;43(1):31-33

REGENERATIVE MEDICINE

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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).

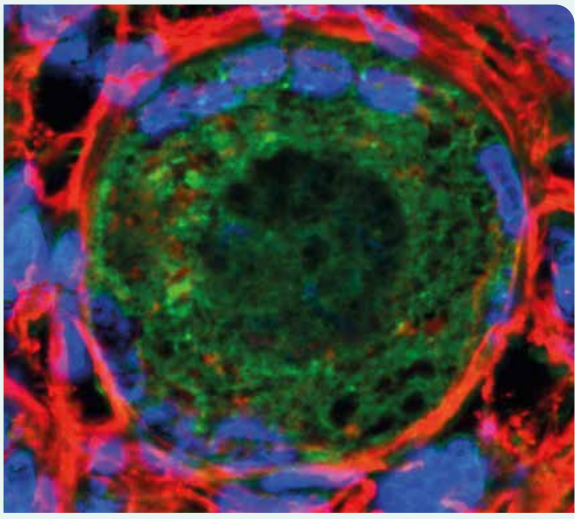

Figure1. FOXO1

Isolation and characterization of human ovarian cell populations

H. Vlieghe, P. Asiabi, C.A. Amorim

Theca cells play a pivotal role in follicle development and production of female steroids. Indeed, follicles cannot go further than the secondary stage without them. As follicles isolated from ovarian tissue are mainly primordial and primary ones and are not yet surrounded by theca cells, we must ensure that once in the engineered ovary, they will be able to recruit isolated ovarian cells to differentiate into theca cells. However, these processes are poorly known in the human ovary. Recently, our group has shown that stromal cells isolated from postmenopausal ovaries could be differentiated in vitro into theca cells (4). Now, our goal is to unveil this population of precursor theca cells and assess if this differentiation process would occur in the engineered ovary.

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).

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 a porcine bioengineered testicular scaffold to incorporate sorted (excluding cancer cells) and propagated human testicular cells with a view to increase knowledge on the SSC niche in vitro, and to achieve in vivo differentiation of SSCs after transplantation (7). 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 (8). Experiments using human ITT to generate hydrogel based -TOs are currently ongoing.

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)

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Research Projects

For two decades, Vascularized Composite tissue Allotransplantation (VCA) has represented a true revolution in the field of reconstructive surgery. However, the indications for such transplants remain very limited (fewer than 200 cases for limbs, 45 cases for the face, world-wide) because of the need for an immunosuppressive treatment, burdened with significant systemic complications. In addition, recent results from long-term follow-up have shown a limited life-span of the graft, due to chronic vascular rejection. Aiming to overcome these limitations, tissue engineering applied to VCA, in a new reconstructive approach we called Vascularized Composite tissue Engineering (VCE), could represent a whole new alternative. Conventional decellularization technique, already used for simple tissues, such as the dermis or heart valves, allows to remove cells and antigens from a native tissue by physical and / or chemical agents, while preserving the extracellular matrix (ECM) and associated growth factors, the complexity of which is currently impossible to be reproduced, even with the most advanced synthesis techniques (i.e. 3D bioprinting). The major limitation here is the size and complexity of the treated tissues, restricted by the passive diffusion of the products, and the absence of an accessible vascular tree. The so-called "perfusion-de-cellularization / recellularization" (PDR) technique, previously described for solid organs (i.e. heart, kidney, lung), represents a variant of conventional bath-stirring techniques: by infusing the products directly by the arterial pedicle, it thus enables the production of very complex matrices, with a preserved, accessible and transplantable vascular system. In a new paradigm, the approach is to take the graft from the donor, transfer it to the laboratory where it will be decellularized, then recellularized into a bioreactor, partially or totally, with the recipient's cells. Thus, transplantation in the recipient will be performed with a totally immunologically compatible graft, removing current allotransplantation barriers. Our work initially hypothesized that the PDR technique could be applied to composite tissues, despite their great variability and tissue associations, characteristic of the body parts grafts. This required the development of a multi-purpose protocol, with recellularization-specific strategies and necessary bioreactors.

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

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

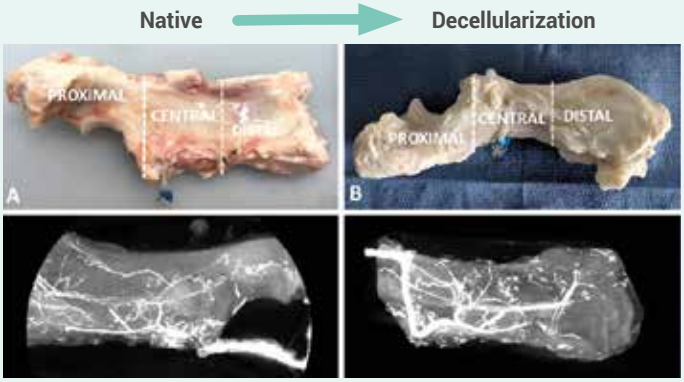
BACKGROUND: Durable reconstruction of critical bone defects still remains a surgical challenge despite the many bone autologous and substitute options available. In this study, we investigate, as a new alternative, the possibility to create a living bone allograft, based on the perfusion/decellularization/recellularization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

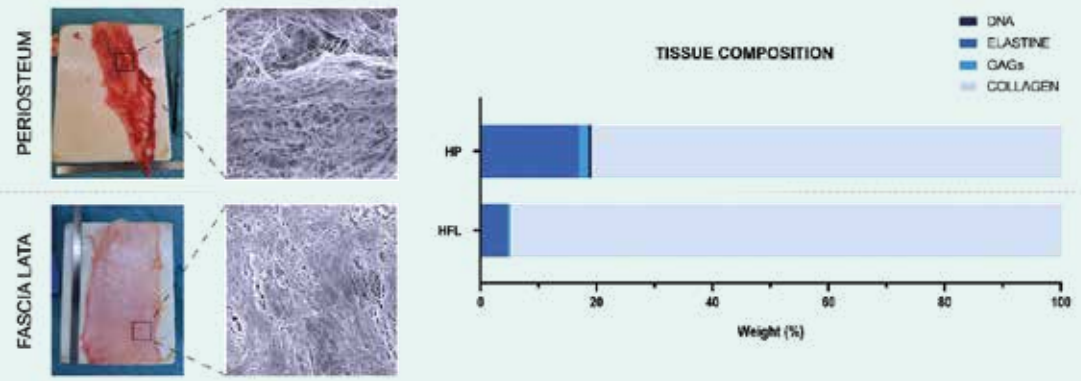
Creation of bioengineered vascularized spleen matrix as an endocrine cell support

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.

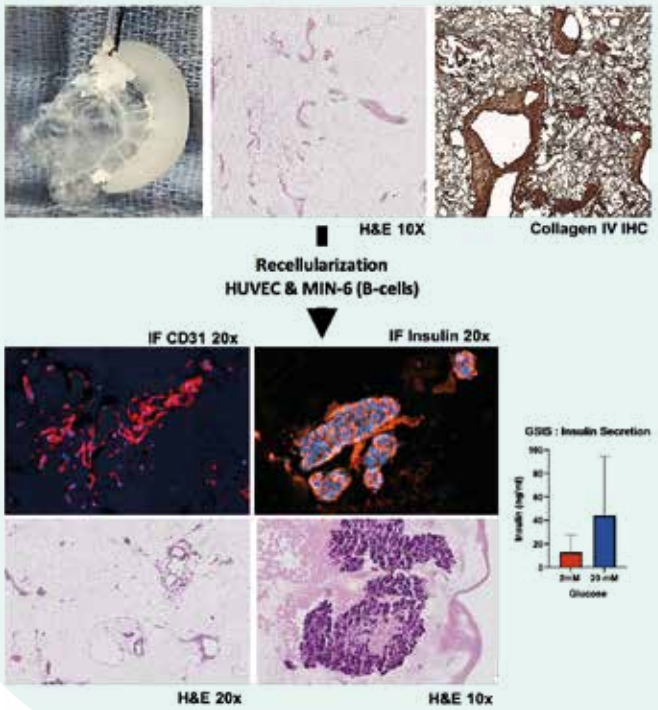
Rat spleen grafts were decellularized with detergent perfusion in their pedicle. DSM was characterized by DNA, collagen, elastin, GAG and residual SDS quantification, as well as histology and immunohistochemistry. PrestoBlue Cell Viability Assay evaluated cytotoxicity in 12 days static culture of MIN-6 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.

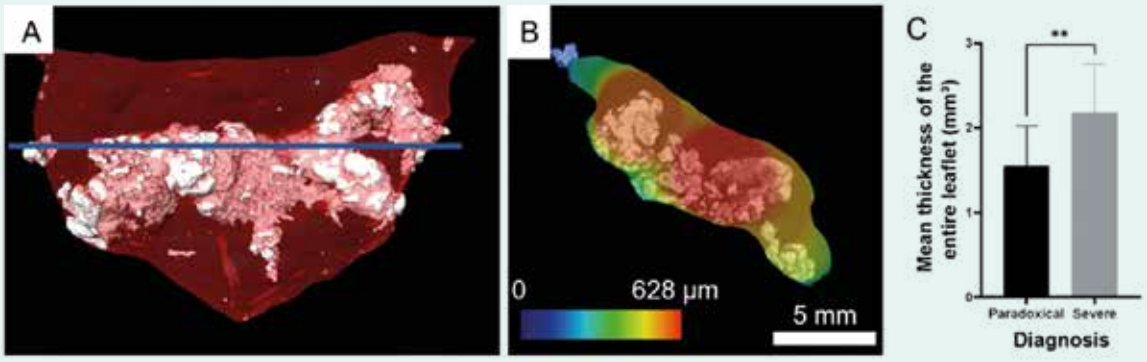
Top: Macroscopic, histological and immunohistochemical (Collagen I) aspects of decellularized spleen. Bottom: Recellularization of spleen matrix with HUVEC (left) and MIN-6 (right) and insulin secretion tested with 2mM and 20mM glucose.



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

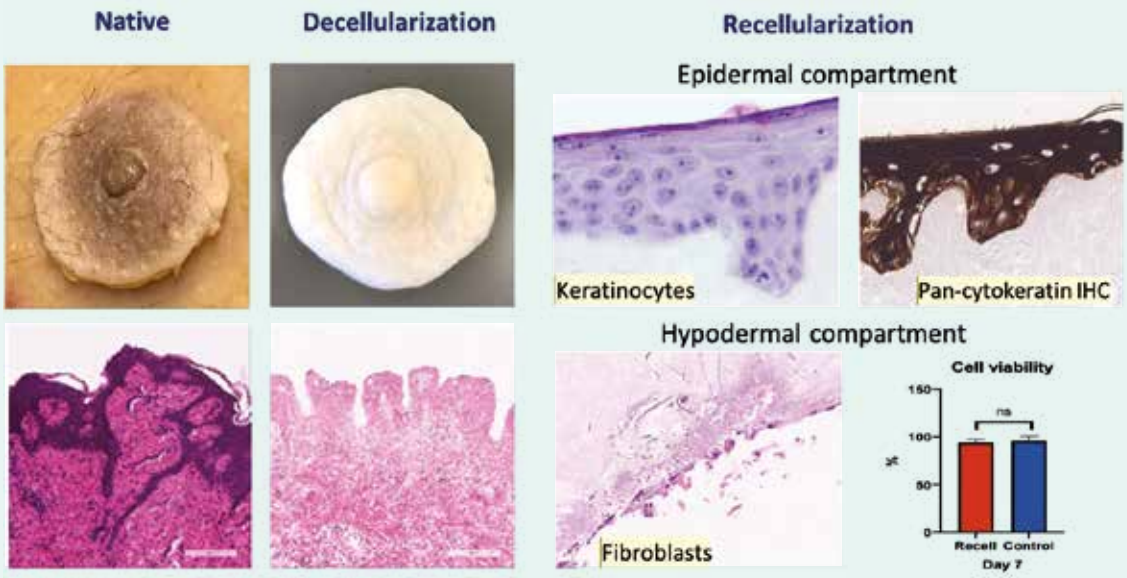
Louis Maistriaux, Vincent Foulon, Maud Coyette, Catherine Behets, Pierre Gianello, Yves Poumay, Benoît Lengelé

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



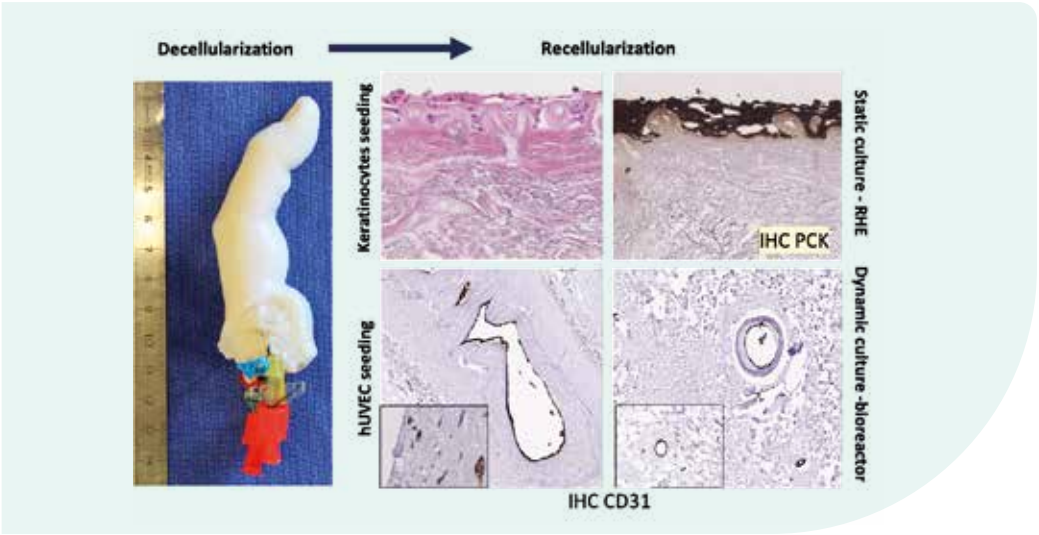
Left: Macroscopic and histological aspect of native and decellularized nipple-areolar complex (NAC). Right: Histological aspect of recellularized NAC matrix with keratinocytes on epidermal side (top) and fibroblasts on hypodermal side (bottom).

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.

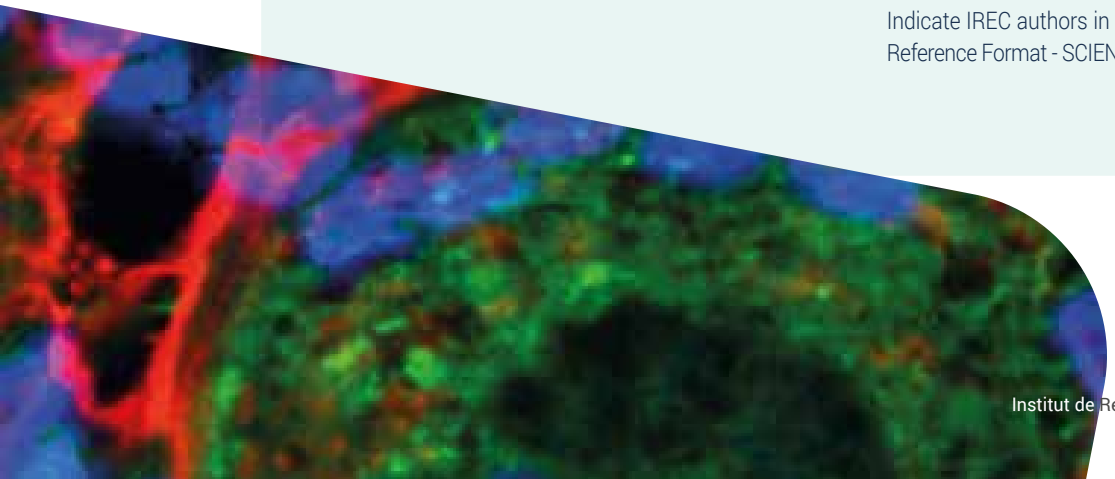


REFERENCES 2021

Duisit, Jérôme ; Maistriaux, Louis ; Bertheuil, Nicolas ; Lellouch, Alexandre. Engineering Vascularized Composite Tissues by Perfusion Decellularization/Recellularization: Review. In: Current Transplantation Reports, Vol. 8, p. 44-56 (2021). doi:10.1007/s40472-021-00317-2. http://hdl.handle.net/2078.1/244105

Leyssens, Lisa ; Pestiaux, Camille ; Kerckhofs, Greet. A Review of Ex Vivo X-ray Microfocus Computed Tomography-B*ased Characterization of the Cardiovascular System. In: International Journal of Molecular Sciences,* Vol. 22, no.6, p. 3263 (2021). doi:10.3390/ijms22063263. http://hdl.handle.net/2078.1/244890

Indicate IREC authors in BOLD, non-IREC authors not BOLD. Reference Format - SCIENCE



METABOLISM, OBESITY AND DIABETES

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

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

The teams of Olivier Feron, Pierre Sonveaux and Cyril Corbet at the Pole of Pharmacology and Therapeutics (FATH) are dedicated to the study of cancer metabolism, including the metabolic plasticity of cancer cells with respect to fluctuating microenvironmental conditions (e.g., hypoxia, uneven bioavailability of nutrients, exposure to therapy and acidosis), tumor progression to metastasis, cancer-host cells relationships and resistance to treatments. Most research programs include translational aspects, with the aim of identifying new anticancer approaches targeting tumor metabolism.

The team of JP Thissen at the EDIN Pole is currently investigating the mechanisms of cancer cachexia, with the aim to identify new targets to mitigate muscle atrophy and to develop new biomarkers for its diagnosis.

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

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Research Projects

HORMONES AND METABOLISM

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

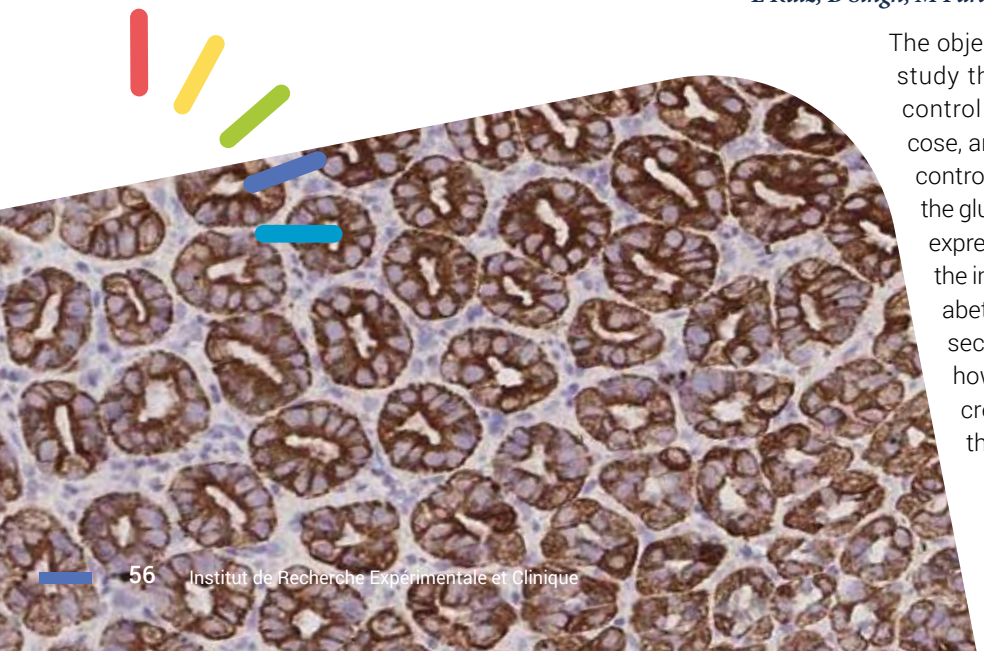
ENDOCRINE PANCREATIC ISLET CELLS IN HEALTH AND DISEASE

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

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, Zhou Y

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



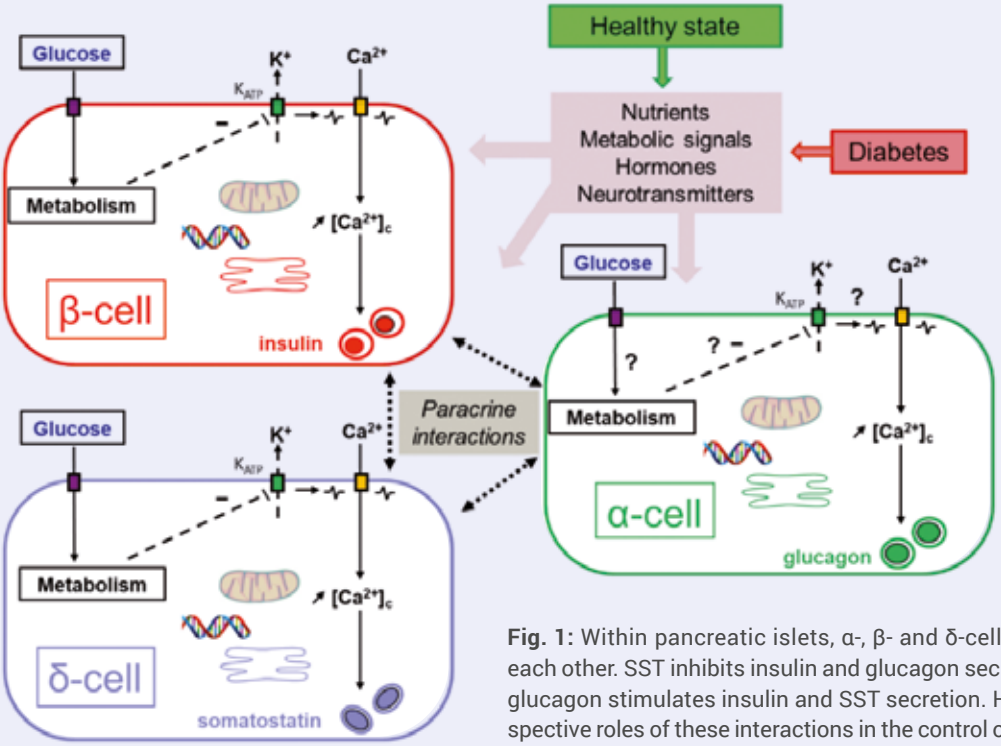


Fig. 1: Within pancreatic islets, α-, β- and δ-cells interact with each other. SST inhibits insulin and glucagon secretion, whereas glucagon stimulates insulin and SST secretion. However, the respective roles of these interactions in the control of islet hormone secretion by nutrients is only partly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

Control of the subcellular redox state in pancreatic β-cells

O Bekhet, AF Close, M Craigie, Y Hajj Hassan, JC Jonas

We use protein-based fluorescent redox probes targeted to specific subcellular compartments to measure the acute and long-term effects of nutrients on β-cell subcellular redox state, and we test their role in the stimulation of insulin secretion and its alterations in diabetes. This project led to several publications, including a review written together with Leticia P Roma from Universität des Saarlandes (Homburg/Saar) (Fig.2).

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

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

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

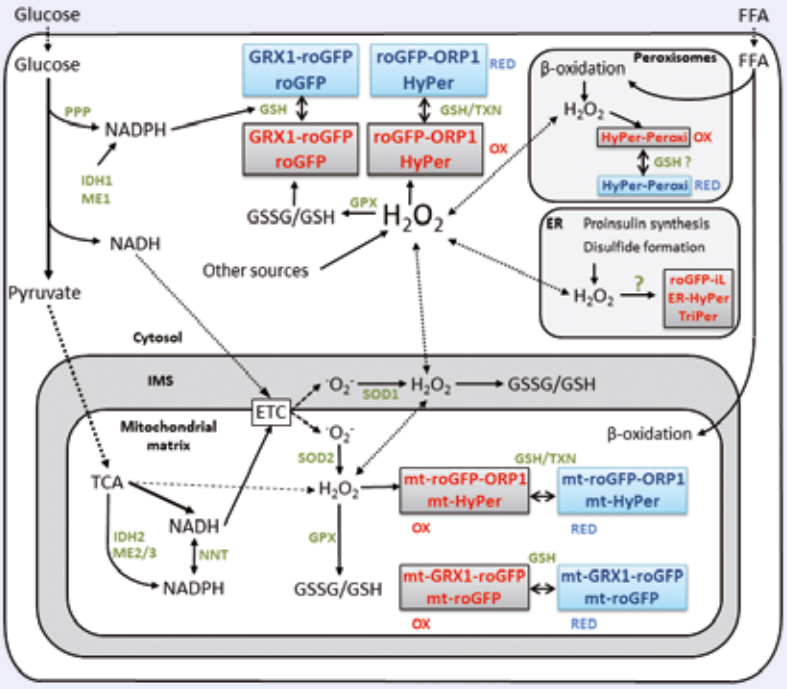


Fig. 2: Compartmentalized redox reactions and the genetically encoded probes used to measure the impact of nutrient metabolism on β-cell subcellular redox state. Schematic representation of the pathways by which nutrients affect NADH, NADPH, and GSH. Enzymes are shown in green, oxidized (OX) probes in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

Decreasing inflammation within islets of Langerhans

P Lysy, O Pollé, S Welsch

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

Improved secretory function of transgenic InsGLP-1Ser8M3R porcine islets

P Gianello, N Mourad, M Ramirez

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)."

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, 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 development 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. We are now exploring the role of the gut microbiota in the BA alterations observed, by investigating the bacterial BA-metabolizing activities.

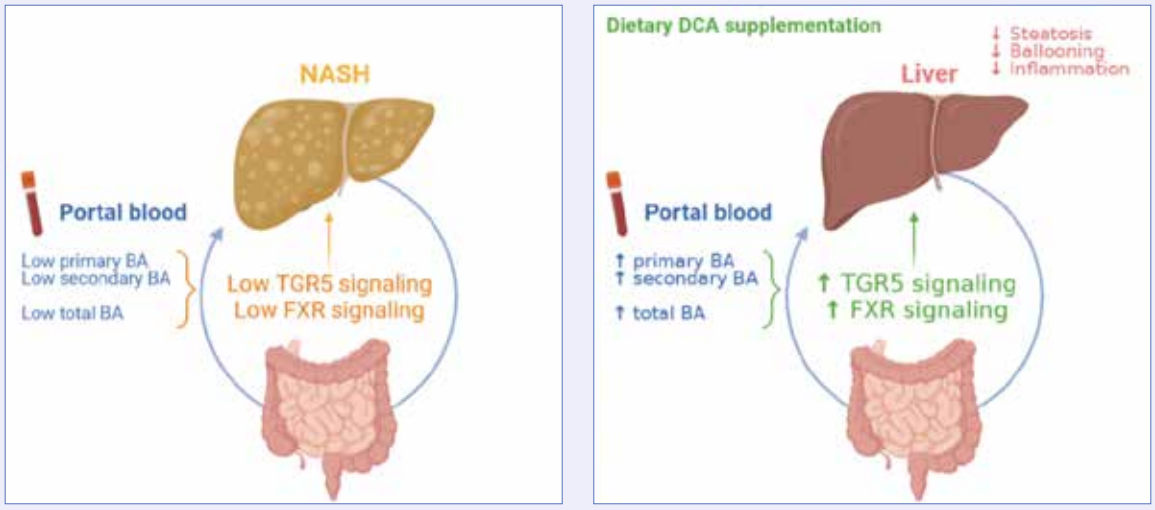
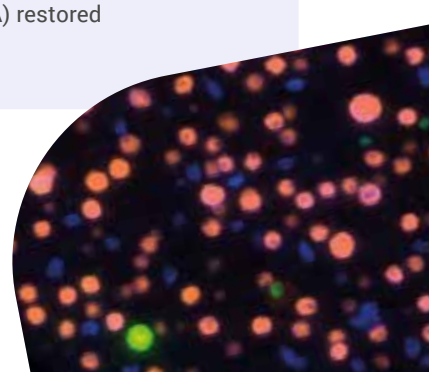


Fig. 3: BA contribute to the development of NASH in mice. In foz/foz mice fed a high fat diet and in C57BL6/J mice fed a western and high fructose diet, the enterohepatic BA composition and signaling are altered compared to their respective controls. Supplementation of the diet with deoxycholic acid (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.

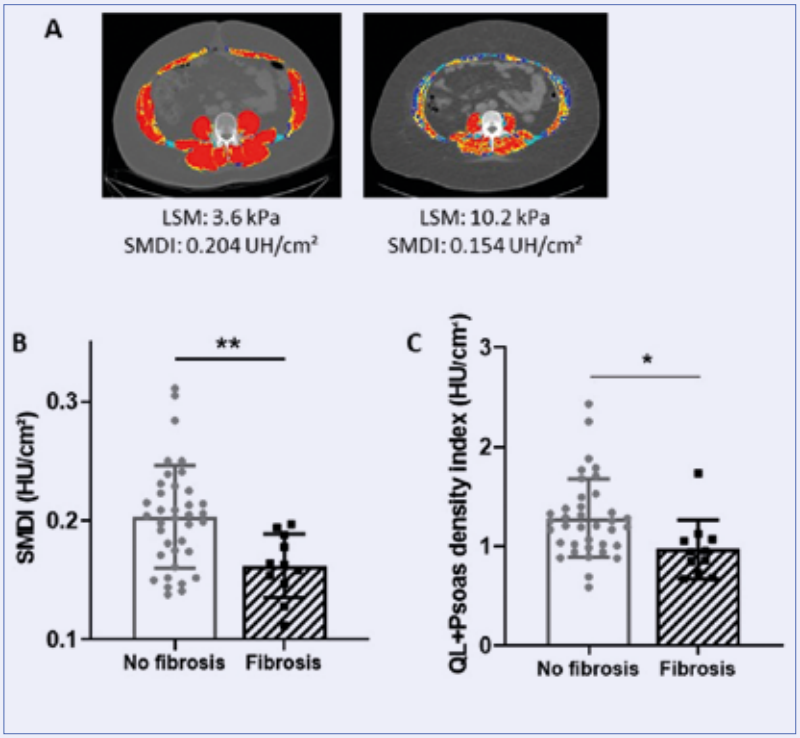
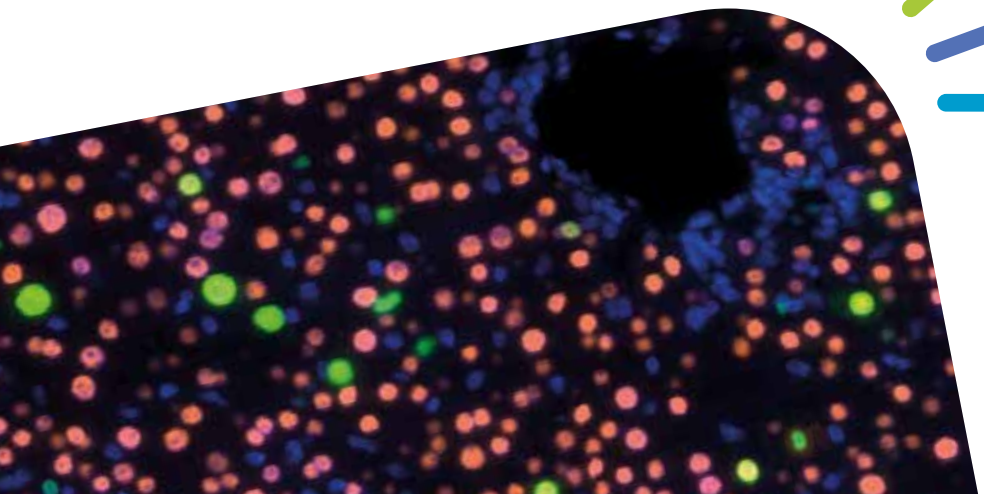
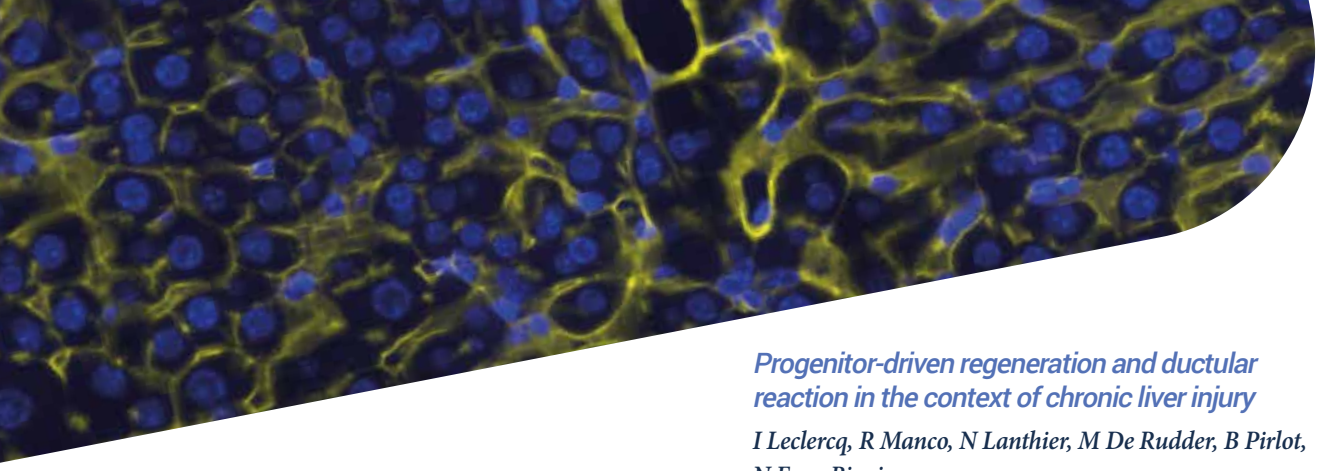


Fig. 4: Analysis of body composition by CT scan according to liver disease severity assessed by elastometry (LSM). (A) Comparison of two patients with MAFLD and obesity: on the left, normal muscle density (muscles in red) and absence of fibrosis at liver elasticity; on the right, low muscle density (muscles 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 microRNAs as a mechanistic link between CVD and MAFLD.





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

P Stärkel, N Lanthier, L Maccioni, S Ravau, B Pirlot

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

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

I Leclercq, R Manco, N Lanthier, M De Rudder, B Pirlot, 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.

Hypoxia for optimal regeneration after extended hepatectomy

I Leclercq, A Dili, M De Rudder, A de Schaetzen, B Pirlot

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.

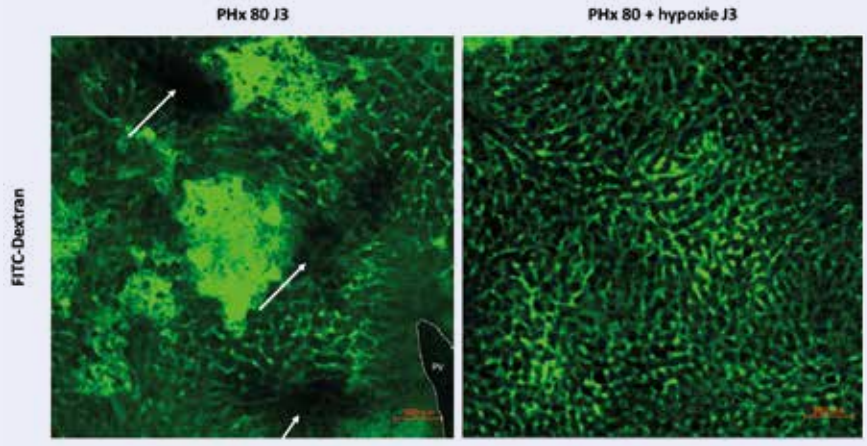


Fig. 5: Hypoxia prevents the appearance of unperfused areas and vascular leaks in the remaining liver parenchyma after small for size hepatectomy . Representative images of liver remnants perfused with FITC-Dextran (green) through the inferior vena cava in normoxia (left panel) and hypoxia (right panel).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

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

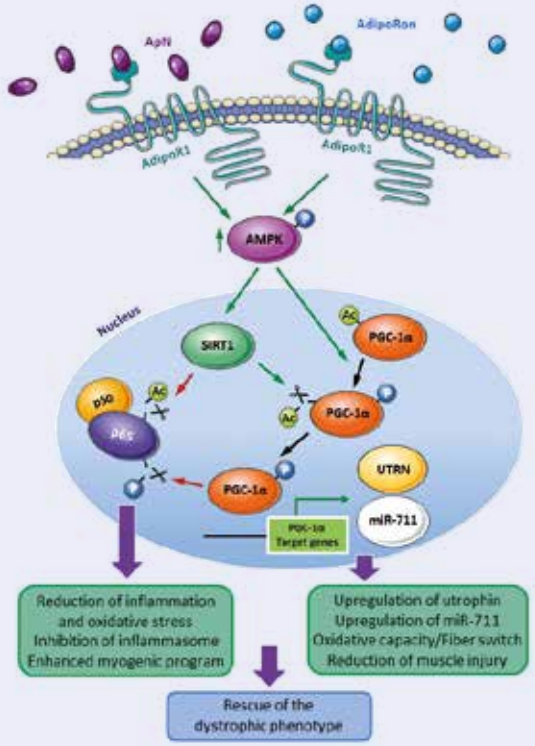


Fig. 6: Signal transduction mediating ApN and AdipoRon protection on dystrophic skeletal muscles: binding to AdipoR1 activates the AMPK/SIRT1/PGC-1α pathway. Briefly, ApN (AdipoRon) leads to AMPK phosphorylation/activation. P-AMPK then phosphorylates PGC-1α and indirectly increases the expression of SIRT1. SIRT1 in turn deacetylates and fully activates PGC-1α. Next, PGC-1α represses NF-κB activity by de-phosphorylation of the p65 subunit, while SIRT1 represses it by deacetylation. This results in upregulation of miR-711 and reduction of inflammation/oxidative stress and muscle injury, improved myogenic program, as well as enhanced utrophin expression, all processes helping rescue the dystrophic phenotype. Green arrow, stimulation; red arrow, inhibition.

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, C Verheyden

Over the past decade, bariatric surgery has been recognized as a therapeutic modality for obesity, but also for type 2 diabetes. We currently characterize the modifications in muscle secretome induced by bariatric surgery and determine their role in the improvement of insulin sensitivity of skeletal muscle and insulin secretion by the B cell. Recent work has identified changes in the expression of several myokines known to control glucose homeostasis.

ADIPOKINES IN METABOLIC AND INFLAMMATORY DISEASES

Adiponectin and its mimics on skeletal muscle

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

The team of S Brichard is mainly involved in the study of hormones secreted by the adipose tissue (adipokines) in metabolic and inflammatory diseases. Their recent discovery that adiponectin receptor activation is beneficial in a model of Duchenne's muscular dystrophy has been recently awarded prizes for the therapeutic perspectives it offers to the patients (Prix Lagast 2020 to M. Abou-Samra). Adiponectin receptor agonists are now also tested in ageing and age-related sarcopenia (Fig.6.)

Human obesity disrupts circadian clock function

E. Maury, L. Noel and SM Brichard

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

CANCER AND METABOLISM

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

JP Thissen, A Loumaye, I Massart, A N Kouakou, 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.

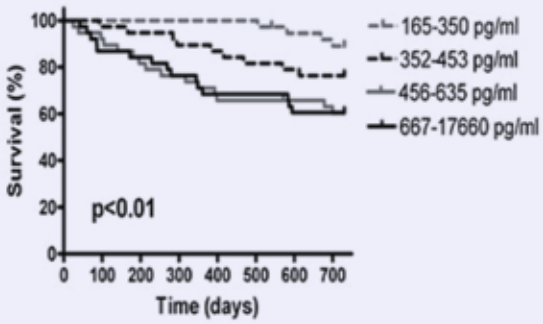


Fig. 7: Kaplan–Meier survival curves according to plasma Activin A levels [quartiles and cut-off statistically determinated (408 pg/mL)] in colorectal or lung cancer patients (n=152).

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

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

Tumor metabolism and metastases

P. Sonveaux

The team of P Sonveaux focuses on three aspects of tumor metabolism: (1) the oxidative pathway of lactate, (2) the metabolic control of (tissue-specific) metastasis, and (3) metabolic resistance to anticancer chemo- and radio- therapies. The team collaboratively develops new drugs targeting cancer metabolism, among which MitoQ is a promising agent to prevent cancer recurrence and metastasis.

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**

REFERENCES 2021

EDIN

Igoillo-Esteve M et *al.*, Exenatide induces frataxin expression and improves mitochondrial function in Friedreich ataxia. *JCI Insight* **5**(2). pii: 134221 (2020).

Roma LP, **Jonas JC**, Nutrient Metabolism, Subcellular Redox State, and Oxidative Stress in Pancreatic Islets and beta-Cells. *J Mol Biol* **432**: 1461-93 (2020).

MAF Close, H Chae, **JC Jonas**, The lack of functional nicotinamide nucleotide transhydrogenase only moderately contributes to the impairment of glucose tolerance and glucose-stimulated insulin secretion in C57BL/6J versus C57BL/6N mice. *Diabetologia* **64**: 2550-2561 (2021)

JY Chan, M Bensellam, RCY Lin, C Liang, K Lee, **JC Jonas**, DR Laybutt, Transcriptome analysis of islets from diabetes-resistant and diabetes-prone obese mice reveals novel gene regulatory networks involved in beta cell compensation and failure. *FASEB J* **35**: e21608 (2021)

Singh, B., Khattab, F., Chae, H., Desmet, L., Herrera, P. L., and Gilon, P. (2021) KATP channel blockers control glucagon secretion by distinct mechanisms: A direct stimulation of alpha-cells involving a [Ca(2+)]c rise and an indirect inhibition mediated by somatostatin. *Mol Metab* **53**, 101268

Sanchez, P. K. M., Khazaei, M., **Gatineau, E.**, Geravandi, S., Lupse, B., Liu, H., Dringen, R., Wojtusciszyn, A., **Gilon, P**., Maedler, K., and Ardestani, A. (2021) LDHA is enriched in human islet alpha cells and upregulated in type 2 diabetes. *Biochem Biophys Res Commun* **568**, 158-166

Boudou, P., Djibre, M., Ibrahim, F., Fellahi, S., **Gilon, P.**, Andreelli, F., Ferre, P., and Boissan, M. (2021) Massive lactic acidosis and ketoacidosis with glucagon deficiency in a chronic alcoholic patient. *Diabetes Metab* **47**, 10117

Abou-Samra M, **Selvais CM**, **Boursereau R**, **Lecompte S**, **Noel L**, **Brichard SM**. AdipoRon, a new therapeutic prospect for Duchenne muscular dystrophy. *J Cachexia Sarcopenia Muscle* **11**(2): 518-533 (2020)

Abou-Samra M, **Selvais CM**, **Dubuisson N**, **Brichard SM**. Adiponectin and its mimics on skeletal muscle: insulin-sensitizers, fat-burners, exercise mimickers, muscling pills … or everything together? *Int J Mol Sci;* **21**(7), 2620 (2020)

Maury E, Navez B, Brichard SM. Circadian clock dysfunction in human omental fat links obesity to metabolic inflammation. *Nat Commun* **12**, 2388 (2021)

Dubuisson N, Versele R, Davis-López de Carrizosa MA, Selvais CM, Brichard SM, Abou-Samra M. Walking down Skeletal Muscle Lane: From Inflammasome to Disease. *Cells* **10**, 3023 (2021)

Bayart JL, Favresse J, Melnik E, Lardinois B, Fillee C., **Maiter D**, **Gruson D** Erroneous thyroid and steroid hormones profile due to anti-streptavidin antibodies. *Clin Chem Lab Med.*57(10):e255–e258 (2019).

Burlacu MC, **Maiter D**, Duprez **T, Delgrange** E. T2-weighted magnetic resonance imaging characterization of prolactinomas and association with their response to dopamine agonists. *Endocrine* **63** :323-331 (2019).

Chanson P, **Maiter D**. The epidemiology, diagnosis and treatment of Prolactinomas: The old and the new. *Best Pract Res Clin Endocrinol Metab.* **33**, 101290 (2019). doi: 10.1016/j.beem.2019.101290

Depommier C, Everard A, Druart C, Plovier H, Van Hul M, Vieira-Silva S, Falony G, Raes J, Maiter D, Delzenne NM, de Barsy M, **Loumaye A**, **Hermans MP**, **Thissen JP**, de Vos WM, Cani PD. Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat Med.* **25**, 1096-1103 (2019)

Fauconnier C, Roy T, Gillerot G, Roy C, **Pouleur AC**, **Gruson D**. FGF23: Clinical usefulness and analytical evolution. C*lin Biochem.* **66**:1–12 (2019).

Favresse J, **Gruson D**, Gheldof D. Comment on "High doses of biotin can interfere with immunoassays that use biotin-strept(avidin) technologies: Implications for individuals with biotin-responsive inherited metabolic disorders". *Mol Genet Metab Rep.* **21**:100506 (2019).

Greaves RF, Bernardini S, Ferrari M, **Gruson D** et al. Key questions about the future of laboratory medicine in the next decade of the 21st century: A report from the IFCC-Emerging Technologies Division. *Clin Chim Acta.* **495**:570–589 (2019).

Gruson D, Helleputte T, Rousseau P. Data science, artificial intelligence, and machine learning: Opportunities for laboratory medicine and the value of positive regulation. *Clin Biochem.***69**:1–7 (2019).

Hemmer A, **Maiter D**, **Buysschaert M**, **Preumont V**. Long-term effects of GLP-1 receptor agonists in type 2 diabetic patients: A retrospective real-life study in 131 patients. *Diabetes Metab Syndr.* **13**, 332-336 (2019).

Hermans MP, **Ahn SA**, **Rousseau M**F. Increased CRP: An extended biomarker of microvascular risk in men with type 2 diabetes. *J Diabetes Complications*. **33**, 107413 (2019)

Hiel S, Bindels LB, Pachikian BD, Kalala G, Broers V, Zamariola G, Chang BPI, Kambashi B, Rodriguez J, Cani PD, Neyrinck AM, **Thissen JP**, Luminet O, Bindelle J, Delzenne NM. Effects of a diet based on inulin-rich vegetables on gut health and nutritional behavior in healthy humans. *Am J Clin Nutr.* **109**,1683-1695 (2019).

Maiter D. Management of Dopamine Agonist-Resistant Prolactinoma. *Neuroendocrinology.* **109**, 42-50 (2019).

Servais T, London F, **Donckier JE**. Graves' disease as a first autoimmune manifestation of a stiff person syndrome. *Ann Endocrinol (Paris).* **80**(2):134-136 (2019).

Trouillas J, **Delgrange E**, Wierinckx A, Vasiljevic A, Jouanneau E, Burman P, Raverot G. Clinical, pathological, and molecular factors of aggressiveness in lactotroph tumours. *Neuroendocrinology* **109** :70-76 (2019).

Assi M, Pirlot B, Stroobant V, **Thissen JP**, Jacquemin P. A Novel KRAS Antibody Highlights a Regulation Mechanism of Post-Translational Modifications of KRAS during Tumorigenesis. Int J Mol Sci. **21**(17):6361 (2020).

Hiel S, Gianfrancesco MA, Rodriguez J, Portheault D, Leyrolle Q, Bindels LB, Gomes da Silveira Cauduro C, Mulders MDGH, Zamariola G, Azzi AS, Kalala G, Pachikian BD, Amadieu C, Neyrinck AM, **Loumaye A**, Cani PD, Lanthier N, Trefois P, Klein O, Luminet O, Bindelle J, Paquot N, Cnop M, **Thissen JP**, Delzenne NM. Link be-

tween gut microbiota and health outcomes in inulin -treated obese patients: Lessons from the Food4Gut multicenter randomized placebo-controlled trial. Clin Nutr. **39**(12):3618-3628 (2020).

Leyrolle Q, Cserjesi R, Mulders MDGH, Zamariola G, Hiel S, Gianfrancesco MA, Rodriguez J, Portheault D, Amadieu C, Leclercq S, Bindels LB, Neyrinck AM, Cani PD, Karkkainen O, Haninheva K, Lanthier N, Trefois P, Paquot N, Cnop M, **Thissen JP**, Klein O, Luminet O, Delzenne NM. Specific gut microbial, biological, and psychiatric profiling related to binge eating disorders: A cross-sectional study in obese patients. Clin Nutr. **S0261-5614**(20)30497-0 (2020).

Massart IS, Paulissen G, **Loumaye A**, **Lause P**, Pötgens SA, Thibaut MM, Balan E, Deldicque L, Atfi A, Louis E, Gruson D, Bindels LB, Meuwis MA, **Thissen JP**. Marked Increased Production of Acute Phase Reactants by Skeletal Muscle during Cancer Cachexia. Cancers (Basel) **12**(11):3221 (2020).

Orioli L, **Hermans MP**, **Thissen JP**, **Maiter D**, **Vandeleene B**, **Yombi JC**. COVID-19 in diabetic patients: Related risks and specifics of management. Ann Endocrinol (Paris) **81**(2-3):101-109 (2020).

Orioli L, Servais T, Belkhir L, Laterre PF, **Thissen JP, Vandeleene B**, **Maiter D**, Yombi JC, **Hermans MP**. Clinical characteristics and short-term prognosis of in-patients with diabetes and COVID-19: A retrospective study from an academic center in Belgium.Diabetes Metab Syndr. **15**(1):149-157 (2020).

Rodriguez J, Hiel S, Neyrinck AM, Le Roy T, Pötgens SA, Leyrolle Q, Pachikian BD, Gianfrancesco MA, Cani PD, Paquot N, Cnop M, Lanthier N, **Thissen JP**, Bindels LB, Delzenne NM. Discovery of the gut microbial signature driving the efficacy of prebiotic intervention in obese patients. Gut. **69**(11):1975-1987 (2020).

Soleimani R, Favresse J, Roy T, **Gruson D**, Fillée C. Macro vitamin B12: an underestimated threat. *Clin Chem Lab Med.* **58**(3):408–415 (2020).

Van Der Schueren B, Gies I, Barea M, Lannoo M, **Beauloye V**, Devlieger R, Dirinck E, Lembo B, Vissers D, Verrijken A, **Thissen JP**. Announcement of an updated Belgian consensus on the assessment and management of obesity. *Acta Clin Belg.* **19**, 1-3 (2020).

De Groote E, Britto FA, Balan E, Warnier G, **Thissen JP**, Nielens H, Sylow L, Deldicque L. Effect of Hypoxic Exercise on Glucose Tolerance in Healthy and Pre-diabetic Adults. Am J Physiol Endocrinol Metab. **320**(1): E43-E54 (2021).

Nachit M, De Rudder M, **Thissen JP,** Schakman O, Bouzin C, Horsmans Y, Vande Velde G, Leclercq IA. Myosteatosis rather than sarcopenia associates with non-alcoholic steatohepatitis in non-alcoholic fatty liver disease preclinical models. J Cachexia Sarcopenia Muscle **12**(1):144-158 (2021).

Thibaut MM, Sboarina M, Roumain M, Pötgens SA, Neyrinck AM, Destrée F, Gillard J, Leclercq IA, Dachy G, Demoulin JB, Tailleux A, Lestavel S, Rastelli M, Everard A, Cani PD, Porporato PE, Loumaye A, **Thissen JP**, Muccioli GG, Delzenne NM, Bindels LB. Inflammation-induced cholestasis in cancer cachexia. J Cachexia Sarcopenia Muscle **12**(1):70-90 (2021)

PEDI

Absil H, Baudet L, **Robert A**, **Lysy PA**. Benefits of physical activity in children and adolescents with type 1 diabetes: A systematic review. *Diabetes Res Clin Pract.* **156**:107810 (2019).

Daems C, **Welsch S**, **Boughaleb H**, et al. Early Treatment with Empagliflozin and GABA Improves β-Cell Mass and Glucose Tolerance in Streptozotocin-Treated Mice. *J Diabetes Res.* **2019**:2813489 (2019).

Oprea A, Bonnet NCG, **Pollé O**, **Lysy PA**. Novel insights into glucocorticoid replacement therapy for pediatric and adult adrenal insufficiency. *Ther Adv Endocrinol Metab.* 2019;10:2042018818821294 (2019)

Tamborlane WV, Barrientos-Pérez M, Fainberg U, et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. *N Engl J Med.* **381**(7):637–646 (2019). In collaborators.

CHEX

Lesari S.,Leclercq I., Joudiou N., Komuta M., Daumerie A., Ambroise J., Dili A., Feza-Bingi N., Xhema D., Bouzin C., Gallez B., Pisani F., Bonaccorsi-Riani E., **Gianello P.**, Selective HIF stabilization alleviates hepatocellular steatosis and ballooning in a rodent model of 70% liver resection. *Clin Sci (Lond)* **135**, 2285-2305 (2021).

Ramirez M, Courtoy G., Kharrat O., de Beukelaer M., **Mourad N.I.**, Guiot Y., Bouzin C ., **Gianello P.**, Semi-automated digital quantification of cellular infiltrates for in vivo evaluation of transplanted islets of Langerhans encapsulated with bioactive materials. X*enotransplantation* **28**, e12704 (2021).

Reys L.L., Vaithilingam V., Sthijns M.M.J.P.E., Soares E., Rademakers T., de Vries R., Mohammed S., de Bont D., Jetten M., Hermanns C., da Silva Filho O.P., Stell A., **Mourad N.I.**, **Gianello P.**, LaPointe V.L.S., Silva S.S., Reis R.L., Silva T.H., van Apeldoorn A.A., Fucoidan hydrogels significantly alleviate oxidative stress and enhance the endocrine function of encapsulated beta cells. Advanced Functional Materials, **31**(35):2011205 (2021).(2019).

GAEN

M. Nachit, M. De Rudder, J. P. Thissen, O. Schakman, C. Bouzin, **Y. Horsmans**, G. Vande Velde, I. **A. Leclercq**, Myosteatosis rather than sarcopenia associates with non-alcoholic steatohepatitis in non-alcoholic fatty liver disease preclinical models. J. *Cachexia. Sarcopenia Muscle.* **12**, 144-158 (2021).

M. M. Thibaut, **J. Gillard**, A. Dolly, M. Roumain, I. **A. Leclercq**, N. M. Delzenne, G. G. Muccioli, L. B. Bindels, Bile Acid Dysregulation Is Intrinsically Related to Cachexia in Tumor-Bearing Mice. *Cancers (Basel).* **13**, 6389 (2021).

M. Nachit, Y. Horsmans, I. Leclercq, Rationale of adding muscle volume to muscle fat infiltration in the definition of an adverse muscle composition is unclear. JHEP Reports. **3**, 100235 (2021).

M. Nachit, W. J. Kwanten, J.-P. Thissen, B. Op De Beeck, L. Van Gaal, L. Vonghia, A. Verrijken, A. Driessen, **Y. Horsmans**, S. Francque, I. **A. Leclercq**, Muscle fat content is strongly associated with NASH: a longitudinal study in patients with morbid obesity. *J. Hepatol.* (2021), doi:10.1016/j.jhep.2021.02.037.

S. E. Minnis-Lyons, S. Ferreira-González, N. Aleksieva, T. Y. Man, V. L. Gadd, M. J. Williams, R. V. Guest, W. Y. Lu, B. J. Dwyer, T. Jamieson, C. Nixon, N. van Hul, F. P. Lemaigre, J. McCafferty, I. **A. Leclercq**, O. J. Sansom, L. Boulter, S. J. Forbes, Notch-IGF1 signaling during liv-

er regeneration drives biliary epithelial cell expansion and inhibits hepatocyte differentiation. *Sci. Signal.* **14** (2021), doi:10.1126/scisignal.aay9185.

M. De Rudder, A. Dili, P. Stärkel, I. A. Leclercq, Critical Role of LSEC in Post-Hepatectomy Liver Regeneration and Failure. *Int. J. Mol. Sci.* **22**, 8053 (2021).

L. Maccioni, I. A. Leclercq, B. Schnabl, **P. Stärkel**, Host Factors in Dysregulation of the Gut Barrier Function during Alcohol-Associated Liver Disease. *Int. J. Mol. Sci.* **22** (2021).

M. M. Thibaut, M. Sboarina, M. Roumain, S. A. Pötgens, A. M. Neyrinck, F. Destrée, J**. Gillard, I. A. Leclercq**, G. Dachy, J. B. Demoulin, A. Tailleux, S. Lestavel, M. Rastelli, A. Everard, P. D. Cani, P. E. Porporato, A. Loumaye, J. P. Thissen, G. G. Muccioli, N. M. Delzenne, L. B. Bindels, Inflammation-induced cholestasis in cancer cachexia. *J. Cachexia. Sarcopenia Muscle.* **12**, 70-90 (2021).

S. Iesari, **I. Leclerc**q, N. Joudiou, M. Komuta, A. Daumerie, J. Ambroise, **A. Dili, N. Feza-Bingi**, D. Xhema, C. Bouzin, B. Gallez, F. Pisani, E. Bonaccorsi-Riani, P. Gianello, Selective HIF stabilization alleviates hepatocellular steatosis and ballooning in a rodent model of 70% liver resection. *Clin. Sci.* **135**, 2285-2305 (2021).

J. Gillard, L. A. Clerbaux, M. Nachit, C. Sempoux, B. Staels, L. B. Bindels, A. Tailleux, **I. A. Leclercq**, Bile acids contribute to the development of non-alcoholic steatohepatitis in mice. *JHEP Reports.* **4**, 100387 (2022).

P. Baldin, M. Van den Eynde, B. Mlecnik, G. Bindea, G. Beniuga, J. Carrasco, N. Haicheur, F. Marliot, L. Lafontaine, T. Fredriksen, **N. Lanthier**, C. Hubert, B. Navez, N. Huyghe, F. Pagès, A. Jouret-Mourin, J. Galon, M. Komuta, Prognostic assessment of resected colorectal liver metastases integrating pathological features, RAS mutation and Immunoscore. *J. Pathol. Clin. Res.* **7**, 27-41 (2021).

M. Nachit, N. Lanthier, J. Rodriguez, A. M. Neyrinck, P. D. Cani, L. B. Bindels, S. Hiel, B. D. Pachikian, P. Trefois, J.-P. Thissen, N. M. Delzenne, A dynamic association between myosteatosis and liver stiffness: Results from a prospective interventional study in obese patients. *JHEP Reports.* **3**, 100323 (2021).

C. Hamoir, **Y. Horsmans, P. Stärkel, G. Dahlqvist, S. Negrin Dastis, N. Lanthier**, Risk of hepatocellular carcinoma and fibrosis evolution in hepatitis c patients with severe fibrosis or cirrhosis treated with direct acting antiviral agents. *Acta Gastroenterol. Belg.* **84**, 25-32 (2021).

N. Lanthier, J. Rodriguez, **M. Nachit**, S. Hiel, P. Trefois, A. M. Neyrinck, P. D. Cani, L. B. Bindels, J. P. Thissen, N. M. Delzenne, Microbiota analysis and transient elastography reveal new extra-hepatic components of liver steatosis and fibrosis in obese patients. *Sci. Rep.* **11** (2021), doi:10.1038/s41598-020-79718-9.

S. I. André-Dumont, N. Lanthier, Quelle alimentation proposer aux patients présentant une stéatohépatite non-alcoolique ? *Nutr. Clin. Métabolisme* (2022), doi:10.1016/j.nupar.2021.11.001.

N. Lanthier, C. Mahiat, S. Henrard, **P. Stärkel**, I. Gilard, I. De Brauwer, P. Cornette, B. Boland, Gastro-intestinal symptoms are associated with a lower in-hospital mortality rate in frail older patients hospitalized for covid-19. *Acta Gastroenterol. Belg.* **84** (2021), p. 135-136.

Q. Leyrolle, R. Cserjesi, M. D.G.H. Mulders, G. Zamariola, S. Hiel, M. A. Gianfrancesco, D. Portheault, C. Amadieu, L. B. Bindels, S. Leclercq, J. Rodriguez, A. M. Neyrinck, P. D. Cani, **N. Lanthier**, P. Trefois, J. Bindelle, N. Paquot, M. Cnop, J. P. Thissen, O. Klein, O. Luminet, N. M. Delzenne, Prebiotic effect on mood in obese patients is determined by the initial gut microbiota composition: A randomized, controlled trial. *Brain. Behav. Immun.* **94**, 289-298 (2021).

L. Spahr, N. Lanthier, M. Tihy, J. L. Frossard, L. Rubbia-Brandt, N. Goossens, Clinical Presentation and Gene Expression of Acute Alcohol-Induced Microvesicular Steatosis Mimicking Alcoholic Hepatitis. *Hepatol. Commun.* **5**, 618-628 (2021).

S. M. Francque, P. Bedossa, V. Ratziu, Q. M. Anstee, E. Bugianesi, A. J. Sanyal, R. Loomba, S. A. Harrison, R. Balabanska, L. Mateva, **N. Lanthier**, N. Alkhouri, C. Moreno, J. M. Schattenberg, D. Stefanova-Petrova, L. Vonghia, R. Rouzier, M. Guillaume, A. Hodge, M. Romero-Gómez, P. Huot-Marchand, M. Baudin, M.-P. Richard, J.-L. Abitbol, P. Broqua, J.-L. Junien, M. F. Abdelmalek, A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. *N. Engl. J. Med.* **385**, 1547-1558 (2021).

Q. Leyrolle, R. Cserjesi, M. D. G. H. Mulders, G. Zamariola, S. Hiel, M. A. Gianfrancesco, J. Rodriguez, D. Portheault, C. Amadieu, S. Leclercq, L. B. Bindels, A. M. Neyrinck, P. D. Cani, O. Karkkainen, K. Hanhineva, **N. Lanthier**, P. Trefois, N. Paquot, M. Cnop, J. P. Thissen, O. Klein, O. Luminet, N. M. Delzenne, Specific gut microbial, biological, and psychiatric profiling related to binge eating disorders: A cross-sectional study in obese patients. *Clin. Nutr.* **40**, 2035-2044 (2021).

N. Lanthier, P. Stärkel, G. Dahlqvist, Muscle mass depletion in chronic liver diseases: An accelerated model of aging or a distinct entity? *Clin. Res. Hepatol. Gastroenterol.* **45**, 101721 (2021).

C. Knudsen, A. M. Neyrinck, Q. Leyrolle, P. Baldin, S. Leclercq, J. Rodriguez, M. Beaumont, P. D. Cani, L. B. Bindels, **N. Lanthier**, N. M. Delzenne, Hepatoprotective Effects of Indole, a Gut Microbial Metabolite, in Leptin-Deficient Obese Mice. J. Nutr. (2021), doi:10.1093/jn/nxab032.

P. Vande Berg, **I. Borbath**, P. Baldin, D. Vande Berg, P. Hainaut, **N. Lanthier**, Granuloma formation within perihepatic lymphadenopathy. *Clin. Res. Hepatol. Gastroenterol.* **45** (2021),, doi:10.1016/j.clinre.2020.07.009.

N. Lanthier, I. Borbath, G. Dahlqvist, B. Delire, O. Dewit, Stéatose métabolique, carcinome hépatocellulaire, prurit cholestatique, encéphalopathie et maladies inflammatoires intestinales : quelles nouveautés en 2020 ? *Louv. Med.* **140**, 108-115 (2021).

M. Salavrakos, P. de Timary, A. Ruiz Moreno, J. P. Thissen, **N. Lanthier**, Fructoholism in adults: The importance of personalised care in metabolic dysfunction-associated fatty liver disease. JHEP Reports. **4** (2022),, doi:10.1016/j.jhepr.2021.100396.

N. Lanthier, P. Stärkel, G. Dahlqvist, Frailty, sarcopenia and mortality in cirrhosis: what is the best assessment, how to interpret the data correctly and what interventions are possible? *Clin. Res. Hepatol. Gastroenterol.* **45**, 101661 (2021).

Ventura-Cots M, Argemi J, Jones PD, Lackner C, El Hag M, Abraldes JG, Alvarado E, Clemente A, Ravi S, Alves A,

Alboraie M, Altamirano J, Barace S, Bosques F, Brown R, Caballeria J, Cabezas J, Carvalhana S, Cortez-Pinto H, Costa A, Degré D, Fernandez-Carrillo C, Ganne-Carrie N, Garcia-Tsao G, Genesca J, Koskinas J, **Lanthier N**, Louvet A, Lozano JJ, Lucey MR, Masson S, Mathurin P, Mendez-Sanchez N, Miquel R, Moreno C, Mounajjed T, Odena G, Kim W, Sancho-Bru P, Warren Sands R, Szafranska J, Verset L, Schnabl B, Sempoux C, Shah V, Shawcross DL, Stauber RE, Straub BK, Verna E, Tiniakos D, Trépo E, Vargas V, Villanueva C, Woosley JT, Ziol M, Mueller S, **Stärkel P**, Bataller R. Clinical, histological and molecular profiling of different stages of alcohol-related liver disease. *Gut.*2022 Jan 6:gutjnl-2021-324295. doi: 10.1136/gutjnl-2021-324295.

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* **14**:2007042 (2022) doi:10.1080/19490976.2021.2007042.

Demir M, Lang S, Hartmann P, Duan Y, Martin A, Miyamoto Y, Bondareva M, Zhang X, Wang Y, Kasper P, Bang C, Roderburg C, Tacke F, Steffen HM, Goeser T, Kruglov A, Eckmann L, **Stärkel P**, Fouts DE, Schnabl B. The fecal mycobiome in non-alcoholic fatty liver disease. J Hepatol. S0168-8278(21)02238-8. (2021) doi: 10.1016/j.jhep.2021.11.029.

Gao B, Zhu Y, Gao N, Shen W, **Stärkel P**, Schnabl B. Integrative Analysis of Metabolome and Microbiome in Patients with Progressive Alcohol-Associated Liver Disease. *Metabolites* **11**(11):766 (2021) doi: 10.3390/metabo11110766.

Leclercq S, Schwarz M, Delzenne NM, **Stärkel P**, de Timary P. Alterations of kynurenine pathway in alcohol use disorder and abstinence: a link with gut microbiota, peripheral inflammation and psychological symptoms. *Transl Psychiatry* **11**(1):503 (2021) doi: 10.1038/s41398-021-01610-5.

Hartmann P, Lang S, Zeng S, Duan Y, Zhang X, Wang Y, Bondareva M, Kruglov A, Fouts DE, **Stärkel P**, Schnabl B. Dynamic Changes of the Fungal Microbiome in Alcohol Use Disorder. *Front Physiol.* **12**:699253 (2021) doi: 10.3389/fphys.2021.699253.

Amadieu C, Leclercq S, Coste V, Thijssen V, Neyrinck AM, Bindels LB, Cani PD, **Piessevaux H, Stärkel P**, de Timary P, Delzenne NM. Dietary fiber deficiency as a component of malnutrition associated with psychological alterations in alcohol use disorder. *Clin Nutr* **40**(5):2673-2682 (2021) doi: 10.1016/j.clnu.2021.03.029.

FATH

Spillier Q, Ravez S, Dochain S, Vertommen D, **Thabault L, Feron O**, Frédérick R. Unravelling the allosteric targeting of PHGDH at the ACT-binding domain with a photoactivatable diazirine probe and mass spectrometry experiments. *Molecules* **26**(2):477 (2021).

Virga F, Cappellesso F, Stijlemans B, Henze AT, Trotta R, Van Audenaerde J, Mirchandani AS, Sanchez-Garcia MA, Vandewalle J, Orso F, Riera-Domingo C, Griffa A, Ivan C, Smits E, Laoui D, Martelli F, Langouche L, Van den Berghe G, **Feron O,** Ghesquière B, Prenen H, Libert C, Walmsley SR, **Corbet C,** Van Ginderachter JA, Ivan M, Taverna D, Mazzone M. Macrophage miR-210 induction and metabolic reprogramming in response to pathogen interaction boost life-threatening inflammation. Sci Adv. **7**(19):eabf0466 (2021).

Vander Linden C, Corbet C, Bastien E, Martherus R, **Guilbaud C**, **Petit L**, Wauthier L, Loriot A, De Smet C, **Feron O**. Therapy-induced DNA methylation inactivates MCT1 and renders tumor cells vulnerable to MCT4 inhibition. *Cell Rep.* **35**(9):109202 (2021).

Dierge E, Debock E, **Guilbaud C, Corbet C**, Mignolet E, Mignard L, **Bastien E**, Dessy C, Larondelle Y, **Feron O**. Peroxidation of n-3 and n-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects. *Cell Metab.* **33**(8):1701-1715 (2021).

Valenti MT, Mottes M, Dalle Carbonare L, **Feron O**. Editorial: Bone Metastases. *Front Oncol.* **11**:741515 (2021).

Vermonden P, Vancoppenolle M, **Dierge E**, Mignolet E, Cuvelier G, Knoops B, Page M, Debier C, **Feron O**, Larondelle Y. Punicic acid triggers ferroptotic cell death in carcinoma cells. *Nutrients* **13**(8):2751 (2021).

Buyse C, Joudiou N, **Corbet C, Feron O**, Mignion L, Flament J, Gallez B. Impact of inhibition of the mitochondrial pyruvate carrier on the tumor extracellular pH as measured by CEST-MRI. *Cancers (Basel)* **13**(17):4278 (2021).

Moghassemi S, Dadashzadeh A, Azevedo RB, **Feron O**, Amorim CA. Photodynamic cancer therapy using liposomes as an advanced vesicular photosensitizer delivery system. *J Control Release.* **339**:75-90 (2021).

Colson A, Sonveaux P, Debieve F, Sferruzzi-Perri A. Adaptations of the human placenta to hypoxia: opportunities for interventions in fetal growth restriction. *Human Reprod. Update* **27**(3):531-569 (2021).

Benyahia Z, Blackman MCNM, Zampieri LX, Capeloa T, Hamelin L, Bedin ML, Vazeille T, Schakman O, **Sonveaux P**. Preclinical in vitro and in vivo characterization of MCT1 inhibitor AZD3965 confirms a safe toxicological profile compatible with breast cancer treatment. *Cancers (Basel)* 13(3):569 (2021).

Thabault L, Liberelle M, Koruza K, Yildiz E, Joudiou N, Messens J, Brisson L, Wouters J, **Sonveaux P,*** Frédérick R. *Co-last and corresponding authors. Deciphering a lactate dehydrogenase tetramerization domain using epitope mapping and peptides. *J. Biol. Chem.* **296**:100422 (2021).

Zampieri LX, Silva-Almeida C, Rondeau JD, Sonveaux P. Mitochondrial transfer in cancer: a comprehensive review. Int. J. Mol. Sci. **22**(6):3245 (2021).

Colson A, Depoix CL, Dessilly G, Baldin P, Danhaive O, Hubinont C, **Sonveaux P**, Debieve F. Clinical and in vitro evidence against placenta infection at term by severe acute respiratory syndrome Coronavirus 2. *Am. J. Pathol.* 191(9):1610-1623 (2021).

Zampieri LX, Sboarina M, Cacace A, Grasso D, Thabault L, Hamelin L, Vazeille T, Dumon E, Rossignol R, Frédérick R, Sonveaux E, Lefranc F, **Sonveaux P**. Olaparib is a mitochondrial Complex I inhibitor that kills temozolomide-resistant human glioblastoma cells. Int. J. Mol. Sci. **22**:11938 (2021).

Gonçalves AC, **Richiardone E**, Jorge J, Polónia B, Xavier CPR, Salaroglio IC, Riganti C, Vasconcelos MH, **Corbet C**, Sarmento-Ribeiro AB. Impact of cancer metabolism on therapy resistance - Clinical implications. *Drug Resist. Updat.* **59**:100797 (2021).

HEALTH AND MOVEMENT

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

"Health and movement" is an interdisciplinary research topic assessing human movement in relationship with biological problems. It aims to better understand the mechanisms of disorders impacting patient's autonomy and physical activity, to improve the quality of treatment and reduce the cost of health care.

It includes fundamental research regarding musculoskeletal pathophysiology and bone biomaterials, assessment of neuro-musculoskeletal system in rehabilitation, orthopedic, cranofacial and neurological patients, as well as assistive technologies for surgery and new standards for surgical accuracy measurements.

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BIOMECHANICS OF BONES AND SOFT TISSUES

A Comparison of Genicular Nerve Blockade with Corticosteroids Using Either Classical Anatomical Targets vs Revised Targets for Pain and Function in Knee Osteoarthritis: A Double-Blind, Randomized Controlled Trial

Olivier Cornu, Pierre-Louis Docquier, Raphael Olszewski, Thomas Schubert, Emmanuel Thienpont, Randy Buzisa Mbuku, Alexandre Englebert, Robin Evrard, Julie Manon, Kevin Wendo

OBJECTIVE: Compare the effectiveness of genicular nerve blockade (GNB) using classical anatomical targets (CT) versus revised targets (RT) in patients suffering from chronic knee osteoarthritis pain

DESIGN: Double-blinded randomized controlled trial.

SETTING: Pain medicine center of a teaching hospital.

METHODS: We randomly assigned 55 patients with chronic knee osteoarthritis pain to receive a GNB (using a fluid mixture of 2ml: lidocaine 1% + 20mg triamcinolone) with either classical targets (CT-group, n=28) or revised targets (RT-group, n=27). Numeric rating pain scale (NRS), Oxford knee score (OKS), Western Ontario and McMaster Universities osteoarthritis index score (WOMAC), Quantitative analgesic questionnaire (QAQ) and global perceived effects were assessed at baseline, and at 1-hour, 24-hours, 1-, 4- and 12-weeks post intervention.

RESULTS: The RT-group showed greater reduction in NRS mean score at 1-hour post-intervention (95% confidence interval (CI) [0.0 – 0.8] vs. [1.6 – 3.2], $p < 0.001$). The proportion of patients achieving more than 50% knee pain reduction was higher in the RT-group at each follow up interval, yet these differences were statistically significant only at 1-hour post intervention (82.1% vs. 100%, $p = 0.02$). The reduction of the mean WOMAC score was greater in RT-group at 4 weeks follow-up (95% CI [4.3 – 8.0] vs [8.4 – 20.8], $p = 0.03$). Both protocols resulted in significant pain reduction and joint function improvement up to 12 weeks post intervention.

CONCLUSION: The revised technique allowed more pain relief as well as greater proportion of successful responders at 1-hour post intervention. The large volume injected during therapeutic GNB could have compensated the lack of precision of the classical anatomical targets, mitigating differences in outcomes between both techniques.

BIOMECHANICS OF HUMAN MOVEMENT

Effects of Mulligan Mobilization with Movement in Subacute Lateral Ankle Sprains: A Pragmatic Randomized Trial

Christine Detrembleur, Philippe Mahaudens, Laurent Pitance, Tim Cayrol, Simon Hinnekens, Nicolas Lambricht, Alexandre Luc, AnhPhong Nguyen, Virginie Otlet, Jean-Louis Peters-Dickie

OBJECTIVE: In a pragmatic and randomized clinical trial, patients with lateral ankle sprains were assessed, under blinded conditions, for their responsiveness and improvements during Mulligan mobilization-with-movement (MWM) therapy. Methods: Overall, 51 participants with subacute lateral ankle sprains (Grade I–II) were recruited. Following an MWM screening procedure, responders were randomized to either an intervention group (MWM) or a sham group. The MWM group received inferior tibiofibular, talocrural, or cubometatarsal MWM. The treatment or sham was administered upon three sessions, each 4 days apart. Changes from baseline were measured and compared between the sessions for dorsiflexion range of motion, pain, stiffness perception, and the Y-balance test. Results: In total, 43 participants were considered responders to MWM. Using a two-way repeated-measure ANOVA, a statistical and clinically meaningful improvement in dorsiflexion range of motion was revealed in the MWM group ($p = 0.004$, 1rst = +1.762 cm; 3rd = +2.714 cm), whereas no improvement following the first session occurred in the sham group ($p = 0.454$, 1rsttrial = +1.091 cm; 3rdtrial = +1.409 cm). Pain and stiffness significantly improved, yet below the clinically meaningful level. The MWM group demonstrated a significant improvement after three sessions for the Y-balance test ($p = 0.001$, +8.857 cm). Conclusion: More than 80% of participants with subacute lateral ankle sprains responded well to the MWM approach. Three sessions of pragmatically determined MWM provided a significant and clinically meaningful benefit in dorsiflexion range of motion and Y-balance test performance compared to a sham treatment.

NEUROREADAPTATION AND NEW TECHNOLOGIES

Self-Rehabilitation for Post-Stroke Motor Function and Activity—A Systematic Review and Meta-Analysis

Thierry Lejeune, Stéphanie Dehem, Gaetan Stoquart, Louise Declerck, Marine Devis, Ioannis Doumas, Gauthier Everard, Virginie Otlet, Clara Selves

BACKGROUND. Due to an increasing stroke incidence, a lack of resources to implement effective rehabilitation and a significant proportion of patients with remaining impairments after treatment, there is a rise in demand for effective and prolonged rehabilitation. Development of self-rehabilitation programs provides an opportunity to meet these increasing demands.

OBJECTIVE. The primary aim of this meta-analysis was to determine the effect of self-rehabilitation on motor outcomes, in comparison to conventional rehabilitation, among patients with stroke. The secondary aim was to assess the influence of trial location (continent), technology, time since stroke (acute/subacute vs chronic), dose (total training duration > vs ≤ 15 hours), and intervention design (self-rehabilitation in addition/substitution to conventional therapy) on effect of self-rehabilitation.

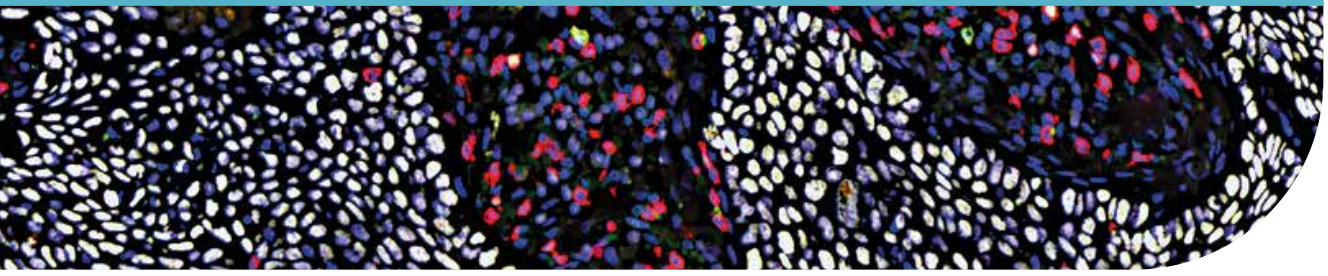
METHODS. Studies were selected if participants were adults with stroke; the intervention consisted of a self-rehabilitation program defined as a tailored program where for most of the time, the patient performed rehabilitation exercises independently; the control group received conventional therapy; outcomes included motor function and activity; and the study was a randomized controlled trial with a PEDro score ≥5.

RESULTS. Thirty-five trials were selected (2225 participants) and included in quantitative synthesis regarding motor outcomes. Trials had a median PEDro Score of 7 [6–8]. Self-rehabilitation programs were shown to be as effective as conventional therapy. Trial location, use of technology, stroke stage, and intervention design did not appear to have a significant influence on outcomes.

CONCLUSION:
This meta-analysis showed low to moderate evidence that self-rehabilitation and conventional therapy efficacy was equally valuable for post-stroke motor function and activity.

EQUIPMENTS

- Serial 6-dof robot
- 6-axis force sensor
- 3D rapid-prototyping printer
- 3D visualisation, simulation and planning platform
- 3D measurement tool
- Dedicated softwares for image analysis and CAD/CAM
- 3D haptic system
- Intraoperative surgical navigation system (sawing, milling)
- Intraoperative robotic imaging system
- Stiffness muscle apparatus
- Lab Gait: instrumented treadmill fitted with 3D force sensors, 8 infrared 3D cameras, 16 channels of Wifi
- EMG, ergospirometer
- 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



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Facemask, covid and exercise

Reychler G, Poncin W, Caty G

The aim of this project is to quantify the effects of different types of facemask on functional exercise capacity and cardio-respiratory parameters. Healthy children and adults, and COVID patients will be investigated.

PHYSIOTHERAPY

Sputum and rheology

Poncin W

The aim of this project is to evaluate the impact of different airway clearances techniques on the sputum properties. In vitro and in vivo studies will be performed.

Bronchiolitis and Nose

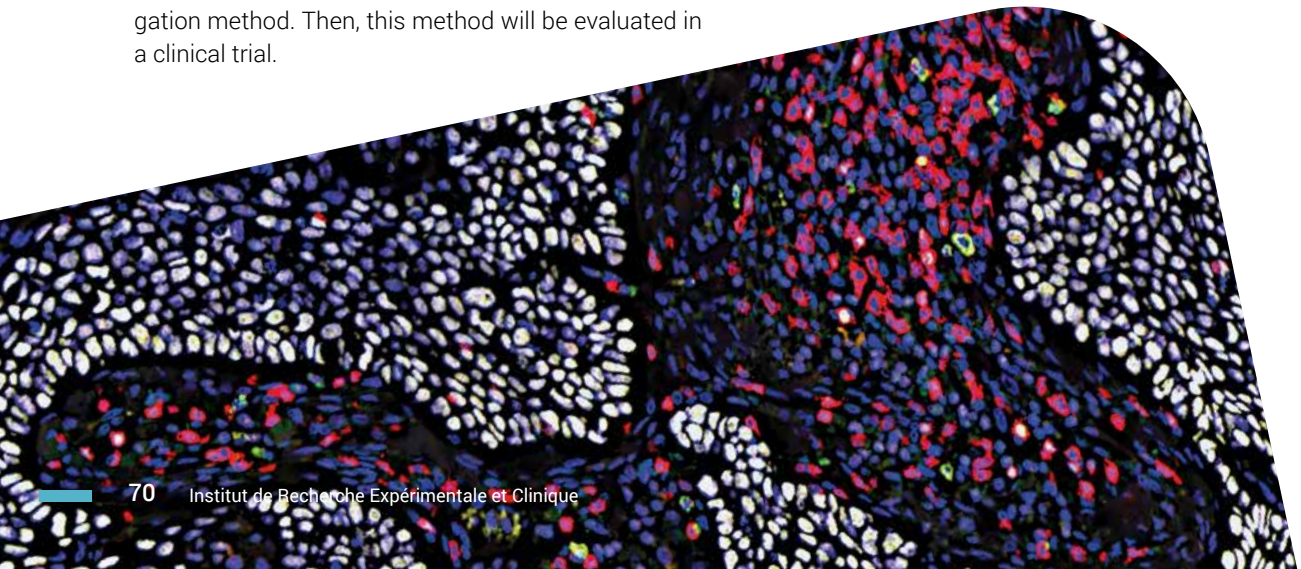
Audag N - Poncin W - Cnockaert P

The aim of this project is to assess the role of nasal irrigation in the bronchiolitis management. A national survey will be realized to note the different nasal irrigation methods used in the population. A Delphi project will be performed to determine the optimal nasal irrigation method. Then, this method will be evaluated in a clinical trial.

AEROSOL

Nebulization and contamination

The aim of this project is to determine if the nebulization in infected patients can represent a risk of contamination for the environment or the healthcare workers. Different virus will be investiguated such as the SARS-CoV-2 or respiratory syncytial virus. In vitro and in vivo studies will be performed.



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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 spinal cord to allow better clinical assessment**

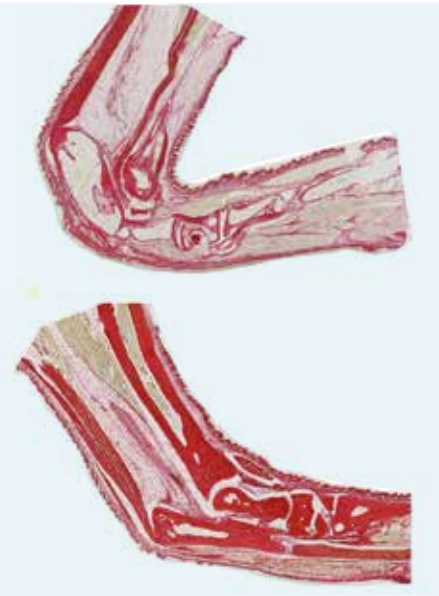


Figure 1. Sagittal section through triceps surae of oim (up) and WT (under) mice, showing fracture of calcaneus, thinner bones and thinner Achilles' tendon in oim than WT. Sirius red staining.

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 2021

NMSK

Fonkoue, Loïc ; Steyaert, Arnaud ; Kouassi, Kouame Jean Eric ; Bandolo, Eric ; Lebleu, Julien ; Fossoh, Hermann ; Behets Wydemans, Catherine ; Detrembleur, Christine ; Cornu, Olivier. A Comparison of Genicular Nerve Blockade With Corticosteroids Using Either Classical Anatomical Targets vs Revised Targets for Pain and Function in Knee Osteoarthritis: A Double-Blind, Randomized Controlled Trial.. In: Pain medicine, Vol. 22, no.5, p. 1116-1126 (2021). doi:10.1093/pm/pnab014. http://hdl.handle.net/2078.1/256240

Haelewijn, Nicolas ; Lobet, Sébastien ; Van Damme, An ; Docquier, Pierre-Louis ; Eerdekens, Maarten ; Deschamps, Kevin. Clinical and Biomechanical Progression after Ankle Joint Distraction in a Young Adolescent Patient with Haemophilia.. In: International journal of environmental research and public health, Vol. 18, no.21, p. 11405 [1-7] (2021). doi:10.3390/ijerph182111405. http://hdl.handle.net/2078.1/253292

Pitance, Laurent ; De Longhi, Benjamin ; Gerard, Eve ; Cayrol, Timothee ; Roussel, Nathalie ; Cescon, Corrado ; Falla, Deborah ; Barbero, Marco. Digital pain drawings are a useful and reliable tool for assessing patients with temporomandibular disorders. In: Journal of Oral Rehabilitation, Vol. 48, no. 7, p. 798-808 (2021). doi:10.1111/joor.13168. http://hdl.handle.net/2078.1/255287

Nguyen, Anh Phong ; Pitance, Laurent ; Mahaudens, Philippe ; Detrembleur, Christine ; David, Yuval ; Hall, Toby ; Hidalgo, Benjamin. Effects of Mulligan Mobilization with Movement in Subacute Lateral Ankle Sprains: A Pragmatic Randomized Trial. In: Journal of Manual & Manipulative Therapy, Vol. 1, no.1, p. 1-12 (2021). doi:10.1080/10669817.2021.1889165. http://hdl.handle.net/2078.1/243817

Deniz, Volkan ; Guzel, Nevin Atalay ; Lobet, Sébastien ; Antmen, Ali Bülent ; Sasmaz, Hatice Ilgen ; Kilci, Abdullah ; Boyraz, Omer Cumhur ; Gunaştı, Ozgür ; Kurdak, Sanli Sadi. Effects of a supervised therapeutic exercise program on musculoskeletal health and gait in patients with haemophilia: A pilot study. In: Haemophilia, (2021). doi:10.1111/hae.14444. http://hdl.handle.net/2078.1/252235

Valet, Maxime ; El Sankari, Souraya ; Van Pesch, Vincent ; Detrembleur, Christine ; Lejeune, Thierry ; Stoquart, Gaëtan. Effects of prolonged-release fampridine on multiple sclerosis-related gait impairments. A crossover, double-blinded, placebo-controlled study. In: Clinical Biomechanics, Vol. 86, no.-, p. 105382 (2021). doi:10.1016/j.clinbiomech.2021.105382. http://hdl.handle.net/2078.1/246184

Lambert, Catherine ; Meité, N'Dogomo ; Sanogo, Ibrahima ; Lobet, Sébastien ; Hermans, Cédric. Feasibility and outcomes of low-dose and low-frequency prophylaxis with recombinant extended half-life products (Fc-rFVIII and Fc-rFIX) in Ivorian children with hemophilia: Two-year experience in the setting of World Federation of Haemophilia humanitarian aid programme. In: Haemophilia, Vol. 27, no. 1, p. 33-40 (2021). doi:10.1111/hae.14216. http://hdl.handle.net/2078.1/239318

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,, p. 100890 (2021). doi:10.1016/j.blre.2021.100890. http://hdl.handle.net/2078.1/253477

Miesbach, Wolfgang ; Barcenilla, Sara Garcia ; Golan, Gaby ; Lobet, Sébastien. Implications of haemophilia gene therapy for the changing role of the multidisciplinary team. In: Haemophilia, (2021). doi:10.1111/hae.14440 (Accepté/Sous

presse). http://hdl.handle.net/2078.1/252234

Ruiz Sorribas, Albert ; Poilvache, Hervé ; Kamarudin, Nur Hidayatul Nazirah ; Braem, Annabel ; Van Bambeke, Françoise. In vitro polymicrobial inter-kingdom three-species biofilm model: influence of hyphae on biofilm formation and bacterial physiology. In: Biofouling, Vol. 37, no.5, p. 481-493 (2021). doi:10.1080/08927014.2021.1919301. http://hdl.handle.net/2078.1/251184

Poilvache, Hervé ; Ruiz Sorribas, Albert ; Cornu, Olivier ; Van Bambeke, Françoise. In-vitro study of the synergistic effect of an enzyme cocktail and antibiotics against biofilms in a prosthetic joint infection model. In: Antimicrobial Agents and Chemotherapy, Vol. 65, no. 4, p. e01699-20 [1-24] (2021). doi:10.1128/AAC.01699-20. http://hdl.handle.net/2078.1/241086

Gayito Adagaba, René Ayaovi ; Kolontchang Gatchou, Albéric Lionel ; Loucheur, Naima ; Boboe, Jordan ; Ganglo, Maturin ; Guedehounsou, Loriano ; Brice Megninou, Mahuklo Ulrich ; Docquier, Pierre-Louis. Incarcération du périoste dans le cartilage de croissance dans une fracture-décollement épiphysaire: à propos d'un cas. In: Pan African Medical Journal, Vol. 39, p. 235 (2021). doi:10.11604/pamj.2021.39.235.27764. http://hdl.handle.net/2078.1/250800

Tomasi, Vincent ; Demurie, Alex ; Ghijselings, Ignace ; Cornu, Olivier ; Van Den Wyngaert, Hans. Influence of outpatient total knee arthroplasty compared to inpatient surgery on medical and economic outcomes. In: Acta Orthopaedica Belgica, Vol. 87, no. 1, p. 103-109 (2021). http://hdl.handle.net/2078.1/231901

Kirchgesner, Thomas ; Stoenoiu, Maria ; Michoux, Nicolas ; Libouton, Xavier ; Houssiau, Frédéric ; Vande Berg, Bruno. Instability of the extensor digitorum tendons in Jaccoud arthropathy assessed by semi-dynamic MRI of the metacarpophalangeal joints.. In: Diagnostic and interventional imaging, Vol. 102, no.9, p. 553-559 (2021). doi:10.1016/j.diii.2021.03.005. http://hdl.handle.net/2078.1/258806

Docquier, Pierre-Louis ; Schubert, Thomas. Kyste osseux essentiel. In: Encyclopedie Médico-Chirurgicale. Appareil Locomoteur,, p. 14-767 [1-11] (2021). doi:10.1016/S0246-0521(21)44861-8. http://hdl.handle.net/2078.1/253303

Everard, Gauthier ; Pietteur, Charlotte ; Stoquart, Gaëtan ; Lejeune, Thierry. La réalité virtuelle après un accident vasculaire cérébral. In: La réalité virtuelle après un accident vasculaire cérébral, Vol. 140, no.02, p. 132-134 (2021). http://hdl.handle.net/2078.1/244080

de Wouters d'Oplinter, Solange ; Petronilia, Steven ; Paulet, Daniel ; de Baere, Tom ; Willemar, Etienne ; Cornu, Olivier. Outpatient Total Hip Arthroplasty : the future?. In: Acta Orthopaedica Belgica, Vol. 87, no. 2, p. 313-319 (2021). http://hdl.handle.net/2078.1/239027

Haoudou, Romeo ; Malghem, Jacques ; Galant, Christine ; Docquier, Pierre-Louis. Painless osteoid osteoma of the distal phalanx of a toe.. In: Journal of surgical case reports, Vol. 2021, no. 2, p. rjaa614 [1-3] (2021). doi:10.1093/jscr/rjaa614. http://hdl.handle.net/2078.1/244166

Ruiz-Sorribas, Albert ; Poilvache, Hervé ; Van Bambeke, Françoise. Pharmacodynamics of Moxifloxacin, Meropenem, Caspofungin and their Combinations Against In Vitro Polymicrobial Inter-kingdom Biofilms. In: Antimicrobial Agents and Chemotherapy, Vol. 66 (epub ahead of print), no.2, p. e02149-21 (2021). doi:10.1128/aac.02149-21. http://hdl.handle.net/2078.1/255272

El Khoury, Ghady ; Penta, Massimo ; Barbier, Olivier ; Libouton, Xavier ; Thonnard, Jean-Louis ; Lefèvre, Philippe. Recognizing Manual Activities Using Wearable Inertial Measurement Units: Clinical Application for Outcome Measurement. In: Sensors, Vol. 21, no. 9, p. 3245 [1-14] (2021). doi:10.3390/s21093245. http://hdl.handle.net/2078.1/250142

Everard, Gauthier ; Luc, Alexandre ; Doumas, Ioannis ; Ajana, Khawla ; Stoquart, Gaëtan ; Edwards, Martin ; Lejeune, Thierry. Self-Rehabilitation for Post-Stroke Motor Function and Activity–A Systematic Review and Meta-Analysis. In: Neurorehabilitation and neural repair, (2021). doi:10.1177/15459683211048773. http://hdl.handle.net/2078.1/252229

Hage, Renaud ; Detrembleur, Christine ; Dierick, Frédéric ; Brismée, Jean-Michel ; Roussel, Nathalie ; Pitance, Laurent. Sensorimotor performance in acute-subacute non-specific neck pain: a non-randomized prospective clinical trial with intervention. In: BMC Musculoskeletal Disorders, Vol. 22, no.1, p. 21 (2021). doi:10.1186/s12891-021-04876-4. http://hdl.handle.net/2078.1/254483

Doumas, Ioannis ; Everard, Gauthier ; Dehem, Stéphanie ; Lejeune, Thierry. Serious games for upper limb rehabilitation after stroke: a meta-analysis. In: Journal of NeuroEngineering and Rehabilitation, Vol. 18, no.1, p. 1-16 (2021). doi:10.1186/s12984-021-00889-1. http://hdl.handle.net/2078.1/248252

Demoulin, Christophe ; Gabriel, Laura ; Nève de Mévergnies, Orléane ; Henket, Laura ; Roussel, Nathalie ; Goubert, Liesbet ; Vanderthommen, Marc ; Pitance, Laurent. Several low back pain-related misbeliefs are still around in 2020: A cross-sectional survey in Belgium. In: Physiotherapy Research International, (2021). doi:10.1002/pri.1927. http://hdl.handle.net/2078.1/255284

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 (2021). doi:10.1016/j.rehab.2021.101583. http://hdl.handle.net/2078.1/253296

Lobet, Sébastien ; Timmer, Merel ; Königs, Christoph ; Stephensen, David ; McLaughlin, Paul ; Duport, Gaetan ; Hermans, Cédric ; Mancuso, Maria Elisa. The Role of Physiotherapy in the New Treatment Landscape for Haemophilia. In: Journal of Clinical Medicine, Vol. 10, no. 13, p. 2822 [1-11] (2021). doi:10.3390/jcm10132822. http://hdl.handle.net/2078.1/248786

Asquini, Giacomo ; Rushton, Alison ; Pitance, Laurent ; Heneghan, Nicola ; Falla, Deborah. The effectiveness of manual therapy applied to craniomandibular structures in the treatment of temporomandibular disorders: protocol for a systematic review. In: Systematic Reviews, Vol. 10, no.1 (2021). doi:10.1186/s13643-021-01623-7. http://hdl.handle.net/2078.1/244226

Heylen, Charles-Edouard ; Docquier, Pierre-Louis ; Dumitriu, Dana Ioana. Transient synovitis of the hip : is systematic radiological screening necessary for the detection of Perthes disease?. In: Acta orthopaedica Belgica, Vol. 87, no.2, p. 263-268 (2021). http://hdl.handle.net/2078.1/252306

Kouassi, Kouame Jean Eric ; Manon, Julie ; Fonkoue, Loïc ; Detrembleur, Christine ; Cornu, Olivier. Treatment of open

tibia fractures in Sub-Saharan African countries: a systematic review. In: Acta orthopaedica Belgica, Vol. 87, no. 1, p. 85-92 (2021). http://hdl.handle.net/2078.1/231902

Fonkoue, Loïc ; Stoenoiu, Maria ; Behets Wydemans, Catherine ; Steyaert, Arnaud ; Kouassi, Kouamé Jean-Eric ; Detrembleur, Christine ; Cornu, Olivier. Validation of a new protocol for ultrasound-guided genicular nerve radiofrequency ablation with accurate anatomical targets: cadaveric study.. In: Regional anesthesia and pain medicine, Vol. 46, no.3, p. 210-216 (2021). doi:10.1136/rapm-2020-101936. http://hdl.handle.net/2078.1/256243

Piraux, Elise ; Reychler, Gregory ; Maertens de Noordhout, louise ; Forget, Patrice ; Deswysen, Yannick ; Caty, Gilles. What are the impact and the optimal design of a physical prehabilitation program in patients with esophagogastric cancer awaiting surgery? A systematic review. In: BMC Sports Science, Medicine and Rehabilitation, Vol. 13, no.1, p. 33 (2021). doi:10.1186/s13102-021-00260-w. http://hdl.handle.net/2078.1/245102

PNEU

Gravier FE, Smondack P, Boujibar F, **Prieur G**, Medrinal C, **Combret Y**, Muir JF, Baste JM, Cuvelier A, Debeaumont D, Bonnevie T. Prehabilitation sessions can be provided more frequently in a shortened regimen with similar or better efficacy in people with non-small cell lung cancer: a randomised trial, J Physiother. 2022 Jan;68(1):43-50. doi: 10.1016/j.jphys.2021.12.010. Epub 2021 Dec 21. PMID: 34952813

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. 2021 Dec 8:1-8. doi: 10.1007/s10877-021-00784-z. Online ahead of print. PMID: 34877626

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. PMID: 34844914

de Terwangne C, Sorgente A, Tortora R, Cheung D, **Duprez F,** Place S, Lechien JR, Capulzini L, Cubber M, Saussez S, Taccone FS, Mashayekhi S. Mortality Rate and Predictors Among Patients with COVID-19 Related Acute Respiratory Failure Requiring Mechanical Ventilation: a Retrospective Single Centre Study, J Crit Care Med (Targu Mures). 2021 Jan 29;7(1):21-27. doi: 10.2478/jccm-2020-0043. eCollection 2021 Jan. PMID: 34722900

Prieur G, Beaumont M, Delorme M, **Combret Y**, Medrinal C, Hilfiker R, Bonnevie T, Gravier FE, Smondack P, Lamia B, **Reychler G**. Short-term effects of menthol on walking dyspnoea in patients with COPD: a randomised, single blinded, cross-over study, ERJ Open Res. 2021 Oct 25;7(4):00450-2021. doi: 10.1183/23120541.00450-2021. eCollection 2021 Oct. PMID: 34708112

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. PMID: 34670855

P**oncin W**, Baudet L, **Reychler G, Duprez F**, Liistro G, Belkhir L, Pothen L, Yildiz H, Yombi JC, De Greef J. Impact of an Improvised System on Preserving Oxygen Supplies in Patients With COVID-19, Arch Bronconeumol. 2021 Jan;57:77-79. doi: 10.1016/j.arbres.2020.07.019. Epub 2020 Aug 27. PMID: 34629673

Smondack P, Gravier FE, **Combret Y**, Muir JF, Cuvelier A, Debeaumont D, Medrinal C, **Prieur G**, Bonnevie T. Factors influencing participation in educational workshops as part of a pulmonary rehabilitation program in patients with chronic obstructive pulmonary disease: a retrospective study, Expert Rev Respir Med. 2021 Nov 2:1-9. doi: 10.1080/17476348.2022.1991793. Online ahead of print. PMID: 34623218

Latiers F, Vandenabeele M, **Poncin W, Reychler G**. Prevalence and risk factors of musculoskeletal pain in patients with chronic obstructive pulmonary disease: A systematic review, Clin Respir J. 2021 Dec;15(12):1286-1301. doi: 10.1111/crj.13443. Epub 2021 Sep 9. PMID: 34459145

Gravier FE, Smondack P, **Prieur G**, Medrinal C, **Combret Y**, Muir JF, Baste JM, Cuvelier A, Boujibar F, Bonnevie T. Effects of exercise training in people with non-small cell lung cancer before lung resection: a systematic review and meta-analysis, Thorax. 2021 Aug 24:thoraxjnl-2021-217242. doi: 10.1136/thoraxjnl-2021-217242. Online ahead of print. PMID: 34429375

Misery L, Shourick J, **Reychler G**, Taieb C. Association between chronic idiopathic cough and sensitive skin syndromes is a new argument in favor of common neuropathic pathways: results from a survey on 4050 subjects, Sci Rep. 2021 Aug 20;11(1):16976. doi: 10.1038/s41598-021-96608-w. PMID: 34417530

Reychler G, Straeten CV, Schalkwijk A, **Poncin W**. Effects of surgical and cloth facemasks during a submaximal exercise test in healthy adults, Respir Med. 2021 Sep;186:106530. doi: 10.1016/j.rmed.2021.106530. Epub 2021 Jul 6. PMID: 34273733

Medrinal C, Gillet A, Boujibar F, Dugernier J, Zwahlen M, Lamia B, Girault C, Creteur J, Fellrath JM, Haesler L, Lagache L, Goubert L, Artaud Macari E, Taton O, Gouin P, Leduc D, Van Hove O, Norrenberg M, **Prieur G**, **Combret Y**, Correvon N, Hilfiker R, Contal O. Role of Non-Invasive Respiratory Supports in COVID-19 Acute Respiratory Failure Patients with Do Not Intubate Orders, J Clin Med. 2021 Jun 24;10(13):2783. doi: 10.3390/jcm10132783. PMID: 34202895

Iturain Barrón A, Quintana Riera S, **Reychler G**. The 3 Minute Step Test is a validated field test to evaluate the functional exercise capacity in children aged 6 to 12, Respir Med Res. 2021 Nov;80:100833. doi: 10.1016/j.resmer.2021.100833. Epub 2021 Jun 4. PMID: 34147867

Reychler G, De Backer MM, **Piraux E, Poncin W**, Caty G. Physical therapy treatment of hypermobile Ehlers-Danlos syndrome: A systematic review, Am J Med Genet A. 2021 Oct;185(10):2986-2994. doi: 10.1002/ajmg.a.62393. Epub 2021 Jun 19. PMID: 34145717

Reychler G, Beaumont M, Latiers AC, Pieters T, Fremault A. Dyspnea could be accurately assessed by a caregiver in hospitalized patients with respiratory diseases: Interrater reliability and agreement study, Braz J Phys Ther. 2021 Nov-Dec;25(6):735-740. doi: 10.1016/j.bjpt.2021.04.010. Epub 2021 May 24. PMID: 34119444

Martin I, Braem F, Baudet L, **Poncin W**, Fizaine S, Aboubakar F, Froidure A, Pilette C, Liistro G, De Greef J, Yildiz

H, Pothen L, Yombi JC, Belkhir L, **Reychler G**. Follow-up of functional exercise capacity in patients with COVID-19: It is improved by telerehabilitation, Respir Med. 2021 Jul;183:106438. doi: 10.1016/j.rmed.2021.106438. Epub 2021 Apr 30. PMID: 33964817

Contal O, **Poncin W**, Vaudan S, De Lys A, Takahashi H, Bochet S, Grandin S, Kehrer P, Charbonnier F. One-Year Adherence to Continuous Positive Airway Pressure With Telemonitoring in Sleep Apnea Hypopnea Syndrome: A Randomized Controlled Trial, Front Med (Lausanne). 2021 Apr 20;8:626361. doi: 10.3389/fmed.2021.626361. eCollection 2021. PMID: 33959620

Saey D, Bellocq A, Gephine S, Lino A, **Reychler G**, Villiot-Danger E. [Which physical tests for which objectives in pulmonary rehabilitation?], Rev Mal Respir. 2021 Jun;38(6):646-663. doi: 10.1016/j.rmr.2021.04.001. Epub 2021 Apr 21. PMID: 33895033

Audag N, Liistro G, Goubau C, Vandervelde L, **Poncin W**, Toussaint M, Van den Bergh P, **Reychler G**. Screening for oropharyngeal dysphagia in adult patients with neuromuscular diseases using the Sydney Swallow Questionnaire, Muscle Nerve. 2021 Sep;64(3):277-284. doi: 10.1002/mus.27254. Epub 2021 May 7. PMID: 33890683

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 JC, Ghaye B. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae, Respir Med. 2021 May;181:106383. doi: 10.1016/j.rmed.2021.106383. Epub 2021 Apr 4. PMID: 33839588

Toussaint M, Chatwin M, Gonçalves MR, Gonzalez-Bermejo J, Benditt JO, McKim D, Sancho J, Hov B, Sansone V, Prigent H, Carlucci A, Wijkstra P, Garabelli B, Escarrabill J, Pinto T, **Audag N**, Verweij-van den Oudenrijn L, Ogna A, Hughes W, Devaux C, Chaulet J, Andersen T; ENMC Respiratory Therapy Consortium. Mouthpiece ventilation in neuromuscular disorders: Narrative review of technical issues important for clinical success, Respir Med. 2021 Apr-May;180:106373. doi: 10.1016/j.rmed.2021.106373. Epub 2021 Mar 24. PMID: 33798870

Piraux E, Reychler G, de Noordhout LM, Forget P, Deswysen Y, Caty G. What are the impact and the optimal design of a physical prehabilitation program in patients with esophagogastric cancer awaiting surgery? A systematic review, BMC Sports Sci Med Rehabil. 2021 Mar 25;13(1):33. doi: 10.1186/s13102-021-00260-w. PMID: 33766107

Bocquet L, Gravier FE, Smondack P, **Prieur G, Combret Y**, Muir JF, Cuvelier A, Boujibar F, Médrinal C, Bonnevie T. Urinary symptoms are very frequent in people with chronic respiratory disease attending pulmonary rehabilitation, Pulmonology. 2021 Jul-Aug;27(4):369-371. doi: 10.1016/j.pulmoe.2021.02.005. Epub 2021 Mar 18. PMID: 33744215

Medrinal C, **Prieur G**, Bonnevie T, Gravier FE, Mayard D, Desmalles E, Smondack P, Lamia B, **Combret Y**, Fossat G. Muscle weakness, functional capacities and recovery for COVID-19 ICU survivors, BMC Anesthesiol. 2021 Mar 2;21(1):64. doi: 10.1186/s12871-021-01274-0. PMID: 33653264

Combret Y, Boujibar F, Gennari C, Medrinal C, Sicinski S, Bonnevie T, Gravier FE, Laurans M, Marguet C, Le Roux P, Lamia B, P**rieur G, Reychler G**. Measurement properties of the one-minute sit-to-stand test in children and adolescents with cystic fibrosis: A multicenter randomized cross-over trial, PLoS One. 2021 Feb 12;16(2):e0246781. doi: 10.1371/journal.pone.0246781. eCollection 2021. PMID: 33577586

Combret Y, Prieur G, Hilfiker R, Gravier FE, Smondack P, Contal O, Lamia B, Bonnevie T, Medrinal C. The relationship between maximal expiratory pressure values and critical outcomes in mechanically ventilated patients: a post hoc analysis of an observational study, Ann Intensive Care. 2021 Jan 13;11(1):8. doi: 10.1186/s13613-020-00791-4. PMID: 33438092 Free PMC article.

Lebret M, **Prieur G**, Bonnevie T, Gravier FE, **Combret Y**, Medrinal C. Correspondence: High positive airway pressure could shorten the drainage period in haemothorax but not physiotherapy intervention, J Physiother. 2021 Jan;67(1):74. doi: 10.1016/j.jphys.2020.11.006. PMID: 33390257

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. 2021 Jan 4:1-9. doi: 10.1080/09593985.2020.1868029. Online ahead of print. PMID: 33390080

Derasse M, Lefebvre S, Liistro G, **Reychler G**. Chest Expansion and Lung Function for Healthy Subjects and Individuals With Pulmonary Disease, Respir Care. 2021 Apr;66(4):661-668. doi: 10.4187/respcare.08350. Epub 2020 Dec 29. PMID: 33376188

Bonnevie T, Smondack P, Elkins M, Gouel B, Medrinal C, **Combret Y**, Muir JF, Cuvelier A, **Prieur G**, Gravier FE. Advanced telehealth technology improves home-based exercise therapy for people with stable chronic obstructive pulmonary disease: a systematic review, J Physiother. 2021 Jan;67(1):27-40. doi: 10.1016/j.jphys.2020.12.006. Epub 2020 Dec 24. PMID: 33358547

Bocquet L, Gravier FE, Smondack P, **Prieur G, Combret Y**, Muir JF, Cuvelier A, Boujibar F, Medrinal C, Bonnevie T. Urinary Incontinence in People Referred for Pulmonary Rehabilitation: An Undisclosed Issue but a Real Problem, Phys Ther. 2021 Mar 3;101(3):pzaa217. doi: 10.1093/ptj/pzaa217. PMID: 33351935

Dubus JC, Becquemin MH, Vecellio L, Chaumuzeau JP, **Reychler G**; GAT (Groupe aérosolthérapie de la Société de pneumologie de langue française). [Good practice for aerosol therapy by nebulization in 2020], Rev Mal Respir. 2021 Feb;38(2):171-176. doi: 10.1016/j.rmr.2020.11.010. Epub 2020 Dec 4. PMID: 33288396

Poncin W, Evrard S, Mareschal A, Gohy S, **Reychler G**. Effects of rehabilitation methods on lower-limb muscle function and functional performance in patients with cystic fibrosis: A systematic review,Clin Rehabil. 2021 Apr;35(4):534-545. doi: 10.1177/0269215520972941. Epub 2020 Nov 23. PMID: 33222526

Piraux E, Caty G, Renard L, Vancraeynest D, Tombal B, Geets X, **Reychler G**. Effects of high-intensity interval training compared with resistance training in prostate cancer patients undergoing radiotherapy: a randomized controlled trial, Prostate Cancer Prostatic Dis. 2021 Mar;24(1):156-165. doi: 10.1038/s41391-020-0259-6. Epub 2020 Jul 27. PMID: 32719354

Reychler G, Cabillic M, **Morales Mestre N, Poncin W, Audag N**, Caty G. Predictive model for the 1-minute sit-to-stand test in healthy children aged 6 to 12 years, Ann Phys Rehabil Med. 2021 Mar;64(2):101410. doi: 10.1016/j.rehab.2020.05.013. Epub 2020 Jul 16. PMID: 32590075

Duprez F, Cocu S, Legrand A, Brimioulle S, Mashayekhi S, Bodur G, Bruyneel A, Roeseler J, Cuvelier G, **Reychler G**. Improvement of arterial oxygenation using the double trunk mask above low flow nasal cannula: a pilot study, J Clin Monit Comput. 2021 Feb;35(1):213-216. doi: 10.1007/s10877-020-00485-z. Epub 2020 Feb 14. PMID: 32060769

Duprez F, Dubois A, Ollieuz S, Cuvelier G, **Reychler G**. Thorpe tube and oxygen flow restrictor: what's flow accuracy?, J Clin Monit Comput. 2021 Apr;35(2):337-341. doi: 10.1007/s10877-020-00476-0. Epub 2020 Feb 10. PMID: 32040793

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

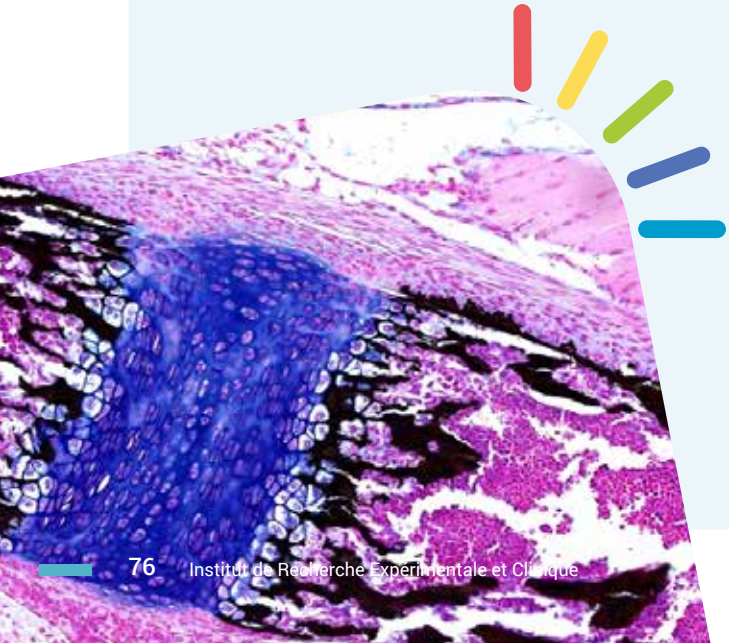
Stanciu Pop, Claudia Maria ; Nollevaux, Marie-Cécile ; Berlière, Martine ; Duhoux, François ; Fellah, Latifa ; Galant, Christine ; Van Bockstal, Mieke. Morphological intratumor heterogeneity in ductal carcinoma in situ of the breast. In: Virchows Archiv, Vol. 479, no. 1, p. 33-43 (2021). doi:10.1007/s00428-021-03040-6.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

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Research Projects

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

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

• Mechanisms of water and solutes transport in peritoneal dialysis;

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

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

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

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

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

FINANCIAL SUPPORT

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

METHODOLOGY AND RESOURCES

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

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).

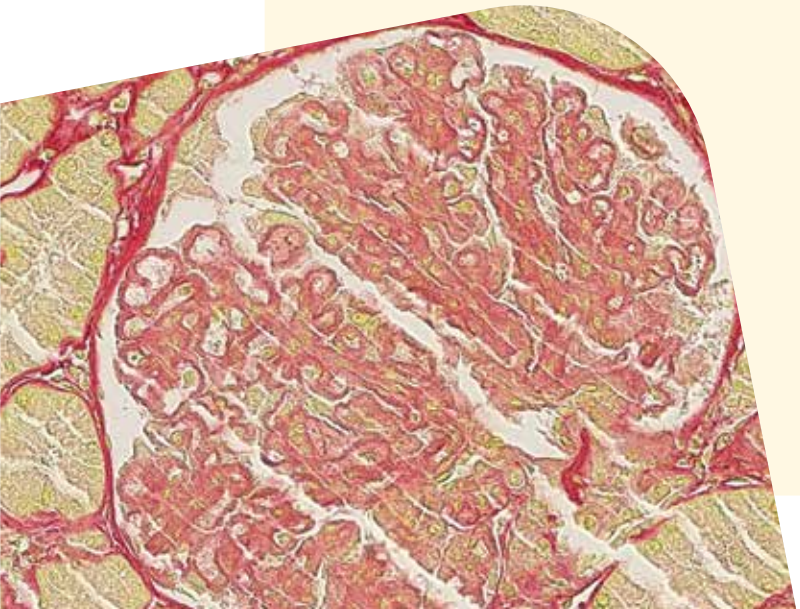
Labriola L, Ruelle J, Scohy A, Seghers F, Perlot Q, De Greef J, Desmet C, Romain C, Yombi JC, Rodriguez-Villalobos H, Kabamba Mukadi B, **Jadoul M.** *Dynamics of spreading of SARS-CoV-2 in a Belgian hemodialysis facility: The importance of the analysis of viral strains.* In: *Journal of medical virology*,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

Research Poles

POLE OF PHARMACOLOGY AND THERAPEUTICS (FATH)

Cyril Corbet, PhD

Olivier Feron, PhD

Pierre Sonveaux, PhD

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

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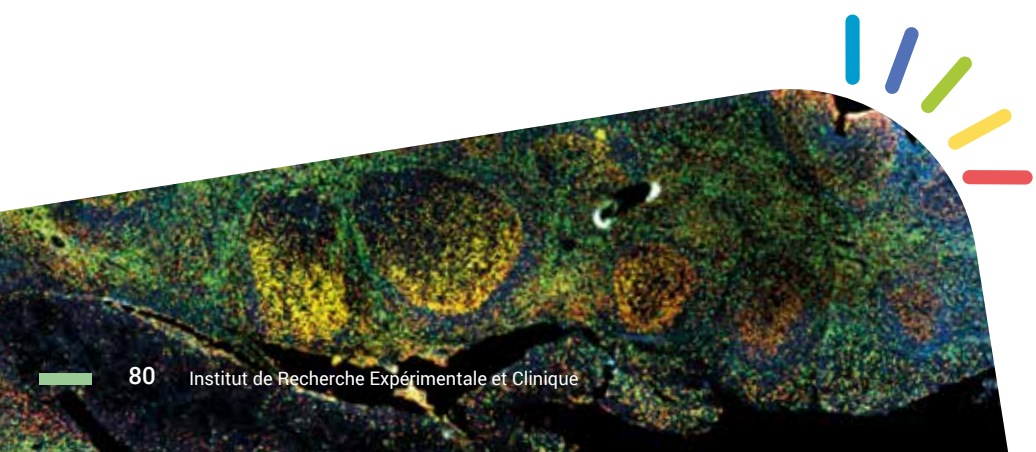

POLE OF MOLECULAR IMAGING, RADIOTHERAPY AND ONCOLOGY (MIRO)

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Benjamin Roberfroid
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Julien Pierrard, MD PhD student

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

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

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

MAJOR FUNDINGS

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

• **F.R.S.-FNRS-PDR-Télévie (2018-2022)** O. Feron and N.E. Sounni (ULg). Lipid droplets: origins and roles upon alterations of the tumor microenvironment.

• **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).

• **Fondation Belge Contre le Cancer (2019-2022):** Fundamental Research Grant. FAF-F/2018/1282. Sonveaux P, Frédérick R. Lactate dehydrogenase B (LDHB) inhibition for anticancer treatment

• **EU Horizon (2019-2023):** Marie Skłodowska-Curie Innovative Training Networks (ITN-ETN) #860245, with Sonveaux P as one of the beneficiaries. International Network for training and innovations in therapeutic radiation (THERADNET).

• **Action de recherches concertées (ARC) (2021-2026)** Sonveaux P, Sterpin E, Heuskin AC, Gallez B. Metabolic control of different responses of human cancer cells to X-ray and proton radiotherapy (MetaRad).

• **F.R.S.-FNRS-PDR-Télévie (2021-2024)** C. Corbet and A. Bellahcène (ULg). Targeting microenvironment-mediated metabolic vulnerabilities to overcome the oncogene-driven resistance to anti-EGFR therapy in colorectal cancers.

• **WALLinov (2018-2022). J**P 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. 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. Current research topics of the group of O Feron include the study of different aspects of the tumor metabolism impacting on, or influenced by, the tumor microenvironment, in particular hypoxia and acidosis. O. Feron has also implemented a technological platform to identify and validate new chemical entities targeting tumor metabolism and stimulating anticancer immunity, as well as innovative prognostic cancer biomarkers. The group of P. Sonveaux currently investigates the contribution of monocarboxylate transporters (MCTs) to tumor development, metabolic remodeling during metastasis and metabolic changes associated with acquired radio- and chemoresistance in cancer. They also collaborate with chemists to develop new drugs targeting the oxidative pathway of lactate in cancer. The group of C. Corbet explores how the issue of resistance to targeted therapies may be tackled by a better understanding of the interplay between TME and oncogenic pathways in part via a comprehensive dissection of associated metabolic preferences. The main oncology-related research programs in the FATH pole include the following studies:

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

REFERENCES 2021 (selected)

Benyahia Z, Blackman MCNM, Hamelin L, Zampieri LX, Capeloa T, Bedin ML, Vazeille T, Schakman O, **Sonveaux P**. In Vitro and In Vivo Characterization of MCT1 Inhibitor AZD3965 Confirms Preclinical Safety Compatible with Breast Cancer Treatment. Cancers (Basel). 2021 Feb 2;13(3):569.

Buyse C, Joudiou N, **Corbet C, Feron O**, Mignion L, Flament J, Gallez B. Impact of Inhibition of the Mitochondrial Pyruvate Carrier on the Tumor Extracellular pH as Measured by CEST-MRI. Cancers (Basel). 2021 Aug 25;13(17):4278.

Colson A, **Sonveaux P**, Debiève F, Sferruzzi-Perri AN. Adaptations of the human placenta to hypoxia: opportunities for interventions in fetal growth restriction. Hum Reprod Update. 2021 Apr 21;27(3):531-569.

Colson A, Depoix CL, Dessilly G, Baldin P, Danhaive O, Hubinont C, **Sonveaux P**, Debiève F. Clinical and in Vitro Evidence against Placenta Infection at Term by Severe Acute Respiratory Syndrome Coronavirus 2. Am J Pathol. 2021 Sep;191(9):1610-1623.

Dierge E, Debock E, Guilbaud C, **Corbet C**, Mignolet E, Mignard L, Bastien E, Dessy C, Larondelle Y, **Feron O**. Peroxidation of n-3 and n-6 polyunsaturated fatty acids in the acidic tumor environment leads to ferroptosis-mediated anticancer effects. Cell Metab. 2021 Aug 3;33(8):1701-1715.e5.

Gonçalves AC, Richiardone E, Jorge J, Polónia B, Xavier CPR, Salaroglio IC, Riganti C, Vasconcelos MH, **Corbet C**, Sarmento-Ribeiro AB. Impact of cancer metabolism on therapy resistance - Clinical implications. Drug Resist Updat. 2021 Dec;59:100797.

Moghassemi S, Dadashzadeh A, Azevedo RB, **Feron O,** Amorim CA. Photodynamic cancer therapy using liposomes as an advanced vesicular photosensitizer delivery system. J Control Release. 2021 Nov 10;339:75-90.

Spillier Q, Ravez S, Dochain S, Vertommen D, Thabault L, **Feron O**, Frédérick R. Unravelling the Allosteric Targeting of PHGDH at the ACT-Binding Domain with a Photoactivatable Diazirine Probe and Mass Spectrometry Experiments. Molecules. 2021 Jan 18;26(2):477.

Thabault L, Liberelle M, Koruza K, Yildiz E, Joudiou N, Messens J, Brisson L, Wouters J, **Sonveaux P,** Frédérick R. Discovery of a novel lactate dehydrogenase tetramerization domain using epitope mapping and peptides. J Biol Chem. 2021 Jan-Jun;296:100422.

Valenti MT, Mottes M, Dalle Carbonare L, **Feron O**. Editorial: Bone Metastases. Front Oncol. 2021 Jul 30;11:741515.

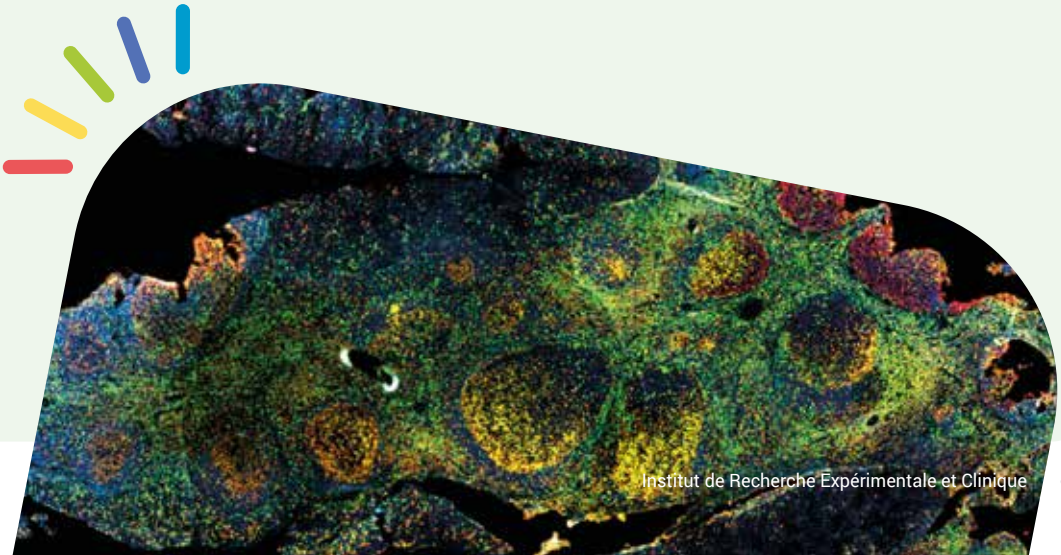
Vander Linden C, Corbet C, Bastien E, Martherus R, Guilbaud C, Petit L, Wauthier L, Loriot A, De Smet C, **Feron O**. Therapy-induced DNA methylation inactivates MCT1 and renders tumor cells vulnerable to MCT4 inhibition. Cell Rep. 2021 Jun 1;35(9):109202.

Vermonden P, Vancoppenolle M, Dierge E, Mignolet E, Cuvelier G, Knoops B, Page M, Debier C, **Feron O**, Larondelle Y. Punicic Acid Triggers Ferroptotic Cell Death in Carcinoma Cells. Nutrients. 2021 Aug 10;13(8):2751.

Virga F, Cappellesso F, Stijlemans B, Henze AT, Trotta R, Van Audenaerde J, Mirchandani AS, Sanchez-Garcia MA, Vandewalle J, Orso F, Riera-Domingo C, Griffa A, Ivan C, Smits E, Laoui D, Martelli F, Langouche L, Van den Berghe G, **Feron O**, Ghesquière B, Prenen H, Libert C, Walmsley SR, Corbet C, Van Ginderachter JA, Ivan M, Taverna D, Mazzone M. Macrophage miR-210 induction and metabolic reprogramming in response to pathogen interaction boost life-threatening inflammation. Sci Adv. 2021 May 7;7(19):eabf0466.

Zampieri LX, Silva-Almeida C, Rondeau JD, **Sonveaux P**. Mitochondrial Transfer in Cancer: A Comprehensive Review. Int J Mol Sci. 2021 Mar 23;22(6):3245.

Zampieri LX, Sboarina M, Cacace A, Grasso D, Thabault L, Hamelin L, Vazeille T, Dumon E, Rossignol R, Frédérick R, Sonveaux E, Lefranc F, **Sonveaux P**. Olaparib Is a Mitochondrial Complex I Inhibitor That Kills Temozolomide- Resistant Human Glioblastoma Cells. Int J Mol Sci. 2021 Nov 3;22(21):11938.



MIRO

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

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

Radiation Oncology -delivered as single modality or in combination with surgery and/or medical treatments- represents one of the most effective options to cure cancer at a local or loco-regional stage. It also has a prominent palliative role for the management of patients with metastatic disease. Although indisputable progresses have been made over the last few decades in the treatment of cancer, patients still die from uncontrolled loco-regional disease. Inaccurate definition of the target volumes, insufficient or sub-optimal radiation dose distribution, and intrinsic radiation resistance are, among others, factors that explain these treatment failures. In this framework, the Laboratory of Molecular Imaging and Radiation Oncology developed several lines of research aiming 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.

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

REFERENCES 2021 (selected)

Barragán-Montero AM, Thomas M, Defraene G, Michiels S, Haustermans K, Lee JA, Sterpin E. Deep learning dose prediction for IMRT of esophageal cancer: The effect of data quality and quantity on model performance. Phys Med. 2021 Mar;83:52-63.

Barragán-Montero A, Javaid U, Valdés G, Nguyen D, Desbordes P, Macq B, Willems S, Vandewinckele L, Holmström M, Löfman F, Michiels S, Souris K, **Sterpin E, Lee JA**. Artificial intelligence and machine learning for medical imaging: A technology review. Phys Med. 2021 Mar;83:242-256.

Buti G, Souris K, Maria Barragán Montero A, Aldo **Lee J, Sterpin E**. Introducing a probabilistic definition of the target in a robust treatment planning framework. Phys Med Biol. 2021 Jul 22;66(15).

d'Abadie P, Walrand S, Hesse M, Annet L, Borbath I, **Van den Eynde M, Lhommel R, Jamar F**. Prediction of tumor response and patient outcome after radioembolization of hepatocellular carcinoma using 90Y-PET-computed tomography dosimetry. Nucl Med Commun. 2021 Jul 1;42(7):747-754.

d'Abadie P, Hesse M, Louppe A, Lhommel R, Walrand S, **Jamar F**. Microspheres Used in Liver Radioembolization: From Conception to Clinical Effects. Molecules. 2021 Jun 29;26(13):3966.

d'Abadie P, Walrand S, Hesse M, Amini N, Lhommel R, Sawadogo K, **Jamar F**. Accurate non-tumoral 99mTc-MAA absorbed dose prediction to plan optimized activities in liver radioembolization using resin microspheres. Phys Med. 2021 Sep;89:250-257.

d'Abadie P, Walrand S, Goffette P, Amini N, Maanen AV, Lhommel R, **Jamar F**. Antireflux catheter improves tumor targeting in liver radioembolization with resin microspheres. Diagn Interv Radiol. 2021 Nov;27(6):768-773.

Dechambre D, Vander Veken L, Delor A, Sterpin E, Vanneste F, **Geets X**. Feasibility of a TPS-integrated method to incorporate tumor motion in the margin recipe. Med Dosim. 2021 Autumn;46(3):253-258.

Gheysens O, Belkhir L, **Jamar F**. Imaging in Post-COVID Lung Disease: Does 18F-FDG PET/CT Have the Key? J Nucl Med. 2022 Feb;63(2):268-269.

Hanseeuw BJ, Malotaux V, Dricot L, Quenon L, Sznajer Y, Cerman J, Woodard JL, Buckley C, Farrar G, Ivanoiu A, **Lhommel R**. Defining a Centiloid scale threshold predicting long-term progression to dementia in pa-

tients attending the memory clinic: an [18F] flutemetamol amyloid PET study. Eur J Nucl Med Mol Imaging. 2021 Jan;48(1):302-310.

van der Geest KSM, Treglia G, Glaudemans AWJM, Brouwer E, Jamar F, Slart RHJA, **Gheysens O**. Diagnostic value of [18F]FDG-PET/CT in polymyalgia rheumatica: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2021 Jun;48(6):1876-1889.

van der Heyden B, Cohilis M, Souris K, de Freitas Nascimento L, **Sterpin E**. Artificial intelligence supported single detector multi-energy proton radiography system. Phys Med Biol. 2021 May 4;66(10).

Vander Veken L, Dechambre D, Sterpin E, Souris K, Van Ooteghem G, **Lee J, Geets X**. Incorporation of tumor motion directionality in margin recipe: The directional MidP strategy. Phys Med. 2021 Nov;91:43-53.

Walrand S, Hesse M, d'Abadie P, **Jamar F**. Hepatic Arterial Buffer Response in Liver Radioembolization and Potential Use for Improved Cancer Therapy. Cancers (Basel). 2021 Mar 26;13(7):1537.

Walrand S, **Jamar F**. Renal and Red Marrow Dosimetry in Peptide Receptor Radionuclide Therapy: 20 Years of History and Ahead. Int J Mol Sci. 2021 Aug 3;22(15):8326.

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 2021 (selected)

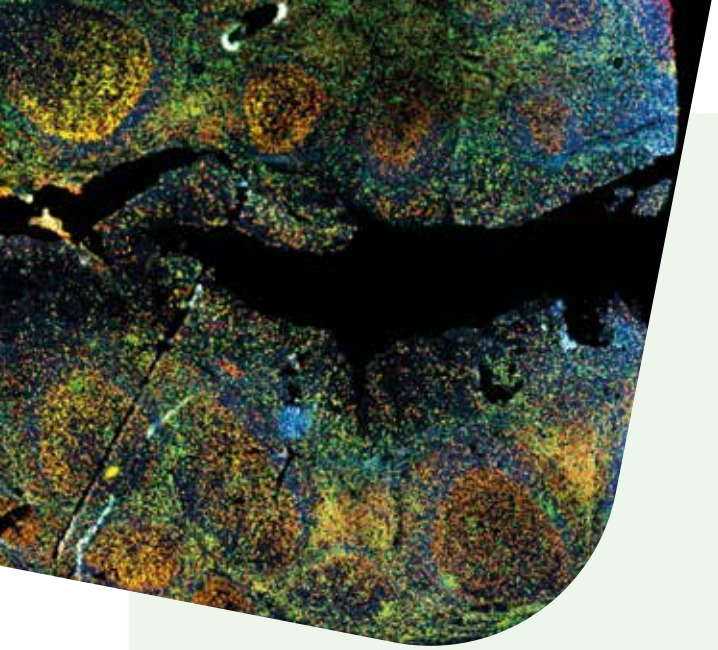
Berliere M, Piette N, Bernard M, Lacroix C, Gerday A, Samartzi V, Coyette M, Roelants F, Docquier MA, Touil N, Watremez C, Piette P, **Duhoux F**. Hypnosis Sedation Reduces the Duration of Different Side Effects of Cancer Treatments in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy. Cancers (Basel). 2021 Aug 18;13(16):4147.

Beyaert S, **Machiels JP, Schmitz S**. Vaccine-Based Immunotherapy for Head and Neck Cancers. Cancers (Basel). 2021 Nov 30;13(23):6041.

Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, Halámková J, Mattheis S, Baujat B, Hardillo J, Smeele L, van Herpen C, Castro A, **Machiels JP**; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org; EURACAN. Nasopharyngeal carcinoma: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2021 Apr;32(4):452-465.

Condorelli M, Bruzzone M, Ceppi M, Ferrari A, Grinshpun A, Hamy AS, de Azambuja E, Carrasco E, Peccatori FA, Di Meglio A, Paluch-Shimon S, Poorvu PD, Venturelli M, Rousset-Jablonski C, Senechal C, Livraghi L, Ponzone R, De Marchis L, Pogoda K, Sonnenblick A, Villarreal-Garza C, Córdoba O, Teixeira L, Clatot F, Punie K, Graffeo R, Dieci MV, Pérez-Fidalgo JA, **Duhoux FP**, Puglisi F, Ferreira AR, Blondeaux E, Peretz-Yablonski T, Caron O, Saule C, Ameye L, Balmaña J, Partridge AH, Azim HA, Demeestere I, Lambertini M. Safety of assisted reproductive techniques in young women harboring germline pathogenic variants in BRCA1/2 with a pregnancy after prior history of breast cancer. ESMO Open. 2021 Dec;6(6):100300.

D'Huyvetter M, Vos J, Caveliers V, Vaneycken I, Heemskerk J, **Duhoux FP**, Fontaine C, Vanhoeij M, Windhorst AD, Aa FV, Hendrikse NH, Eersels JLE, Everaert H, Gykiere P, Devoogdt N, Raes G, Lahoutte T, Keyaerts M.



Phase I Trial of 131I-GMIB-Anti-HER2-VHH1, a New Promising Candidate for HER2-Targeted Radionuclide Therapy in Breast Cancer Patients. J Nucl Med. 2021 Aug 1;62(8):1097-1105.

Galot R, Le Tourneau C, Saada-Bouzid E, Daste A, Even C, Debruyne P, Henry S, Zanetta S, Rutten A, Licitra L, Canon JL, Kaminsky MC, Specenier P, Rottey S, Guigay J, Kong A, Tinhofer I, Borcoman E, Dirix L, Raveloarivahy T, Fortpied C, Vanlancker M, Morfouace M, Govaerts AS, **Machiels JP**. A phase II study of monalizumab in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: The I1 cohort of the EORTC-HNCG-1559 UPSTREAM trial. Eur J Cancer. 2021 Oct 9;158:17-26.

Harrington KJ, Soulières D, Le Tourneau C, Dinis J, Licitra LF, Ahn MJ, Soria A, **Machiels JP**, Mach N, Mehra R, Burtness B, Ellison MC, Cheng JD, Chirovsky DR, Swaby RF, Cohen EEW. Quality of Life With Pembrolizumab for Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: KEYNOTE-040. J Natl Cancer Inst. 2021 Feb 1;113(2):171-181.

Honoré N, Galot R, van Marcke C, Limaye N, **Machiels JP**. Liquid Biopsy to Detect Minimal Residual Disease: Methodology and Impact. Cancers (Basel). 2021 Oct 26;13(21):5364.

Jhaveri K, Juric D, Yap YS, Cresta S, Layman RM, **Duhoux FP**, Terret C, Takahashi S, Huober J, Kundamal N, Sheng Q, Balbin A, Ji Y, He W, Crystal A, De Vita S, Curigliano G. A Phase I Study of LSZ102, an Oral Selective Estrogen Receptor Degrader, with or without Ribociclib or Alpelisib, in Patients with Estrogen Receptor-Positive Breast Cancer. Clin Cancer Res. 2021 Nov 1;27(21):5760-5770.

Kuemmel S, Campone M, Loirat D, Lopez RL, Beck JT, De Laurentiis M, Im SA, Kim SB, Kwong A, Steger GG, Adelantado EZ, **Duhoux FP**, Greil R, Kuter I, Lu YS, Tibau A, Özgüroğlu M, Scholz CW, Singer CF, Vega E, Wimberger P, Zamagni C, Couillebault XM, Fan L, Guerreiro N, Mataraza J, Sand-Dejmek J, Chan A. A Randomized Phase II Study of Anti-CSF1 Monoclonal Antibody Lacnotuzumab (MCS110) Combined with Gemcitabine and Carboplatin in Advanced Triple-Negative Breast Cancer. Clin Cancer Res. 2022 Jan 1;28(1):106-115.

Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V; EHNS Executive Board, ESMO Guidelines Committee, ESTRO Executive Board. Reprint of "Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up". Oral Oncol. 2021 Feb;113:105042.

Migeotte A, Dufour V, van Maanen A, Berliere M, Canon JL, Taylor D, **Duhoux FP**. Impact of the line of treatment on progression-free survival in patients treated with T-DM1 for metastatic breast cancer. BMC Cancer. 2021 Nov 11;21(1):1204.

Nathan P, Hassel JC, Rutkowski P, **Baurain JF**, Butler MO, Schlaak M, Sullivan RJ, Ochsenreither S, Dummer R, Kirkwood JM, Joshua AM, Sacco JJ, Shoushtari AN, Orloff M, Piulats JM, Milhem M, Salama AKS, Curti B, Demidov L, Gastaud L, Mauch C, Yushak M, Carvajal RD, Hamid O, Abdullah SE, Holland C, Goodall H, Piperno- Neumann S; IMCgp100-202 Investigators. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med. 2021 Sep 23;385(13):1196-1206.

van Caloen G, Schmitz S, van Marcke C, Caignet X, Mendola A, Pyr Dit Ruys S, Roger PP, Vertommen D, **Machiels JP.** Preclinical Evaluation of the Association of the Cyclin-Dependent Kinase 4/6 Inhibitor, Ribociclib, and Cetuximab in Squamous Cell Carcinoma of the Head and Neck. Cancers (Basel). 2021 Mar 12;13(6):1251.

van den Bent MJ, Tesileanu CMS, Wick W, Sanson M, Brandes AA, Clement PM, Erridge S, 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, Reijneveld J, Enting RH, Caparrotti F, Lesimple T, Clenton S, Gijtenbeek A, Lim E, Herrlinger U, Hau P, Dhermain F, de Heer I, Aldape K, Jenkins RB, Dubbink HJ, Kros JM, Wesseling P, Nuyens S, Golfinopoulos V, Gorlia T, French P, Baumert BG. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol. 2021 Jun;22(6):813-823.

van Marcke C, Honoré N, van der Elst A, Beyaert S, Derouane F, Dumont C, Aboubakar Nana F, Baurain JF, Borbath I, Collard P, Cornélis F, De Cuyper A, Duhoux FP, Filleul B, Galot R, Gizzi M, Mazzeo F, Pieters T, Seront E, Sinapi I, Van den Eynde M, Whenham N, Yombi JC, Scohy A, van Maanen A, **Machiels JP**. Safety of systemic anti-cancer treatment in oncology patients with non-severe COVID-19: a cohort study. BMC Cancer. 2021 May 20;21(1):578.

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 human reproduction, both male and female:

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

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

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

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OVARIAN TISSUE CRYOPRESERVATION AND TRANSPLANTATION

Cryobanking

C. Hossay, M-M. Dolmans

Chemotherapy and/or radiotherapy can induce premature menopause in young cancer patients, especially if alkylating agents or bone marrow transplantation are needed (1,2). Certain benign conditions also carry the risk of premature ovarian failure, such as recurrent ovarian cysts and some autoimmune and hematological disorders requiring chemotherapy (3). Fertility preservation options proposed to women are cryopreservation of oocytes or ovarian tissue freezing (3,4). In case of prepubertal patients, fertility preservation remains even more challenging due to immaturity of the ovary (5).

The ovarian tissue bank at Cliniques Universitaires St Luc (one of the first and largest in the world) contains tissue from more than 750 patients. The pregnancy rate after autotransplantation is 38% (6), which is highly encouraging. Noteworthy, we recently highlighted the deleterious effect of previous radiation to the pelvis on the outcomes of ovarian tissue cryopreservation (OTC) and transplantation, which appears to considerably decrease the likelihood of a successful pregnancy upon transplantation and may constitute a contraindication to reimplantation (6).

Development of optimal transport conditions for human ovarian tissue

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

Recently, we have been concentrating on the influence of the transport procedure on ovarian tissue (7). To this end, we have been analyzing the effects of the most widely used transport media. We observed high lactate release from ovarian tissue transported for up to 24 hours at 4°C, as well as low rates of necrosis and apoptosis.

Safety of ovarian tissue autotransplantation

T.Y.T. Nguyen, C. Hossay, M-M. Dolmans

One of the main drawbacks of OTC and transplantation is the risk of reimplanting malignant cells together with the ovarian tissue. Ovarian metastasis potential upon transplantation has been documented in patients with leukaemia, borderline ovarian tumours, advanced breast cancer and Ewing sarcoma. However, data on the safety of transplanting frozen-thawed ovarian tissue from patients suffering from central nervous system (CNS) tumours, which is the second most prevalent cancer type (26%) in patients aged 0-14 years and the most prevalent cancer type in patients aged 15-19 years, were still lacking. Our study clearly demonstrates no tumor seeding in the frozen-thawed and xenografted tissue of patients with CNS cancers (8,9), indicating that the risk of disseminated disease in CNS patients is minimal (10). This information is vital for doctors to provide patients with meaningful and accurate advice on the possibilities and risks of ovarian tissue reimplantation.

Ovarian tissue cryopreservation in prepubertal girls

M-M. Dolmans, A. Camboni

OTC is the only available option for fertility preservation in prepubertal patients. However, due to the lack of published studies, human prepubertal ovarian tissue is poorly understood. Experimental studies have demonstrated the capacity of prepubertal follicles to grow to advanced stages (11), but adequate growth competence and maturity are still to be assessed. We reported differences in the number, activity, and morphology of mitochondria in prepubertal versus adult ovarian follicles, suggesting that consequential modifications might occur during puberty, which could be the window of opportunity required by mitochondria to undergo changes needed to reach maturity, and hence the capacity for ovulation and fertilization (12). We also demonstrated that the basal lamina around prepubertal follicles is less mature than around adult follicles, but that grafting could induce maturation of the basal lamina around prepubertal follicles (13).

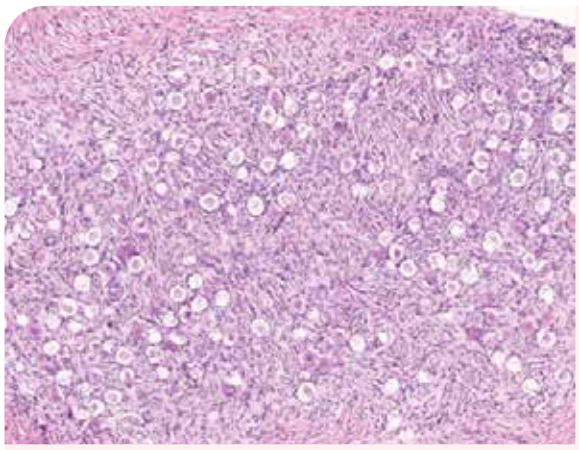


Figure 1. Prepubertal ovarian tissue

Follicle activation after ovarian tissue cryopreservation

C. Hossay, A. Camboni, M-M. Dolmans

While OTC and transplantation is an effective strategy for fertility preservation and restoration, the massive burnout in the primordial follicle pool occurring after transplantation limits the grafts longevity and in turn the effectiveness of the procedure. We investigated the potential causes for primordial follicle pool depletion in cryopreserved human ovarian tissue by assessing the impact of freezing, in vitro culture (IVC) and chorioallantoic membrane (CAM)-grafting on early follicle dynamics (14). Based on our findings and data from literature, we demonstrated that freezing and thawing procedures have no impact on initial follicle

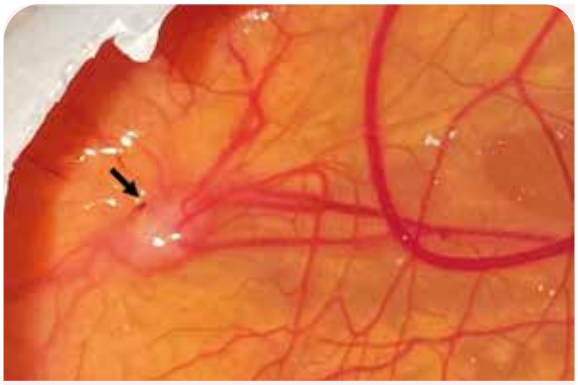


Figure 2. Ovarian tissue grafted on CAM (day 6)

dynamics. The primordial follicle pool depletion appeared to be rather due to ovarian cortical strips preparation and IVC itself, through both follicle activation, by upregulation of the PI3K/Akt/FOXO pathway, and increased follicle apoptosis. However, CAM-grafting was able to counteract primordial follicle pool exhaustion by inhibiting its activation through downregulation of the PI3K/Akt/FOXO pathway and decreasing the apoptotic follicle rates, presumably as a result of rapid graft revascularization and/or a probable role of circulating embryonic AMH as suggested in literature.

Improving in vitro primordial follicle survival rates (ongoing project)

F. Vitale, M-M. Dolmans

As aforementioned, there are still considerable limitations that must be addressed to improve outcomes of OTC, such as the comparatively short half-life of grafted tissue, and potential reintroduction of malignant cells in transplanted tissue. In order to rise to these challenges, IVC of ovarian tissue has been proposed as an alternative fertility preservation approach, which would potentially generate mature and fertilizable oocytes. Although this technique has been widely studied, short-term in vitro survival rates of primordial follicles (PFs) remains a serious concern. The first part of the project aims to determine how oxygen concentrations affect in vitro activation and subsequent growth of human PFs. These data will bring us one step closer to identifying the best IVC conditions for early-stage follicles. In the second part, we will investigate whether adding adipose tissue-derived stem cells (ASCs) to IVC preparations protects the PMF pool from direct follicle death and/or abnormal activation. We hope to provide insights into the role of ASCs and their secretome in the context of in vitro PMF activation and follicle survival. This strategy will optimize follicle IVC outcomes in terms of enhancing both the number and quality of growing follicles.

REFERENCES 2021

1. Donnez J, Dolmans MM. Fertility preservation in men and women: Where are we in 2021? Are we rising to the challenge? **Fertil Steril**. 115:1089-1090, 2021.

2. Dolmans MM, Donnez J. Chemotherapy with alkylating agents: Is follicle activation the only mechanism responsible for the loss of primordial follicles? **Fertil Steril**. 115:1166-1167, 2021.

3. Dolmans MM, Donnez J. Fertility preservation in women for medical and social reasons: Oocytes vs ovarian tissue. **Best Pract Res Clin Obstet Gynaecol**. 70:63-80, 2021.

4. Dolmans MM, Donnez J, Cacciottola L. Fertility Preservation: The Challenge of Freezing and Transplanting Ovarian Tissue. **Trends Mol Med**.27:777-791, 2021.

5. Dolmans MM, Hossay C, Nguyen TYT, Poirot C. Fertility Preservation: How to Preserve Ovarian Function in Children, Adolescents and Adults. **J Clin Med.** 10:5247, 2021.

6. 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.

7. Vilela JMV, Dolmans MM, Amorim CA. Ovarian tissue transportation: a systematic review. **Reprod Biomed Online.** 42:351-365, 2021.

8. Nguyen TYT, Cacciottola L, Camboni A, et al. Ovarian tissue cryopreservation and transplantation in patients with central nervous system tumours. **Hum Reprod.** 36:1296-1309, 2021.

9. Nguyen TYT, Camboni A, Masciangelo R, Donnez J, Dolmans MM. Investigation of malignant cells in ovarian tissue from a patient with central nervous system primitive neuroectodermal tumor relapse after ovarian tissue transplantation. **Acta Obstet Gynecol Scand.** 100:555-556, 2021.

10. Nguyen TYT, Camboni A, Masciangelo R, Donnez J, Dolmans M-M. Is Ovarian Tissue Transplantation Safe in Patients with Central Nervous System Primitive Neuroectodermal Tumors? **J Clin Med.** 9:4101, 2020.

11. Masciangelo R, Chiti MC, Philippart C, Amorim CA, Donnez J, Camboni A, Dolmans MM. Follicle populations and vascularization in ovarian tissue of pediatric patients before and after longterm grafting. **Fertil Steril.** 114:1330–8, 2020.

12. Masciangelo R, Chiti MC, Camboni A, Amorim CA, Donnez J, Dolmans MM. Mitochondrial content, activity, and morphology in prepubertal and adult human ovaries. J **Assist Reprod Genet.** 38:2581-2590, 2021.

13. Philippart C, Masciangelo R, Camboni A, Donnez J, Dolmans MM. Basal lamina characterization in frozen-thawed and long-term grafted human prepubertal ovarian tissue. **Reprod Biomed Online.** 42:859-869, 2021.

14. Hossay C, Tramacere F, Camboni A, Cacciottola L, Squifflet J, Donnez J, Dolmans MM. Follicle burnout in human ovarian tissue: effect of freezing, culture and grafting. Submitted to Hum Reprod.

ENDOMETRIOSIS

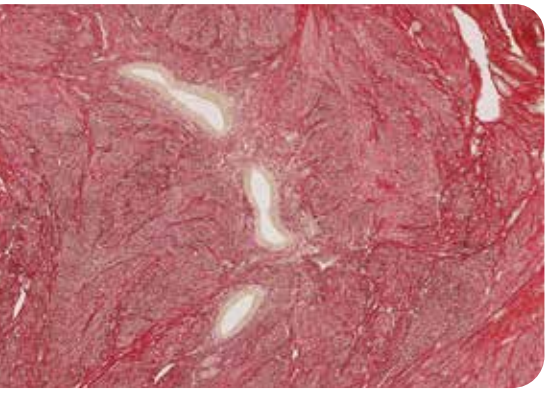
Endometriosis is a female reproductive disorder characterized by growth of uterine tissue in distant sites, affecting around 2–10% of women of reproductive-age and causing chronic pelvic pain and infertility. Its pathogenesis is complex and still partially unexplained. Determining its mechanisms is vital for early identification, as well as disease management and development of novel therapeutic strategies (1). Although oral contraceptives and progestogens work well in two thirds of patients, the rest present with progestogen resistance, rendering the treatment ineffective. Since clinical evidence shows that estrogens play a critical role in disease pathogenesis, lowering their levels with oral gonadotropin-releasing hormone (GnRH) antagonists takes all its sense (2). Oral GnRH antagonists have proved to be effective, and may represent an alternative therapeutical approach, especially in women with progestogen resistance (3). Furthermore, there is increasing evidence of the role and interaction of chronic inflammation and oxidative stress in disease development and progression (4). Targeting oxidative stress looks to be a promising strategy to both curb endometriotic lesion progression and alleviate endometriosis-associated symptoms (5). More investigations are nevertheless needed to develop effective therapeutic strategies for clinical application. functions underlines how important the role of chronic inflammation is in this pathological condition. Targeting oxidative stress looks to be a promising strategy to both curb endometriotic lesion progression and alleviate endometriosis-associated symptoms of chronic pain and infertility (5). More investigations are nevertheless needed to develop effective therapeutic strategies for clinical application.

REFERENCES 2021

1. Kapoor R, Stratopoulou CA, Dolmans MM. Pathogenesis of Endometriosis: New Insights into Prospective Therapies. Int J Mol Sci. 22:11700, 2021.
2. Donnez J, Dolmans MM. Endometriosis and Medical Therapy: From Progestogens to Progesterone Resistance to GnRH Antagonists: A Review. J Clin Med. 10:1085, 2021.
3. Donnez J, Dolmans MM. GnRH Antagonists with or without Add-Back Therapy: A New Alternative in the Management of Endometriosis?. Int J Mol Sci. 22:11342, 2021.
4. Cacciottola L, Donnez J, Dolmans MM. Oxidative stress, mitochondria, and infertility: Is the relationship fully established?. Fertil Steril. 116:306-308., 2021.
5. Cacciottola L, Donnez J, Dolmans MM. Can Endometriosis-Related Oxidative Stress Pave the Way for New Treatment Targets?. Int J Mol Sci. 22:7138, 2021.

ADENOMYOSIS

C.A. Stratopoulou, M. d'Argent, S. Cussac, A. Camboni, M-M. Dolmans



Uterine adenomyosis is a commonly encountered chronic condition, estimated to affect 20% of gynecology patients, causing them heavy menstrual bleeding, intense pelvic pain, and infertility (1, 2). Despite its high prevalence, the causes and pathogenesis of adenomyosis are not yet fully understood and there is no drug to specifically treat the disease (2). Our team aims to shed light on the complex pathogenic mechanisms of adenomyosis, in view of contributing to the ongoing research into novel therapeutic options. We are currently investigating the mechanisms of autophagy and apoptosis in endometrium, to understand their role and determine whether there are differences between healthy tissue and the lesions, which promote the disease. We have also focused on the potential link between adenomyosis and deep endometriotic nodules, as the notion of a common pathogenesis of the two is becoming increasingly popular (3, 4). Indeed, we observed multiple common pathogenic characteristics, including increased accumulation of macrophages, extensive fibrosis, and a dysregulated mechanism of angiogenesis (4). These findings pave the way for more rigorous research into the potential common origin of adenomyosis and endometriosis, and its clinical value in the management of these debilitating conditions

REFERENCES 2021

1. Donnez J, Stratopoulou CA, Dolmans MM. Uterine Adenomyosis: From Disease Pathogenesis to a New Medical Approach Using GnRH Antagonists. **Int J Environ Res Public Health.** 18:9941, 2021.
2. Stratopoulou CA, Donnez J, Dolmans MM. Conservative Management of Uterine Adenomyosis: Medical vs. Surgical Approach. Stratopoulou CA, Donnez J, Dolmans MM. **J Clin Med.** 10:4878, 2021.
3. Kapoor R, Stratopoulou CA, Dolmans MM. Pathogenesis of Endometriosis: New Insights into Prospective Therapies. **Int J Mol Sci**. 22:11700, 2021.
4. Stratopoulou CA, Camboni A, Donnez J, Dolmans MM. Identifying Common Pathogenic Features in Deep Endometriotic Nodules and Uterine Adenomyosis. **J Clin Med.** 10:4585, 2021.

FERTILITY PRESERVATION AND RESTORATION APPROACHES FOR PREPUBERTAL BOYS

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

Solutions to preserve fertility before puberty are therefore eagerly awaited (1).

Our research focuses on two main areas:

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

b) Creation of a bioengineered testicular organoid as an in vitro study model for the pathophysiology of the spermatogonial stem cell (SSC) niche and as an alternative fertility restoration method.

Fertility preservation and restoration from cryopreserved ITT containing SSCs

J. Poels, D. Kourta, S. De Windt, F. Del Vento, M. Kanbar, C. Wyns

Banking of ITT from prepubertal boys undergoing gonadotoxic treatments was initiated after the establishment and optimization of a cryopreservation protocol able to preserve the integrity of the tissue. However, fertility restoration with human slow-frozen-thawed ITT has not yet been achieved. As azoospermia occurred during adulthood in 29% of our patient population, clinically applicable fertility restorations strategies are urgently needed. Our research is therefore investigating two different fertility restoration strategies with frozen ITT:

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

Encapsulation of murine ITT in hydrogels supplemented with VEGF nanoparticles was shown to improve vascular density, VEGFR2 activation and endothelial proliferation, doubling spermatogonial survival following encapsulation of ITT in alginate (1). When alginate hydrogels were supplemented with nanoparticles loaded with an anti-necrotic factor or with VEGF + PDGF, spermatogonial survival and vascular network maturation were also respectively improved (3). These strategies can be applied to human ITT in order to improve the avascular grafting procedure.

2) In vitro maturation of SSCs as a procedure that circumvents the risk of reintroducing cancer cells in cured patients (4).

An organotypic culture system was developed to achieve Sertoli cell maturation, Leydig cell functionality and partial establishment of the blood-testis barrier. After optimizing culture media, we were the first team to demonstrate successful differentiation of SSCs up to the haploid stage. Aiming at improving the efficiency of ITT culture and completing the final maturation steps, static and dynamic silicone-based culture system were compared. While preliminary results show promising outcomes compared to classical approaches, optimization of culture-media components is also explored.

Deciphering the physiopathology of Klinefelter syndrome (KS)

J. Poels, MG. Giudice, C. Wyns

We analyzed functional and morphological alterations to the somatic compartment of KS testes and showed that expression of BTB proteins, i.e. connexin-43 and claudin-11, was significantly reduced and disorganized. Androgen receptors in Sertoli cells and INSL3 in Leydig cells were also significantly reduced. Induced pluripotent stem cells from KS fibroblasts appeared a useful tool to unravel KS physiopathology. Currently, we explore how a testicular organoid (see section on Regenerative Medicine), applied as a novel investigative tool, could be useful to further elucidate germ and somatic cells behaviour in KS.

REFERENCES

1. Wyns C, Kanbar M, Giudice MG, Poels J. Fertility preservation for prepubertal boys: lessons learned from the past and update on remaining challenges towards clinical translation. Hum Reprod Update. 27(3), 433–459, 2021.

2. 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.

3. Del Vento F, Poels J, Vermeulen M, Ucakar B, Giudice MG, Kanbar M, des Rieux A, Wyns C. Accelerated and Improved Vascular Maturity after Transplantation of Testicular Tissue in Hydrogels Supplemented with VEGF- and PDGF-Loaded Nanoparticles. Int J Mol Sci, 22(11), 5779, 2021.

4. Wyns C, Kanbar M. In vitro spermatogenesis, in Female and Male fertility preservation (Springer Cham., 2022), pp 587–607.

5. Botman O, Hibaoui Y, Giudice MG, Ambroise J, Creppe C, Feki A, Wyns C. Modeling Klinefelter Syndrome Using Induced Pluripotent Stem Cells Reveals Impaired Germ Cell Differentiation. Front Cell Dev Biol, 8, 567454, 2020

FIBROIDS

Uterine fibroids are the most common form of benign uterine tumors, causing heavy menstrual bleeding (HMB), pelvic pain, infertility and pressure symptoms. In women of childbearing age and with a desire to preserve fertility, the treatment aims to preserve the uterus to the maximum, taking into account the number, size and location of fibroids (1). In women requiring in vitro fertilization, fibroids more than 3-4 centimeters should be surgically removed (2). Medical treatment with oral contraceptives and progestogens may curtail HMB in case of moderate disease. However, they do not reduce myoma size, and therefore have limited benefits for women with fibroid-related infertility. Moreover, it is clear that progesterone and progestogens promote myoma growth. Gonadotropin-releasing hormone (GnRH) agonists can be also considered, as they boost hemoglobin levels and significantly decreases fibroid volume, but long-term treatment is contraindicated because of hypoestrogenism resulting in bone mineral density loss and hot flushes. An emerging therapeutical approach with GnRH antagonists with add-back therapy, is yielding promising outcomes in terms of volume reduction, control of fibroid-related HMB, without the deleterious side-effects of prolonged hypoestrogenism (1).

REFERENCES

1. Dolmans MM, Cacciottola L, Donnez J. Conservative Management of Uterine Fibroid-Related Heavy Menstrual Bleeding and Infertility: Time for a Deeper Mechanistic Understanding and an Individualized Approach. **J Clin Med.** 10:4389, 2021.

2. Dolmans MM, Isaacson K, Zhang W, et al. Intramural myomas more than 3-4 centimeters should be surgically removed before in vitro fertilization. **Fertil Steril.** 116:945-958, 2021.

MEDICAL MICROBIOLOGY

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

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

The pole of microbiology includes the virology and the bacteriology groups and is devoted to clinical microbiology research. It acts as a Belgian National AIDS Reference Laboratory (ARL), and houses the National Reference Centers for *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, viral hepatitis and cytomegalovirus infection.

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BACTERIOLOGY

Diagnosis and epidemiology of Clostridioides difficile Infections (CDI))

Eléonore Ngyuvula Mantu, Kate Soumillion, Michel Delmée, Ahalieyah Anantharajah

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

Our group has acquired a nationally and internationally renowned expertise in the diagnosis and the study of the epidemiology of C. *difficile* infections and is the National Reference Center (NRC) for this pathogen, a contract with Sciensano, the National Institute of Public Health was renewed in 2020 for 4 years in order to conduct national epidemiological surveys in collaboration with Sciensano and Belgian hospitals.

Cultured isolates are collected and typed by ribotyping. 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 and antimicrobial susceptibility to monitor the emergence of hypervirulent and/or multi-resistant strains. 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 (poster; 31st ECCMID 9-12 july 2021). The NRC also participates in several European programs coordinated by the ECDC.

Development of metagenomic analysis of microbiome for clinical use

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

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

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

Microbiological diagnosis of septicemia

Alexia Verroken, 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 (MALDI-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. The development of rapid AST tools has taken some additional time. Ultimately local protocols of direct automated AST from a centrifuged positive blood culture pellet were validated with varying results including reduced performances for Gram positive bacteria. Alongside commercial rapid AST systems 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%.

Very recently, a distinct approach has been developed named the FAST™ System (Qvella, Richmond Hill, Canada) designed to isolate and concentrate microorganisms directly from a positive blood culture bottle and resulting in the recovery of a liquid colony (LC) within 30 minutes. Ultimately the LC can be used for ID and AST as an equivalent of a solid subcultured colony.

We performed a study in order to evaluate the per-

formances of the FAST™ System and the FAST-PBC Prep™ cartridges (FAST testing) through the use of the resulting LC to perform

- Direct MALDI-TOF MS identification
- Direct manual and automated AST
- Direct detection of resistance through the use of rapid resistance detection tests

Approximately 200 positive blood culture bottles were tested. Data analysis and comparison to routine microbiological results and turnaround times are ongoing.

Tuberculosis and Mycobacteriology

Hector Rodriguez-Villalobos, Imane Saad Albichr

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

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

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

Borrelia burgdorferi

Benoît Kabamba-Mukadi, 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 will conduct a set of experiments on *Borrelia burgdorferi sensu lato*: identification and species characterization, culture, strain selection, quantification, challenge tests, viability tests. This ongoing study aiming 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 conducted by Laurence Geebelen is ongoing with the overall objective of estimating the health and cost burden of Lyme borreliosis and other tick-borne infections in Belgium.

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

VIROLOGY

Antiretroviral drug resistance

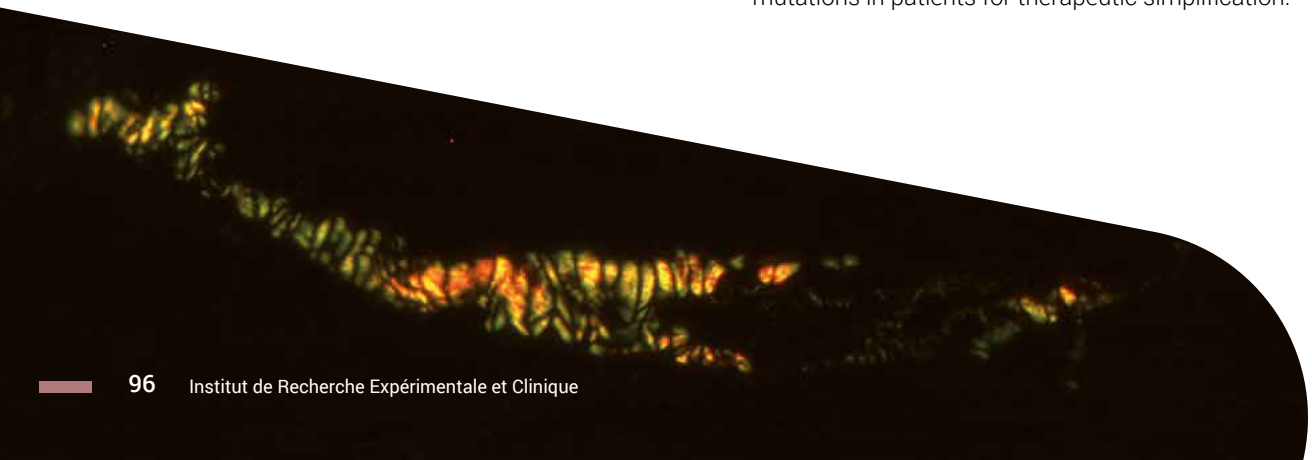
Benoît Kabamba-Mukadi, Géraldine Dessilly, Anne-Thérèse Vandenbroucke, Eléonore Ngyuvula Mantu, Kate Soumillion, Najet Lamarti

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

The recent widespread use of integrase inhibitors (INSTI) to treat people who are infected with HIV led to a surveillance program of potential transmission of resistance. The significance and impact of several natural genetic polymorphisms on drug efficacy is currently investigated within national and international collaborations. Since end of 2017, INSTI resistance mutations are investigated by the semi-automated NGS platform.

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

An ongoing study is also investigating the utility of NGS on HIV-1 proviral DNA for the detection of resistance mutations in patients for therapeutic simplification.



Towards an HIV cure

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

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

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

HIV-2 and restriction factors

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

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

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

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

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

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

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

The MBLG unit also carries out the viral culture of SARS-CoV-2 on the cell line VERO 76, clone E6 (Vero ATCC CRL-1586) in the laboratory of security level BSL3. Viral culture is the best indicator of viral infectivity, thus reflecting the infectious potential of an infected person, especially in persisting positive PCR. A seroneutralization test has also been developed.

Since 2020, collaborations are ongoing to assess the antiviral effect of certain compounds (drug, disinfectant, etc.), the persistence of disinfectants on different surfaces.

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

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

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

Viral Hepatitis

Benoît Kabamba-Mukadi, Géraldine Dessilly, Eléonore Ngyuvula Mantu, Kate Soumillion, 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 naïve 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.

EQUIPMENTS

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

REFERENCES 2021

Lardinois, Benjamin ; Belkhir, Leïla ; **Verroken, Alexia**. : *A Review of Microbiological and Clinical Features.. In: Frontiers in microbiology,* Vol. 12, p. 814944 (2021). doi:10.3389/fmicb.2021.814944. http://hdl.handle.net/2078.1/259738

Labriola, Laura ; **Scohy, Anaïs** ; Seghers, François ; Perlot, Quentin ; De Greef, Julien ; Desmet, Christine ; Romain, Cécile ; Morelle, Johann ; Yombi, Jean Cyr ; **Kabamba-Mukadi, Benoît** ; **Rodriguez-Villalobos, Hector** ; Jadoul, Michel. *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). doi:10.2215/CJN.12490720. http://hdl.handle.net/2078.1/238070

De Greef, Julien ; Devresse, Arnaud ; **Saad Albichr, Imane ; Scohy, Anais** ; Kanaan, Nada ; Georgery, Hélène ; Belkhir, Leila ; **Kabamba, Benoit** ; Yombi, Jean Cyr ; Goffin, Eric. *Better late than never: eventual seroconversion against SARS-CoV-2 in a kidney transplant recipient after repeated immune challenge and monoclonal antibody therapy.*. In: Kidney international, Vol. 100, no.5, p. 1131-1132 (2021). doi:10.1016/j.kint.2021.08.018. http://hdl.handle.net/2078.1/259745

Colson, Arthur ; Depoix, Christophe ; **Dessilly, Géraldine** ; Baldin, Paméla ; Danhaive, Olivier ; Hubinont, Corinne ; Sonveaux, Pierre ; Debieve, Frédéric. COVID-19 *during Pregnancy: Clinical and In Vitro Evidence against Placenta Infection at Term by SARS-CoV-2.*. In: *The American journal of pathology*, Vol. 191, no. 9, p.

1610-1623 (2021). doi:10.1016/j.ajpath.2021.05.009. http://hdl.handle.net/2078.1/248239

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*, , p. 1-4 (2021). doi:10.1080/10428194.2021.1998485. http://hdl.handle.net/2078.1/254705

Soleimani, Reza ; Khourssaji, Mehdi ; Gruson, Damien ; **Rodriguez-Villalobos, Hector** ; Berghmans, Mathilde ; Belkhir, Leïla ; Yombi, Jean Cyr ; **Kabamba-Mukadi, Benoît**. *Clinical usefulness of fully automated chemiluminescent immunoassay for quantitative antibody measurements in COVID-19 patients.*. In: *Journal of medical virology*, Vol. 93, no. 3, p. 1465-1477 (2021). doi:10.1002/jmv.26430. http://hdl.handle.net/2078.1/243825

De Greef, Julien ; **Scohy, Anaïs** ; Zech, Francis ; Aboubakar Nana, Frank ; Pilette, Charles ; Gérard, Ludovic ; Pothen, Lucie ; Yildiz, Halil ; Belkhir, Leïla ; Yombi, Jean Cyr. *Determinants of IgG antibodies kinetics after severe and critical COVID-19.. In: Journal of medical virology*, Vol. 93, no. 9, p. 5416-5424 (2021). doi:10.1002/jmv.27059. http://hdl.handle.net/2078.1/246689

Georgery, Hélène ; Devresse, Arnaud ; Yombi, Jean Cyr ; Belkhir, Leïla ; De Greef, Julien ; Darius, Tom ; Buemi, Antoine ; **Scohy, Anaïs** ; **Kabamba-Mukadi, Benoît** ; Goffin, Eric ; Kanaan, Nada. *Disappointing Immunization Rate After 2 Doses of the BNT162b2 Vaccine in a Belgian Cohort of Kidney Transplant Recipients.*. In: *Transplantation*, Vol. 105, no. 12, p. e283-e284 (2021). doi:10.1097/TP.0000000000003861. http://hdl.handle.net/2078.1/249364

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*, (2021). doi:10.1002/jmv.27471. http://hdl.handle.net/2078.1/255302

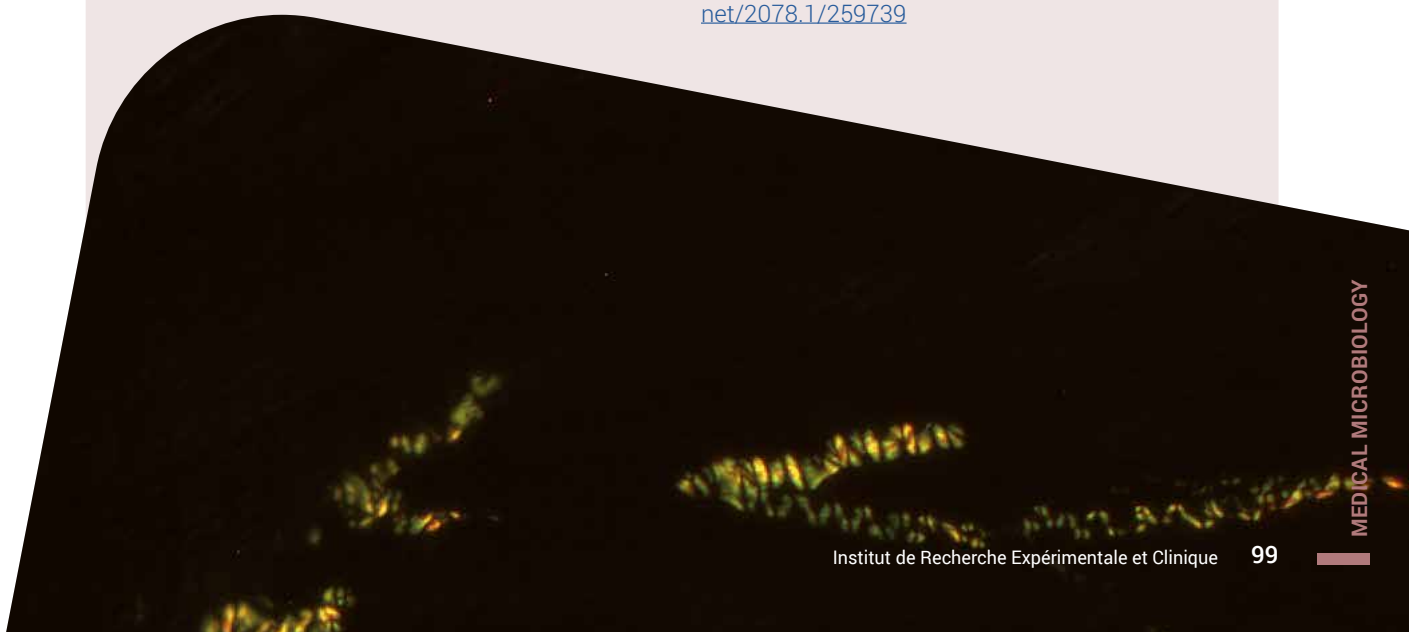
Kabamba Tshikongo, Arsène ; Kalunga, B T ; Mwamba, Claude Mulumba ; Nyembo, Christophe M. ; **Dufrasne, François** ; **Dessilly, Géraldine ; Kabamba-Mukadi, Benoît** ; Longanga, Albert Otshudi. *Epidemiological aspects and molecular characterization of the hepatitis B virus among blood donors in Lubumbashi, Democratic Republic of Congo.*. In: *Transfusion clinique et biologique*, Vol. 28, no. 1, p. 30-37 (2021). doi:10.1016/j.tracli.2020.10.012. http://hdl.handle.net/2078.1/243826

Yerbanga, Isidore W ; Resendiz-Sharpe, Agustin ; Bamba, Sanata ; Lagrou, Katrien ; Nakanabo Diallo, Seydou ; **Rodriguez-Villalobos, Hector** ; DENIS, Olivier ; Montesinos, Isabel. *First Investigative Study of Azole-Resistant in the Environment in Burkina Faso.*. In: *International journal of environmental research and public health*, Vol. 18, no. 5 (2021), p. 2250 (2021). doi:10.3390/ijerph18052250. http://hdl.handle.net/2078.1/245248

Yehouenou, Carine ; Bogaerts, Bert ; Vanneste, Kevin ; Roosens, Nancy H. C. ; De Keersmaecker, Sigrid C. J. ; Marchal, Kathleen ; Affolabi, Dissou ; Soleimani, Reza ; **Rodriguez-Villalobos, Hector** ; Van Bambeke, Françoise ; Dalleur, Olivia ; Simon, Anne. *First detection of a plasmid-encoded New-Delhi metallo-beta-lactamase-1 (NDM-1) producing Acinetobacter baumannii using whole genome sequencing, isolated in a clinical setting in Benin*. In: *Annals of Clinical Microbiology and Antimicrobials*, Vol. 20, no.1, p. 1-7 (2021). doi:10.1186/s12941-020-00411-w. http://hdl.handle.net/2078.1/240639

Rodriguez, Cristina ; Mith, Hasika ; Taminiau, Bernard ; Bouchafa, Lamia ; Van Broeck, Johan ; **Soumillion, Kate ; Ngyuvula, Eleonore** ; García-Fuentes, Eduardo ; Korsak, Nicolas ; **Delmée, Michel** ; Daube, Georges. *First isolation of Clostridioides difficile from smoked and dried freshwater fish in Cambodia*. In: *Food Control*, Vol. 124, p. 107895 (2021). doi:10.1016/j.foodcont.2021.107895. http://hdl.handle.net/2078.1/251064

Georgery, Hélène ; Devresse, Arnaud ; Yombi, Jean-Cyr ; Belkhir, Leila ; De Greef, Julien ; **Scohy, Anais** ; Kanaan, Nada ; **Kabamba, Benoit** ; Morelle, Johann ; Goffin, Eric. *High response rate to BNT162b2 mRNA COVID-19 vaccine among self-care dialysis patients.*. In: *Clinical kidney journal*, Vol. 14, no.9, p. 2129-2131 (2021). doi:10.1093/ckj/sfab101. http://hdl.handle.net/2078.1/259739



Anantharajah, Ahalieyah ; Helaers, Raphaël ; Defour, Jean-Philippe ; Olive, Nathalie ; Kabera, Florence ; Croonen, Luc ; Deldime, Françoise ; Vaerman, Jean-Luc ; Barbée, Cindy ; Bodéus, Monique ; **Scohy, Anais ; Verroken, Alexia ; Rodriguez-Villalobos, Hector ; Kabamba-Mukadi, Benoît**. *How to choose the right real-time RT-PCR primer sets for the SARS-CoV-2 genome detection?*. In: *Journal of virological methods*, Vol. 295, p. 114197 (2021). doi:10.1016/j.jviromet.2021.114197. http://hdl.handle.net/2078.1/259734

Berzow, Dirk ; Descamps, Diane ; Obermeier, Martin ; Charpentier, Charlotte ; Kaiser, Rolf ; Guertler, Lutz ; Eberle, Josef ; Wensing, Annemarie ; Sierra, Saleta ; **Ruelle, Jean** ; Gomes, Perpetua ; Mansinho, Kamal ; Taylor, Ninon ; Jensen, Björn ; Döring, Matthias ; Stürmer, Martin ; Rockstroh, Jürgen ; Camacho, Ricardo. Human Immunodeficiency Virus-2 (HIV-2): *A Summary of the Present Standard of Care and Treatment Options for Individuals Living with HIV-2 in Western Europe.*. In: *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, Vol. 72, no.3, p. 503-509 (2021). doi:10.1093/cid/ciaa275. http://hdl.handle.net/2078.1/243908

Guilmot, Antoine ; Maldonado Slootjes, Sofia Ijke ; Sellimi, Amina ; Bronchain, Maroussia ; Hanseeuw, Bernard ; Belkhir, Leïla ; Yombi, Jean Cyr ; De Greef, Julien ; Pothen, Lucie ; Yildiz, Halil ; Duprez, Thierry ; Fillee, Catherine ; **Anantharajah, Ahalieyah** ; Capes, Antoine ; Hantson, Philippe ; Jacquerye, Philippe ; Raymackers, Jean-Marc ; London, Frédéric ; El Sankari, Souraya ; Ivanoiu, Adrian ; Maggi, Pietro ; Van Pesch, Vincent. *Immune-mediated neurological syndromes in SARS-CoV-2-infected patients*.. In: *Journal of neurology*, Vol. 268, no. 3, p. 751-757 (2021). doi:10.1007/s00415-020-10108-x. http://hdl.handle.net/2078.1/232183

Labriola, Laura ; **Scohy, Anaïs** ; Van Regemorter, Elliott ; Robert, Arnaud ; Clerbaux, Gaëtan ; Gillerot, Gaelle ; Pochet, Jean-Michel ; Biller, Pauline ; De Schuiteneer, Manuel ; Morelle, Johann ; Yombi, Jean Cyr ; **Kabamba, Benoît ; Rodriguez-Villalobos, Hector** ; Jadoul, Michel. *Immunogenicity of BNT162b2 SARS-CoV-2 Vaccine in a Multicenter Cohort of Nursing Home Residents Receiving Maintenance Hemodialysis*.. In: *American journal of kidney diseases : the official journal of the National Kidney Foundation*, Vol. 78, no.5, p. 766-768 (2021). doi:10.1053/j.ajkd.2021.07.004. http://hdl.handle.net/2078.1/259740

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. *Impact of Kidney Transplantation on Humoral Immunity against SARS-CoV-2: a Case-Series from Belgium*.. In: *Transplantation*, Vol. 105, no. 11, p. e257-e258 (2021). doi:10.1097/TP.0000000000003910. http://hdl.handle.net/2078.1/249897

Blairon, Laurent ; Mokrane, Saphia ; Wilmet, Alain ; **Dessilly, Géraldine ; Kabamba-Mukadi, Benoît** ; Beukinga, Ingrid ; Tré-Hardy, Marie. *Large-scale, molecular and serological SARS-CoV-2 screening of healthcare workers in a 4-site public hospital in Belgium after COVID-19 outbreak*.. In: *The Journal of infection*, Vol. 82, no. 1, p. 159-198 (2021). doi:10.1016/j.jinf.2020.07.033. http://hdl.handle.net/2078.1/232670

Demoulin, Nathalie ; **Scohy, Anaïs** ; Gillion, Valentine ; Godefroid, Nathalie ; Jadoul, Michel ; Morelle, Johann. *Low rates of humoral response to BNT162b2 SARS-CoV-2 vaccination in patients with immune-mediated kidney diseases treated with rituximab*.. In: *Clinical kidney journal*, Vol. 14, no.9, p. 2132-2133 (2021). doi:10.1093/ckj/sfab102. http://hdl.handle.net/2078.1/259741

Garrigos, Thomas ; Dollat, Manon ; Magallon, Arnaud ; Chapuis, Angélique ; Varin, Véronique ; Bador, Julien ; Makki, Nadia ; Cremet, Lise ; Persyn, Elise ; Cardot-Martin, Emilie ; Echahidi, Fedoua ; Peeters, Charlotte ; Pierard, Denis ; Vandamme, Peter ; **Verroken, Alexia** ; Neuwirth, Catherine ; Amoureux, Lucie. *Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry for Rapid Detection of Isolates Belonging to the Epidemic Clones Achromobacter xylosoxidans ST137 and Achromobacter ruhlandii DES from Cystic Fibrosis Patients*.. In: *Journal of clinical microbiology*, Vol. 59, no.10, p. e0094621 (2021). doi:10.1128/JCM.00946-21. http://hdl.handle.net/2078.1/259732

Gato, Eva ; **Anantharajah, Ahalieyah** ; Arroyo, Manuel J ; Artacho, María José ; Caballero, Juan de Dios ; Candela, Ana ; Chudějová, Kateřina ; Constanso, Ignacio Pedro ; Elías, Cristina ; Fernández, Javier ; Jiménez, Jesús ; Lumbreras, Pilar ; Méndez, Gema ; Mulet, Xavier ; Pérez-Palacios, Patricia ; Rodríguez-Sánchez, Belén ; Cantón, Rafael ; Hrabák, Jaroslav ; Mancera, Luis ; Martínez-Martínez, Luis ; Oliver, Antonio ; Pascual, Álvaro ; **Verroken, Alexia** ; Bou, Germán ; Oviaño, Marina. *Multicenter Performance Evaluation of MALDI-TOF MS for Rapid Detection of Carbapenemase Activity in Enterobacterales: The Future of Networking Data Analysis With Online Software*.. In: *Frontiers in microbiology*, Vol. 12, p. 789731 (2021). doi:10.3389/fmicb.2021.789731. http://hdl.handle.net/2078.1/259731

Xavier, Basil Britto ; Coppens, Jasmine ; De Koster, Sien ; Rajakani, Sahaya Glingston ; Van Goethem, Sam ; Mzougui, Samy ; **Anantharajah, Ahalieyah** ; Lammens, Christine ; Loens, Katherine ; Glupczynski, Youri ; Goossens, Herman ; Matheeussen, Veerle. *Novel vancomycin resistance gene cluster in ST1486, Belgium, June 2021*.. In: *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, Vol. 26, no.36 (2021). doi:10.2807/1560-7917.ES.2021.26.36.2100767. http://hdl.handle.net/2078.1/259733

van Marcke, Cédric ; Honoré, Natasha ; van der Elst, Athénaïs ; Beyaert, Simon ; Derouane, Françoise ; Dumont, Caroline ; Aboubakar Nana, Frank ; Baurain, Jean-François ; Borbath, Ivan ; Collard, Philippe ; Cornelis, Frank ; De Cuyper, Astrid ; Duhoux, Francois ; Filleul, Bertrand ; Galot, Rachel ; Gizzi, Marco ; Mazzeo, Filomena ; Pieters, Thierry ; Seront, Emmanuel ; Sinapi, Isabelle ; Van Den Eynde, Marc ; Whenham, Nicolas ;

Yombi, Jean Cyr ; **Scohy, Anaïs** ; van Maanen, Aline ; Machiels, Jean-Pascal. *Safety of systemic anti-cancer treatment in oncology patients with non-severe COVID-19: a cohort study.*. In: *BMC cancer*, Vol. 21, no.1, p. 578 [1-12] (2021). doi:10.1186/s12885-021-08349-8. http://hdl.handle.net/2078.1/253283

Scohy, Anaïs ; Gruson, Damien ; Simon, Anne ; **Kabamba-Mukadi, Benoît** ; De Greef, Julien ; Belkhir, Leïla ; **Rodriguez-Villalobos, Hector** ; Robert, Annie ; Yombi, Jean Cyr. *Seroprevalence of SARS-CoV-2 infection in health care workers of a teaching hospital in Belgium: self-reported occupational and household risk factors for seropositivity.*. In: *Diagnostic microbiology and infectious disease*, Vol. 100, no.4, p. 115414 [1-6] (2021). doi:10.1016/j.diagmicrobio.2021.115414. http://hdl.handle.net/2078.1/249111

Dufour, Inès ; Wérion, Alexis ; Belkhir, Leïla ; Wisniewska, Anastazja ; Perrot, Marie ; De Greef, Julien ; Schmit, Gregory ; Yombi, Jean Cyr ; Wittebole, Xavier ; Laterre, Pierre-François ; Jadoul, Michel ; Gerard, Ludovic ; Morelle, Johann. *Serum uric acid, disease severity and outcomes in COVID-19*, **collab. CUSL COVID-19 Research Group.** In: *Critical Care*, Vol. 25, no. 1, p. 212 [1-12] (2021). doi:10.1186/s13054-021-03616-3. http://hdl.handle.net/2078.1/248266

Devresse, Arnaud ; **Saad Albichr, Imane** ; Georgery, Hélène ; Yombi, Jean Cyr ; De Greef, Julien ; Belkhir, Leïla ; Mzougui, Samy ; **Scohy, Anaïs** ; Darius, Tom ; Buemi, Antoine ; Goffin, Eric ; **Kabamba-Mukadi, Benoît** ; Kanaan, Nada. *T cell and Antibody Response after two Doses of the BNT162b2 Vaccine in a Belgian Cohort of Kidney Transplant Recipients.* In: *Transplantation*, Vol. 105, no. 10, p. e142-e143 (2021). doi:10.1097/tp.0000000000003892. http://hdl.handle.net/2078.1/249538

Jashari, Ramadan ; Vanzeebroeck, Sarah ; Petit, Pieter ; **Rodriguez-Villalobos, Hector** ; Zahra, Sharon ; Ben Said, Naziha ; Bouzet, Vanessa ; Mastrobuoni, Stefano. *The BD BACTEC FX blood culture system with the gentlemacs dissociator is suitable for sterility testing of heart valve and vascular allografts-A validation study.*. In: *Cell and tissue banking*, (2021). doi:10.1007/s10561-020-09893-6. http://hdl.handle.net/2078.1/243855

Georgery, Hélène ; Devresse, Arnaud ; **Scohy, Anaïs ; Kabamba-Mukadi, Benoît** ; Darius, Tom ; Buemi, Antoine ; De Greef, Julien ; Belkhir, Leïla ; Yombi, Jean Cyr ; Goffin, Eric ; Kanaan, Nada. *The Second Wave of COVID-19 Disease in a Kidney Transplant Recipient Cohort: A Single-center Experience in Belgium.*. In: *Transplantation*, Vol. 105, no. 3, p. e41-e42 (2021). doi:10.1097/TP.0000000000003596. http://hdl.handle.net/2078.1/243753

Leonard, Marie-Françoise ; **Rodriguez-Villalobos, Hector** ; Boisen, Nadia ; Scheutz, Flemming ; Laterre, Pierre-François ; Hantson, Philippe. *The causal relationship between O2:K7:H6 extra-intestinal pathogenic Escherichia coli (ExPEC) and native valve endocarditis: a case report.*. In: *BMC infectious diseases*, Vol. 21, no.1, p. 370 [1-4] (2021). doi:10.1186/s12879-021-06066-y. http://hdl.handle.net/2078.1/259139

Reza, Soleimani ; Mehdi, Khourssaji ; Antoine, Aupaix ; **Rodriguez-Villalobos, Hector ; SCOHY, Anaïs ; Kabamba-Mukadi, Benoît**. *Usefulness of a multiplex immunodot in case of discordant results between automated COVID-19 serological assays.*. In: Journal of virological *methods*, , p. 114129 (2021). doi:10.1016/j.jviromet.2021.114129. http://hdl.handle.net/2078.1/244723

Yildiz, Halil ; Castanares Zapatero, Diego ; Pierman, Guillaume ; Pothen, Lucie ; De Greef, Julien ; Aboubakar Nana, Frank ; **Rodriguez-Villalobos, Hector** ; Belkhir, Leïla ; Yombi, Jean Cyr. *Validation of Neutrophil-to-Lymphocyte Ratio Cut-off Value Associated with High In-Hospital Mortality in COVID-19 Patients.*. In: *International journal of general medicine*, Vol. 14, p. 5111-5117 (2021). doi:10.2147/IJGM.S326666. http://hdl.handle.net/2078.1/253281

Georgery, Hélène ; Devresse, Arnaud ; Yombi, Jean Cyr ; Belkhir, Leïla ; De Greef, Julien ; Darius, Tom ; Buemi, Antoine ; **SCOHY, Anaïs ; Kabamba-Mukadi, Benoît** ; Goffin, Eric ; Kanaan, Nada. *Very low Immunization Rate in Kidney Transplant Recipients after one Dose of the BNT162b2 Vaccine: Beware not to Lower the Guard!.* In: *Transplantation*, Vol. 105, no. 10, p. e148-e149 (2021). doi:10.1097/TP.0000000000003818. http://hdl.handle.net/2078.1/246202

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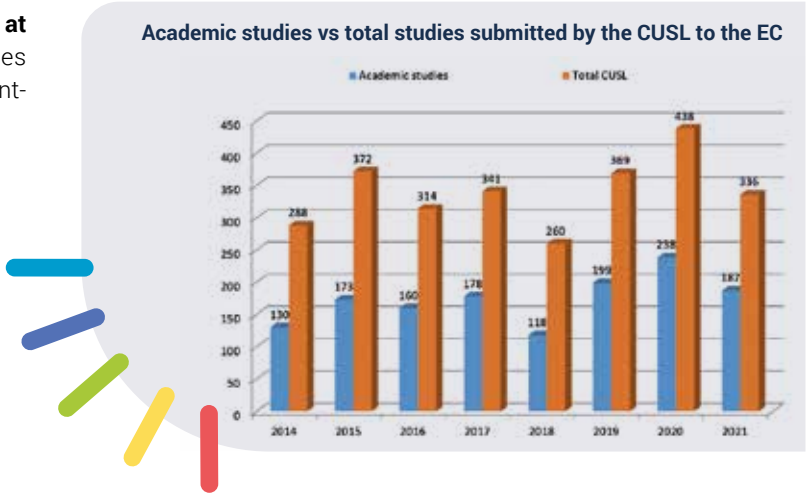
Clinical research at the Cliniques universitaires Saint-Luc (CUSL) :

DEVELOPMENT OF CLINICAL RESEARCH AT THE CUSL

Ethics Committee (EC) submissions at the CUSL: in 2021, 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	Total
Starting grant	4	4	5	3	2	**3**	**21**

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

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total
TOTAL : Clinical researchers (CUSL)	7	9	13	3	8	5	14	18	13	26	20	**30**	**167**
Of which renewals :		1	7	0	4	2	5	5	6	11	6	**17**	**65**
TOTAL : Researchers (UCL)	12	9	9	3	12	11	8	10	7	2	0	**0**	**83**
Of which renewals :		1	7	1	2	2	3	6	3	2	0	**0**	**27**

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

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
TOTAL	6	8	8	9	10	12	10	8	6	6	**7**	**90**

FNRS MANDATES SINCE 2012 (NEW APPOINTMENTS AND RENEWAL)

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
Clinicians (Clinical service)	6	11	11	9	13	13	13	13	14	**10**	**113**
Researchers (Poles)	5	4	3	3	4	4	2	7	16	**9**	**57**

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 2021, the total FTE increased from 11,8 to 12,2 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 increased by 0,3 FTE to better respond to needs. In 2021 the Strategic Council has initiated a reflection whose aim is to improve the support to academic studies sponsored by the CUSLs. To this end, a gap analysis was carried out by an external company in December.

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
Commercial (new + amendments+ CD+CTR)	291	309	282	344	484	441
Academic (external and internal agreements, MTA, DTA, grants, CTR)	74	77	165	183	257	219

In addition, 110 commercial grant contracts were managed by the CTC.

EUROPEAN PROJECTS SUPPORT (TYPE H2020)

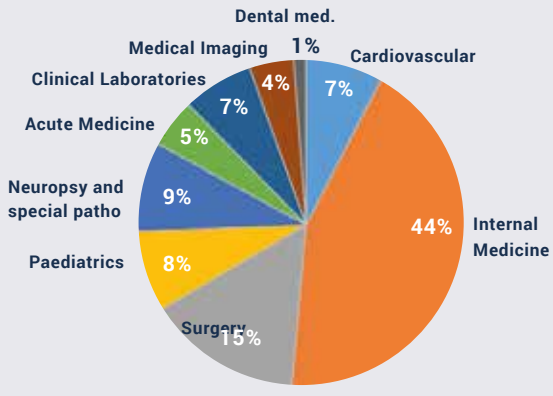
The European projects support officer coordinates the administrative management of research projects financed by European funds.

Eleven European projects are ongoing on December 31 , 2021

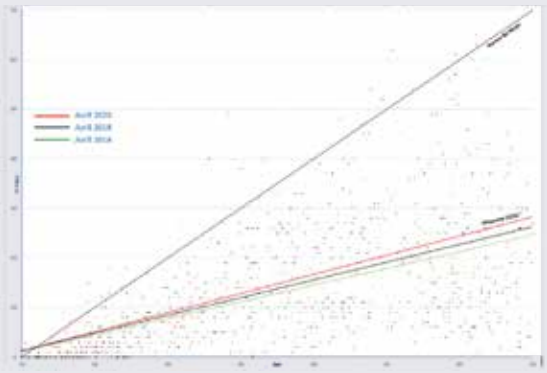
- Types of projects: 7 H2020/RIA (Research Innovation Action), 4 IMI (Innovative Medicine Initiative)
- Types of contracts : 1 where the CUSL are a linked third party and 10 where the CUSL are direct contractors.

REPORTING AND ACADEMIC INDICATORS FOR THE CUSL MEDICAL DEPARTMENTS

2021 total credits /department

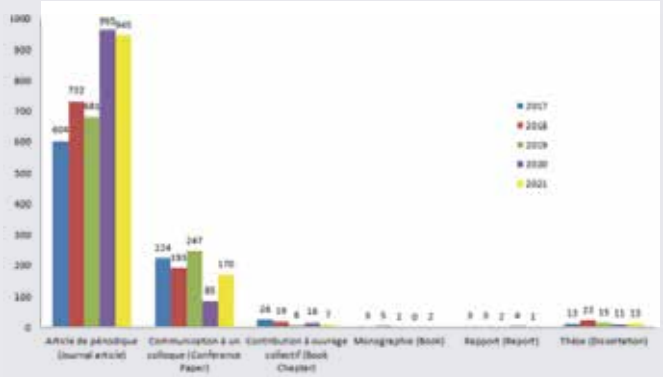


INDIVIDUAL H-INDEX (career managerial physicians) BY AGE



Publications CUSL 2017 to 2021

(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 (CEHF).
- In 2021, 149 commercial studies were submitted to the Ethics Committee. Among them 103 were submitted directly by the central desk. In addition, 29 CTR pilot studies and 17 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 2021

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**
22	**62**	**16**	**71**	**16**	0	94	28	**187**

This represents a 63% increase between 2017 and 2021.
Additionally, 6 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 32 studies and 6 master theses involving UCLouvain researchers performed at the CUSL and 34 studies performed only at the UCLouvain.

QUALITY AND ACCREDITATION

The CUSL were granted from the full AAHRPP (Association for the Accreditation of Human Research Protection Programs) re-accreditation in September 2018 for a period of 5 years. In 2021, the focus was on the development of procedures to support academic studies sponsored by the CUSL as well as the preparation of the implementation of the MDR and CTR. The website is regularly updated (https://www.saintluc.be/en/research/index.php).

OPERATIONAL SUPPORT FOR THE STUDY COORDINATORS

The CTC is coordinating the financial aspect of the hiring and the training of the study coordinators.
Fifty new study coordinators were hired in 2021. Among them, 33 have received a permanent contract.

Study coordinators at the CUSL on February 18, 2022:
91 employees: 80 FTE allocated to 30 medical services.

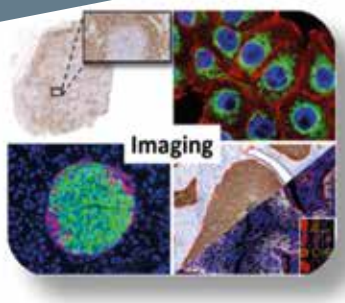
LEGAL SUPPORT

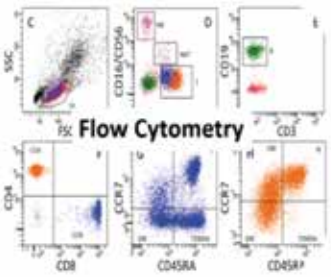
Since August 2018, a half-time legal officer from the legal department of the CUSL is dedicated to the CTC.

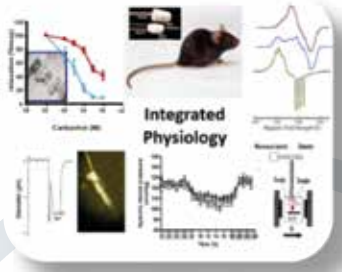
Together with other members of the legal department, she is involved in the legal review and advices for research contracts, consultancy agreements, master agreements, etc

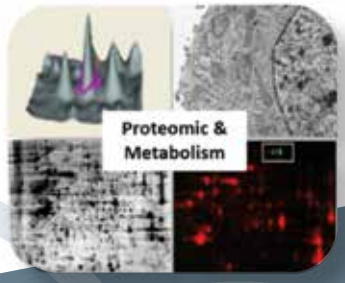
The legal officers provided support for 156 contracts, 25 legal advices and 9 support documents revision.

IREC TECHNOLOGICAL PLATFORMS









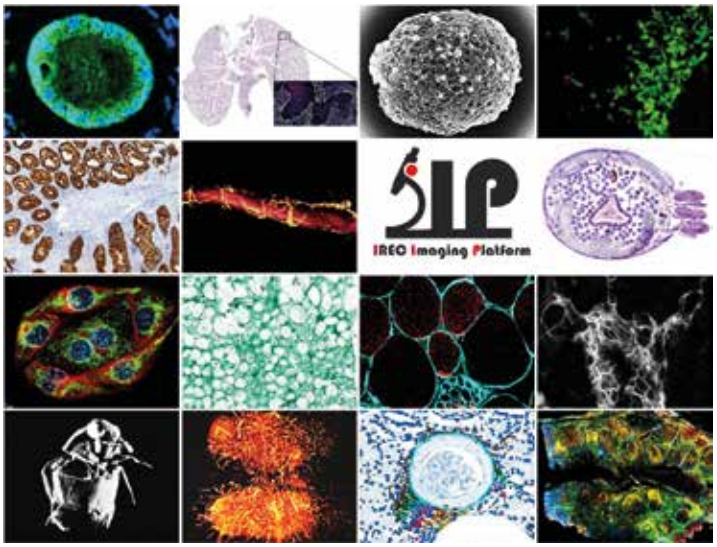
THE OBJECTIVES TARGETED BY OUR TECHNOLOGICAL PLATFORMS:

- 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 2021 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

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

Sample preparation services (service or Histo-lab access):

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

Image acquisition:

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

Image analysis:

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

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Through sustained collaborations, 2IP was also involved in the following projects published in 2021:

Octave et al. **Int J Mol Sci.** 2021 Dec 4 ;22(23) :13129

Acetyl-CoA Carboxylase Inhibitor CP640.186 Increases Tubulin Acetylation and Impairs Thrombin-Induced Platelet Aggregation.

Tilman et al. **RMD Open**. 2021 Oct;7(3): e001844

High p16INK4a, a marker of cellular senescence, is associated with renal injury, impairment and outcome in lupus nephritis.

Collin et al. **J Cyst Fibros.** 2021 Nov;20(6): e129-e139

Loss of ciliated cells and altered airway epithelial integrity in cystic fibrosis.

Iesari et al. **Clin Sci (Lond).** 2021 Oct 15;135(19):2285-2305

Selective HIF stabilization alleviates hepatocellular steatosis and ballooning in a rodent model of 70% liver resection.

-Gerard et al. **Am J Respir Crit Care Med.** 2021 Nov 1;204(9):1024-1034

Increased Angiotensin-Converting Enzyme 2 and Loss of Alveolar Type II Cells in COVID-19-related Acute Respiratory Distress Syndrome.

Ramirez et al. **Xenotransplantation**. 2021 Jul ;28(4) : e12704
Semi-automated digital quantification of cellular infiltrates for in vivo evaluation of transplanted islets of Langerhans encapsulated with bioactive materials.

Van Bockstal et al. **Mod Pathol.** 2021 Dec;34(12):2130-2140
Interobserver variability in the assessment of stromal tumor-infiltrating lymphocytes (sTILs) in triple-negative invasive breast carcinoma influences the association with pathological complete response: the IVITA study.

Orsi et al. **Front Immunol.** 2021 Jun 14; 12:666107.
Monocytic Ontogeny of Regenerated Macrophages Characterizes the Mesotheliomagenic Responses to Carbon Nanotubes.

Perez et al. **Food Chem Toxicol.** 2021 Aug; 154:112352
Dietary nanoparticles alter the composition and function of the gut microbiota in mice at dose levels relevant for human exposure.

Gourgue et al. **Sci Rep.** 2021 May 10;11(1):9922
Tumor apelin and obesity are associated with reduced neoadjuvant chemotherapy response in a cohort of breast cancer patients.

Dufeys et al. **Basic Res Cardiol**. 2021 Feb 9;116(1):10
AMPKα1 deletion in myofibroblasts exacerbates post-myocardial infarction fibrosis by a connexin 43 mechanism.

van den Brule et al. **Part Fibre Toxicol.** 2021 Feb 9;18(1):7
Diesel exhaust particles alter the profile and function of the gut microbiota upon subchronic oral administration in mice.

Nachit et al. **J Cachexia Sarcopenia Muscle.** 2021 Feb;12(1):144-158
Myosteatosis rather than sarcopenia associates with non-alcoholic steatohepatitis in non-alcoholic fatty liver disease preclinical models.

Slimani et al. J**ACC Cardiovasc Imaging.** 2021 Mar;14(3):525-536
Structural and Functional Correlates of Gradient-Area Patterns in Severe Aortic Stenosis and Normal Ejection Fraction.

CTMA

PROPOSED SERVICES

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

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

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

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

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

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

- Resequencing of Bacterial, viral (e.g. SARS-COV2) and protist whole genome.
- RNAsequencing
- 16S Metagenomic analysis

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

CTMA 2021 AT A GLANCE

8	Research groups
1205	NGS Libraries Preparation/analysis
	ILLUMINA: MiSeq/HiSeq/NovaSeq
120	- TRANSCRIPTOMIC (RNA-SEQ or scRNA-SEQ)
40	- GENOMIC (De NOVO / Resequencing)
45	- METAGENOMIC (Targeted – 16s)
75	- METAGENOMIC (Shot**gun)**
400	- CRISPR Validation
500	- SARS-CoV-2 Whole genome sequencing
	OXFORD NANOPORE: MinION
20	- GENOMIC (De NOVO / Resequencing)
5	- METAGENOMIC (Shotgun)
450	GB of NGS DATA sequenced/analyzed

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

A- Elaboration Antibody-based lateral flow

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

B- Development of nucleic acid lateral flow

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

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REFERENCES 2021

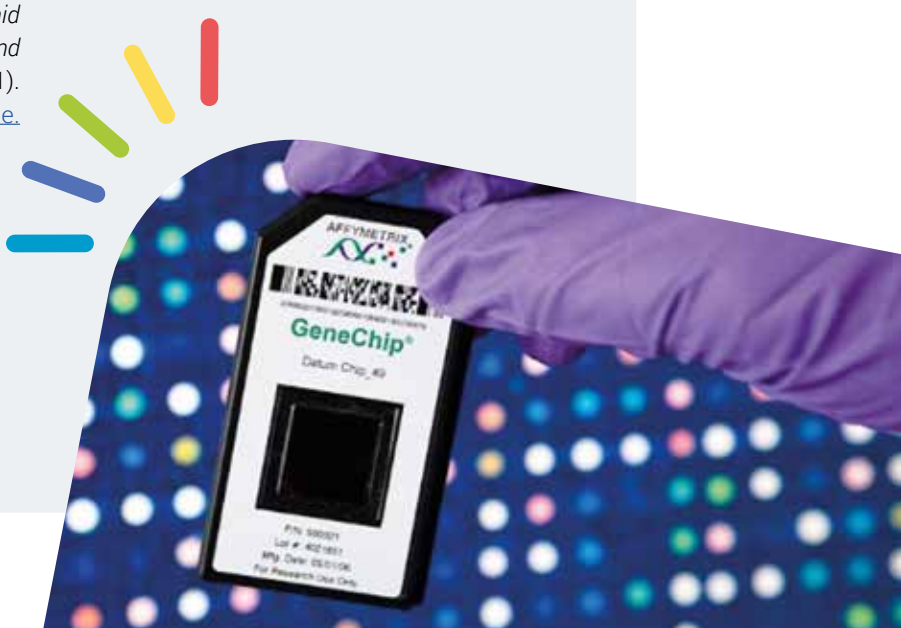
CTMA has been involved in the following IREC collaborative project published in 2021. This list excludes papers that only involves CTMA research activities and papers that only involve biostatistics/bioinformatics analyses.

Dufeys, Cécile ; Daskalopoulos, Evangelos-Panagiotis ; Castanares-Zapatero, Diego ; Conway, Simon J. ; Ginion, Audrey ; Bouzin, Caroline ; **Ambroise, Jérôme ; Bearzatto, Bertrand** ; Gala, Jean-Luc ; Heymans, Stephane ; Papageorgiou, Anna-Pia ; Vinckier, Stefan ; Cumps, Julien ; Balligand, Jean-Luc ; Vanhaverbeke, Maarten ; Sinnaeve, Peter ; Janssens, Stefan ; Bertrand, Luc ; Beauloye, Christophe ; Horman, Sandrine. *AMPKα1 deletion in myofibroblasts exacerbates post-myocardial infarction fibrosis by a connexin 43 mechanism.* In: *Basic Research in Cardiology,* Vol. 116, no. 10, p. 1-20 (2021). doi:10.1007/s00395-021-00846-y (Accepté/Sous presse). http://hdl.handle.net/2078.1/243647

Renoz, François ; Foray, Vincent ; **Ambroise, Jérôme** ; Baa-Puyoulet, Patrice ; **Bearzatto, Bertrand** ; Lima Mendez, Gipsi ; Grigorescu, Alina S. ; Mahillon, Jacques ; Mardulyn, Patrick ; **Gala, Jean-Luc** ; Calevro, Federica ; Hance, Thierry. *At the Gate of Mutualism: Identification of Genomic Traits Predisposing to Insect-Bacterial Symbiosis in Pathogenic Strains of the Aphid Symbiont Serratia symbiotica.* In: *Frontiers in Cellular and Infection Microbiology,* Vol. 11, no.660007, p. 1 (2021). doi:10.3389/fcimb.2021.660007. http://hdl.handle.net/2078.1/249248

Perez, Laeticia ; Scarcello, Eleonora ; Ibouraadaten, Saloua ; Yakoub, Yousof ; Leinardi, Riccardo ; **Ambroise, Jérôme ; Bearzatto, Bertrand ; Gala, Jean-Luc** ; Paquot, Adrien ; Muccioli, Giulio ; Bouzin, Caroline ; Van Den Brûle, Sybille ; Lison, Dominique. *Dietary nanoparticles alter the composition and function of the gut microbiota in mice at dose levels relevant for human exposure.*. In: *Food and chemical toxicology,* Vol. 154, p. 112352 [1-13] (2021). doi: 10.1016/j.fct.2021.112352. http://hdl.handle.net/2078.1/252340

Orsi, Micaela ; Palmai-Pallag, Mihaly ; Yakoub, Yousof ; Ibouraadaten, Saloua ; De Beukelaer, Michèle ; Bouzin, Caroline ; **Bearzatto, Bertrand ; Ambroise, Jérôme ; Gala, Jean-Luc** ; Brusa, Davide ; Lison, Dominique ; Huaux, François. *Monocytic Ontogeny of Regenerated Macrophages Characterizes the Mesotheliomagenic Responses to Carbon Nanotubes.* In: *Frontiers in Immunology,* Vol. 12, no.12, p. 12 (2021). doi:10.3389/fimmu.2021.666107. http://hdl.handle.net/2078.1/248444



FLOW CYTOMETRY PLATFORM

CYTOFLUX 2021 AT A GLANCE

73	Users
38	Research groups
25	Trained people
741	Bookings
515	Flow cytometry hours
389	Cell Sorting hours

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PROPOSED SERVICES

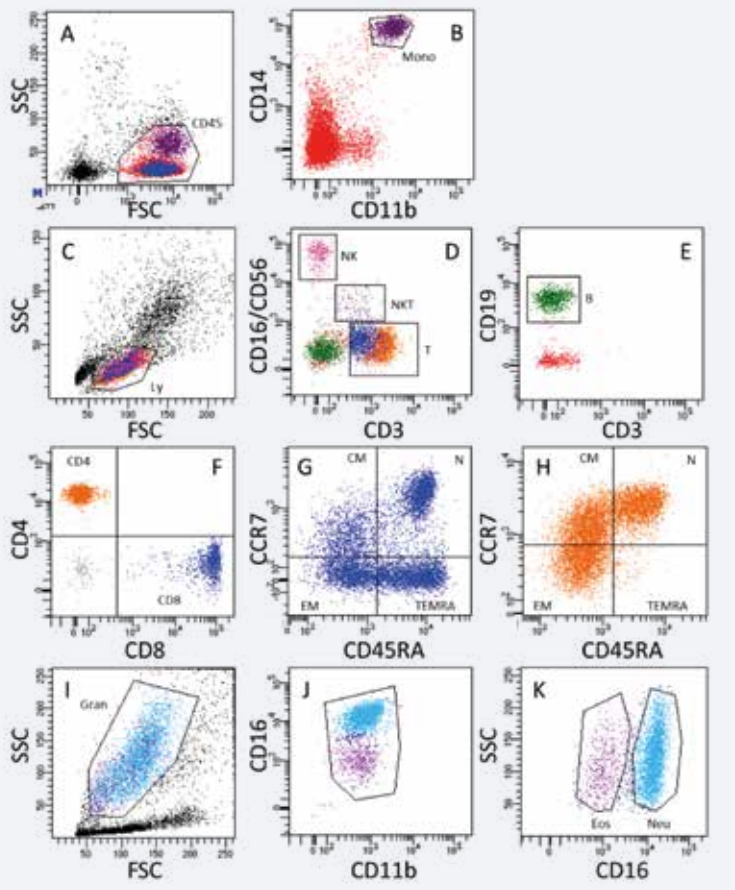
The platform logistician Davide Brusa welcomes you to the CytoFlux platform to discuss about projects involving the use of flow cytometry technology.

The Flow Cytometry Platform offers the following services

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

The platform is equipped with the following instrumentations:

- GentleMACS dissociator with heaters (new acquisition in 2019);
- FACSCalibur, analyzer, 2 lasers, 4 fluorescences;
- FACSCantoII, analyzer, 3 lasers, 8 fluorescences;
- FACSAriaIII, cell sorter, 4 lasers, 16 fluorescences;
- Analysis workstation, equipped with FACSDiva, FlowJo, FACSkin and R softwares.



REFERENCES 2021

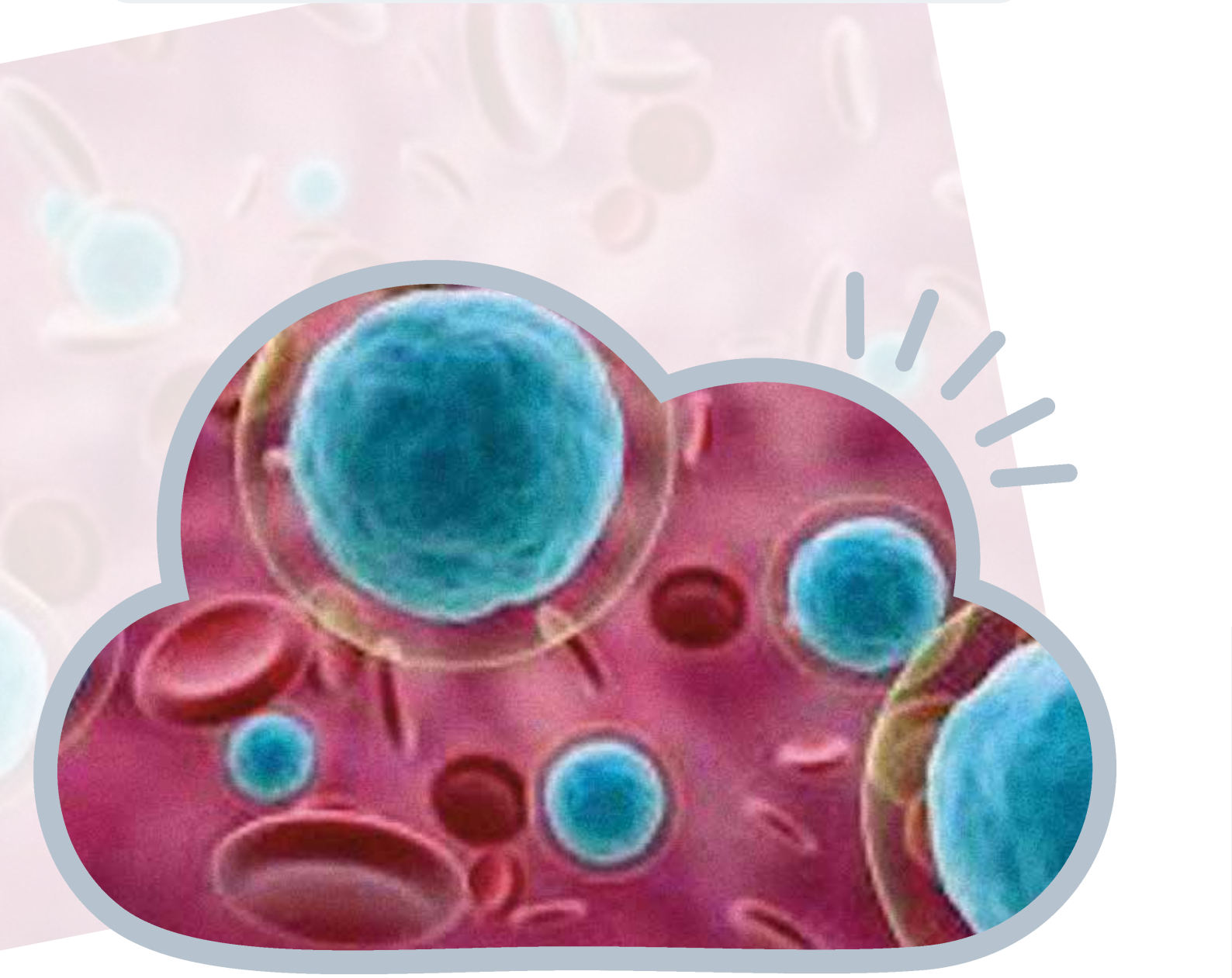
van Dievoet MA, Brusa D, Octave M, Horman S, Stephenne X. Anti-GPVI (HY101) activates platelets in a multicolor flow cytometry panel. Platelets. 2022 Jan 17:1-4.

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.

Schoonjans CA, Mathieu B, Joudiou N, Zampieri LX, Brusa D, Sonveaux P, Feron O, Gallez B. Targeting Endothelial Cell Metabolism by Inhibition of Pyruvate Dehydrogenase Kinase and Glutaminase-1. J Clin Med. 2020 Oct 15;9(10):3308.



ANIMAL FACILITY

PROPOSED SERVICES

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

The Animal Facility Platform offers the following services:

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

The platform is serviced with the following equipment:

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

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

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

THE IREC ANIMAL FACILITY AT A GLANCE

3	Rodent confinement zones: Conventional, Linné-like and SOPF areas
1	New zone opened in 2021: SOPF area
1	BSL2 lab, opened in 2021
1600	Mice cages available (480 in the Conventional area, and 560 each in the Linné-like and SOPF areas)
420	Rat cages available (140 in the Conventional area, and 105 each in the Linné-like and SOPF areas)
17	Research groups
126	Users trained to get access to the Facility

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INTEGRATED PHYSIOLOGY

PROPOSED SERVICES

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

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

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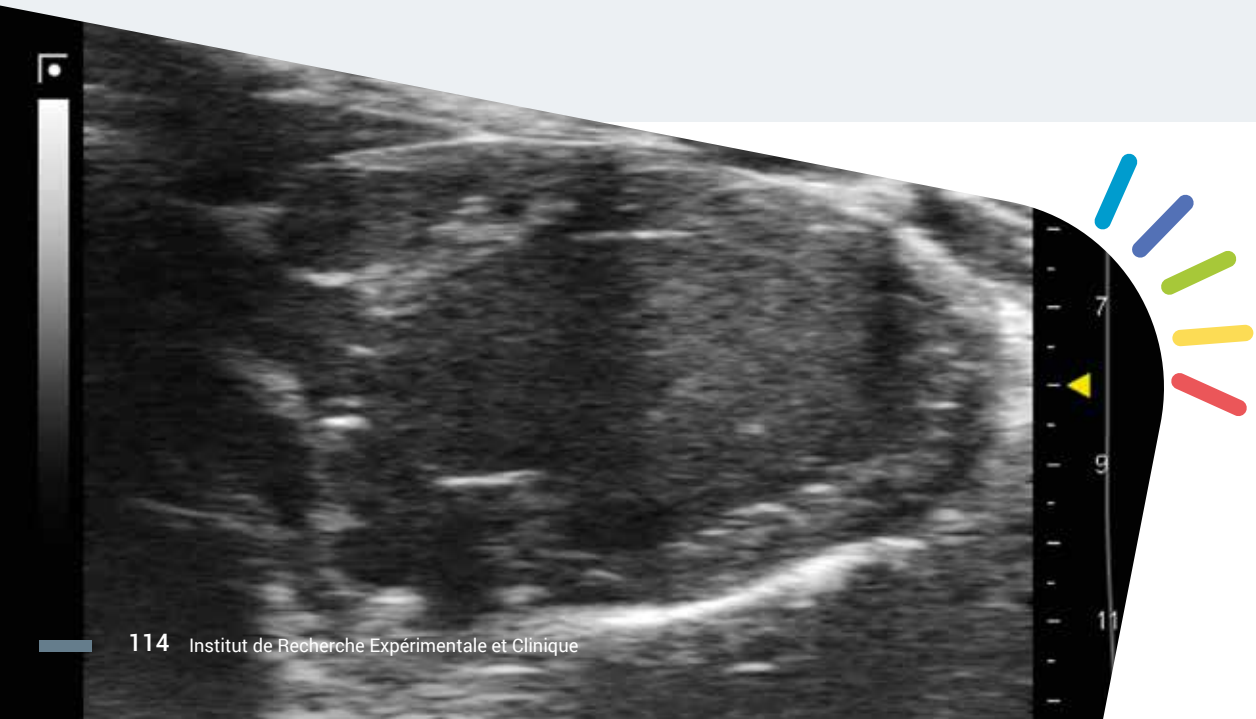

REFERENCES

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.

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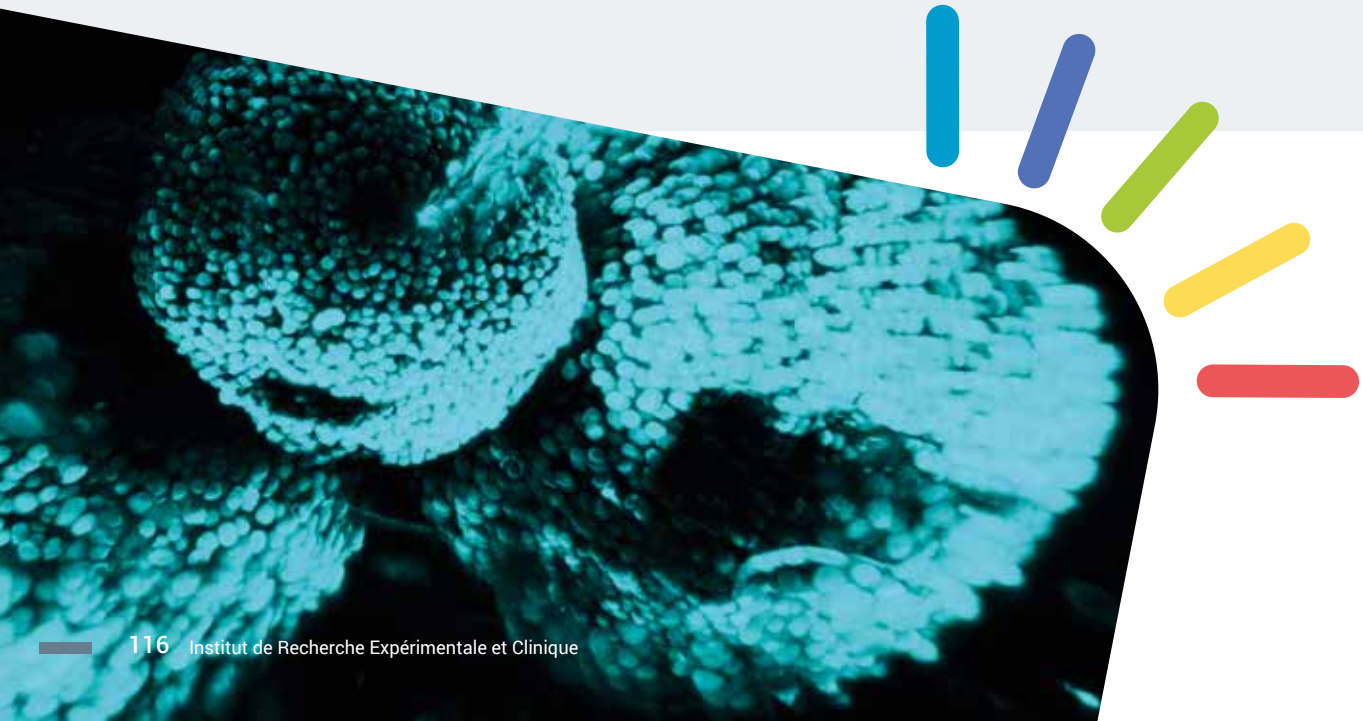
https://uclouvain.be/fr/instituts-recherche/irec/proteomics-and-metabolomics.html



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.

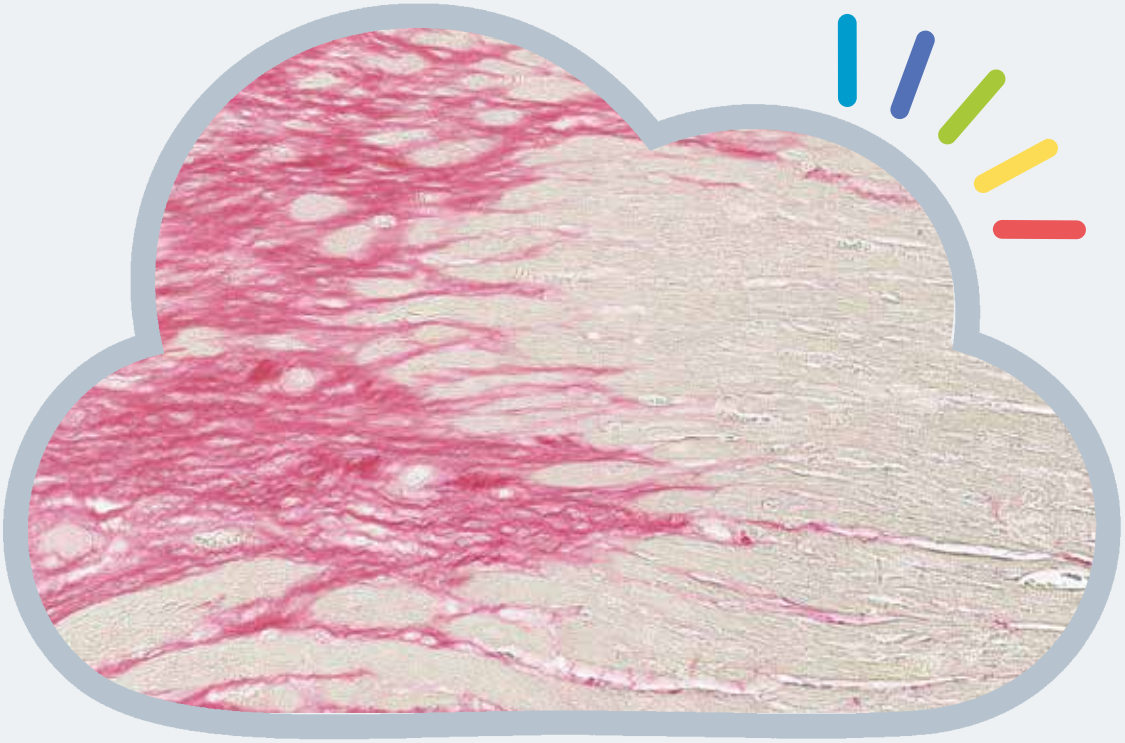
Strickaert A, Corbet C, Spinette SA, Craciun L, Dom G, Andry G, Larsimont D, Wattiez R, Dumont JE, Feron O, Maenhaut C. Reprogramming of Energy Metabolism: Increased Expression and Roles of Pyruvate Carboxylase in Papillary Thyroid Cancer. Thyroid. 2019 Jun;29(6):845-857

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

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.
- 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.

CTMA is also conducting research to better control the biological risks related to the CBRN (Chemical, Bacteriological, Radiological and Nuclear threats spectrum).

Inside its CTMA-Myco premises, CTMA is actively developing service activity for industry by producing fungal biomass for the preparation of vaccines.

RESEARCH POLES

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.

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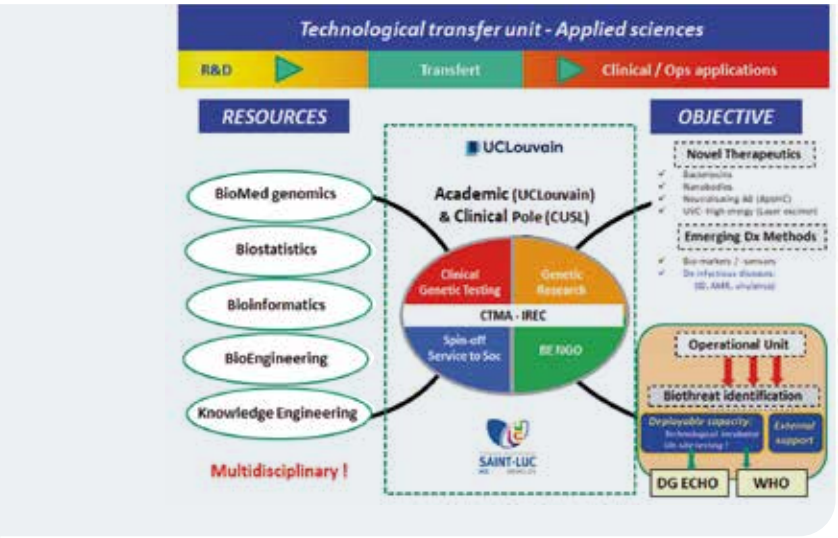
** CUSL: Cliniques universitaires Saint-Luc ** MOD: Ministry of Defense*

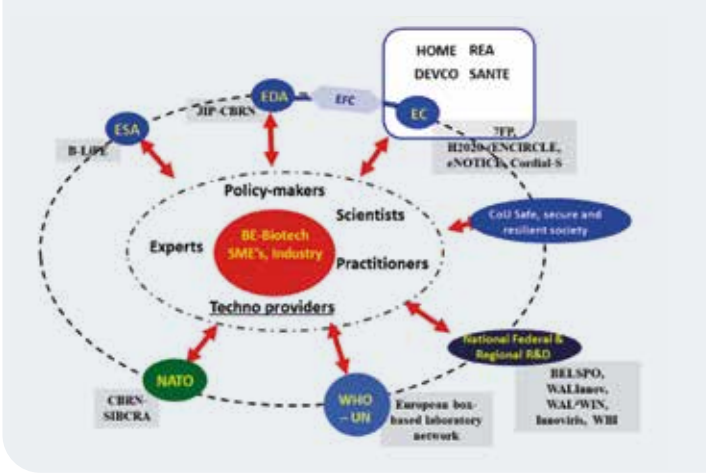
Whereas novel therapeutics developments encompass bacteriocins, camelids immunoglobulins, neutralization AB and UVC- High energy (laser excimer), new rapid diagnostic tools focus on isothermal amplification, multiplex immuno-chromatographic lateral flow assay and 3d generation sequencing for a better detection and protection against known and unknown biological agents.

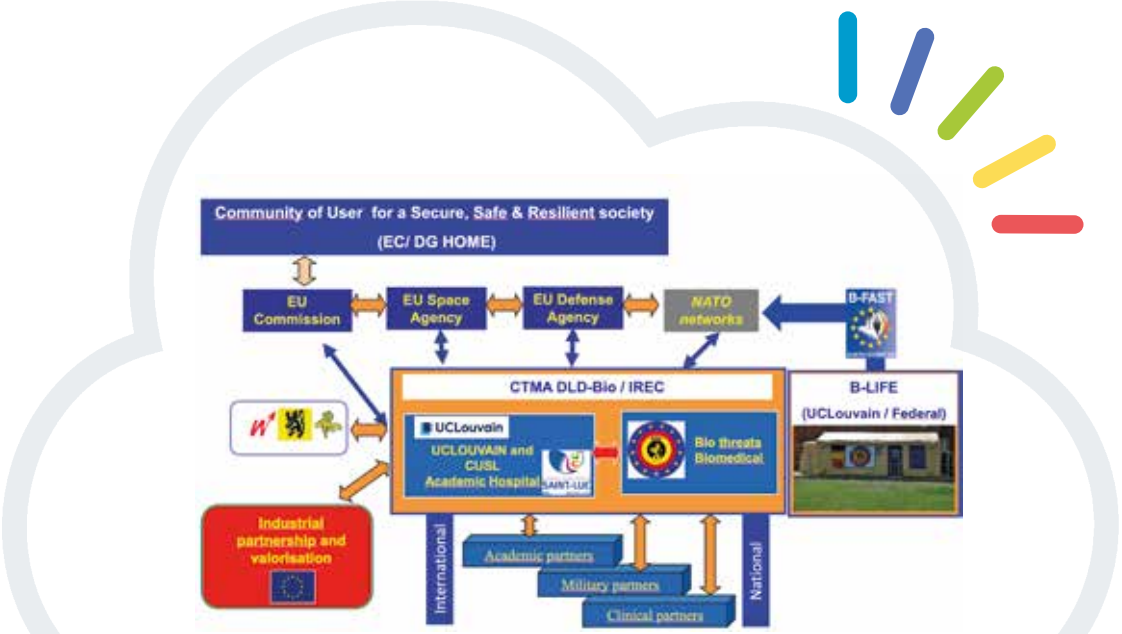
All these tools are designed to meet the constraints of use in the EU-certified deployable box-based laboratory B-LiFE (Biological Light Fieldable Laboratory for Emergencies) developed by CTMA for national and international missions justified by public health crisis. B-LiFE is part of the European box-based 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 WIN²WAL) Regions, Federal (BELSPO, Food Chain Safety) and international institutions (EC, EDA and ESA).





SARS-COV-2 VIRUS AND COVID-19

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

SARS-CoV-2 DETECTION
Improving Diagnostic Tests

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

RT-PCR

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

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

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

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

RT-LAMP

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

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

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

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

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

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 small scale of V.cholerae DNA samples 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)

Rapid test QuickZen COVID-19 IgM/IgG

This is a colorimetric lateral flow assay carried out on drop blood collected by using a prick test. The test is based on the recognition and binding of IgM and/or IgG in the patient's blood

to the Spike protein present in the test membrane. The test allows then identification of patients in the acute phase (IgM positive only), the intermediate phase (IgM/IgG positive) and in the convalescent phase (IgG positive only).

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

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 18 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 organize 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 Vandenberghe, 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 Optoeletronics, 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)
- Institute 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

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 salvia samples.

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

CTMA 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 will be deployable on the field on mobile laboratory like our B-LIFE.

EU H2020 eNOTICE: European Network Of CBRN TraIning 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 organizes joint activities, training and debriefing, using real-life or simulated situations (e.g. field exercises, table top, serious gaming and simulations), with external partners, in order to foster the identification of 'genuine users' needs with users-driven technological solutions.

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 specialized, efficient and sustainable industry. Competitiveness requests a less fragmented EU market.

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

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

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

The community now has 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, Axelle LORIOT, 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.

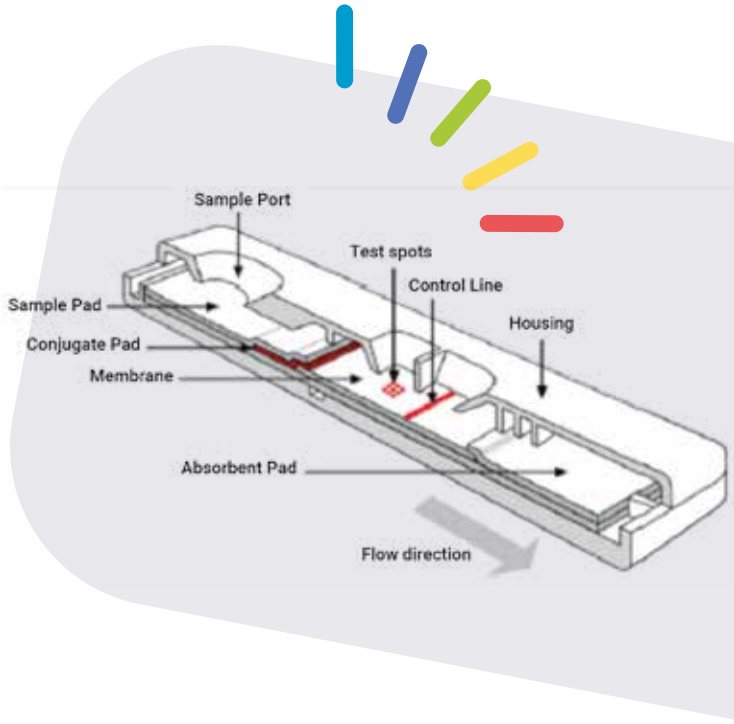
There is a lack of robustness in European preparedness for biotoxin incidents. Using current best practice, the EuroBioTox core members will develop and validate improved analytical tools, reagents and standard operating procedures based on realistic incident scenarios. Certified Reference Materials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

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

Jamal BADIR, Mostafa BENTAHIR, Benjamin SMITS, Omar NYABI

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

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



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

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

Mostafa BENTAHIR, Jamal BADIR, Omar NYABI, Nawfal CHIBANI, Pierre VANDENBERGHE

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

The objective is to develop an innovative Point of Care Tests (POCT) device, fast, convenient and easy to use diagnostic assay that shorten turnaround time of intervention. The assay will be robust and must achieve rapid differential diagnosis of acute human infections by flavivirus pathogens. In addition, this assay will incorporate the advantages of the lateral flow immunoassay (LFA) and the isothermal nucleic acid amplification (RPA) for the differential diagnosis of 3 arboviruses: ZIKV, DENV and YFV.

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

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.

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

(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 in-

volved 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.

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

Bertrand BEARZATTO, Jérôme AMBROISE

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

Adaptation of an NGS kit for pharmacogenetic targets in ALL to new sequencing chemistries and optimization 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 Leukemia) 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 (Rhumatology, CUSL) are studying factors that can predict the development of pulmonary fibrosis in patients with recently diagnosed rheumatoid arthritis. There is potential link between pulmonary fibrosis and a variant gain-of-function of the MUC5B gene's promoter, which codes for mucine (a protein that makes up the mucus in the lungs). CTMA is now characterizing by high throughput sequencing this variant among patients included in the study.

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

Antimicrobial resistance: bacteriocins in the fight against Mycobacterium tuberculosis and Vibrio cholerae

Funding: Syngulon

Anandi MARTIN (SYNGULON researcher), Jérôme AMBROISE, Leonid IRENGE MWANA WA BENE

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

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

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 specialized 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.

ESA Secure Satcom for Safety & Security (2021 – 2022)

Funding: Global Mobile Lab

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 will be 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 will provide 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. This telecommunication infrastructure allows the reliable channels for the developed ICT-toolbox called MIML LIMS – full LIMS (Laboratory Information management System) for Multi Institutions – Multi-Missions- Multi-laboratories. Fully configurable manually or via web-services and fully integrated with cartography in real time for data analysis. This ICT-toolbox will also contain mapping and real time situation awareness modules. All ICT applications will use the secure infrastructure of European Distributed Datacentres developed and supported by one of the partners of the consortium.

REFERENCES 2021

Kitane DL, Loukman S, Marchoudi N, Fernandez-Galiana A, El Ansari FZ, Jouali F, **Badir J, Gala JL**, Bertsimas D, Azami N, Lakbita O, Moudam O, Benhida R, Fekkak J
A simple and fast spectroscopy-based technique for Covid-19 diagnosis. Sci Rep. 11(1): 16740, 2021.

Fakhour S, Renoz F, **Ambroise J,** Pons I, Noël C, **Gala JL**, Hance T. Insight into the bacterial communities of the subterranean aphid Anoecia corni. PLoS One 16(8): e0256019, 2021.

Ambroise J, Benaissa E, **Irenge Mwana Wa Bene** L, Belouad EM, **Bearzatto B, Durant JF, Badir J**, Elouennass M, **Gala JL**. Genomic characterisation of extended-spectrum β-lactamase-producing multidrug-resistant Escherichia coli in Rabat, Morocco. J Glob Antimicrob Resist 26:335-341, 2021.

Dufeys C, Daskalopoulos EP, Castanares-Zapatero D, Conway SJ, Ginion A, Bouzin C, **Ambroise J, Bearzatto B, Gala JL**, Heymans S, Papageorgiou AP, Vinckier S, Cumps J, Balligand JL, Vanhaverbeke M, Sinnaeve P, Janssens S, Bertrand L, Beauloye C, Horman S. AMPKα1 deletion in myofibroblasts exacerbates post-myocardial infarction fibrosis by a connexin 43 mechanism. Basic Res Cardiol 116(1): 10, 2021.

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 12: 666107, 2021.

Jarosz W, **Durant JF, Irenge Mwana Wa Bene L**, Fogt-Wyrwas R, Mizgajska-Wiktor H, **Gala JL.** Optimized DNA-based identification of Toxocara spp. eggs in soil and sand samples. Parasit Vectors 14(1):426, 2021.

Renoz F, Foray V, **Ambroise J**, Baa-Puyoulet P, **Bearzatto B**, Mendez GL, Grigorescu AS, Mahillon J, Mardulyn P, **Gala JL**, Calevro F, Hance T. At the gate of mutualism: identification of genomic traits predisposing to insect-bacterial symbiosis in pathogenic strains of the Aphid symbiont serratia symbiotica. Front Cell Infect Microbiol 11: 660007, 2021.

Gala JL, Rebane O, **Ambroise J**, Babichenko S, **Nyabi O,** Hance T. Acaricidal efficacy of ultraviolet-C irradiation of Tetranychus urticae adults and eggs using a pulsed krypton fluoride excimer laser. Parasit Vectors 14(1): 578, 2021.

Nyabi O, Bentahir M, Ambroise J, Bearzatto B, Chibani N, Smits B, Durant JF, Vybornov A, Thellin O, El Moualij B, **Gala JL**. Diagnostic value of IgM and IgG detection in COVID-19 diagnosis by the mobile laboratory B-LiFE: a massive testing strategy in the Piedmont region. Int J Environ Res Public Health 18(7): 3372, 2021.

Perez L, Scarcello E, Ibouraadaten S, Yakoub Y, Leinardi R, **Ambroise J, Bearzatto B, Gala JL**, Paquot A, Muccioli GG, Bouzin C, van den Brule S, Lison D. Dietary nanoparticles alter the composition and function of the gut microbiota in mice at dose levels relevant for human exposure. Food Chem Toxicol 154: 112352, 2021.

Vybornov A, Nyabi O, Vybornova O, Gala JL. Telecommunication facilities, key support for data management and data sharing by a biological mobile laboratory deployed to counter emerging biological threats and improve public health crisis preparedness. Int J Environ Res Public Health 18(17): 9014, 2021.

Octave M, Pirotton L, Ginion A, Robaux V, Lepropre S, **Ambroise J**, Bouzin C, Guigas B, Giera M, Foretz M, Bertrand L, Beauloye C, Horman S. Acetyl-CoA Carboxylase Inhibitor CP640.186 Increases Tubulin Acetylation and Impairs Thrombin-Induced Platelet Aggregation. Int J Mol Sci 22(23): 13129, 2021.

Lesari S, Leclercq I, Joudiou N, Komuta M, Daumerie A, **Ambroise J**, Dili A, Feza-Bingi N, Xhema D, Bouzin C, Gallez B, Pisani F, Bonaccorsi-Riani E, Gianello P. Selective HIF stabilization alleviates hepatocellular steatosis and ballooning in a rodent model of 70% liver resection. Clin Sci (Lond) 135(19):2285-2305, 2021.

Lison D, **Ambroise J**, Leinardi R, Ibouraadaten S, Yakoub Y, Deumer G, Haufroid V, Paquot A, Muccioli GG, van den Brûle S. Systemic effects and impact on the gut microbiota upon subacute oral exposure to silver acetate in rats. Arch Toxicol 95(4): 1251-1266, 2021.

Bredeck G, Kämpfer AAM, Sofranko A, Wahle T, Lison D, **Ambroise J,** Stahlmecke B, Albrecht C, Schins RPF. Effects of dietary exposure to the engineered nanomaterials CeO2, SiO2, Ag, and TiO2 on the murine gut microbiome. Nanotoxicology 15(7): 934-950, 2021.

van den Brule S, Rappe M, **Ambroise J**, Bouzin C, Dessy C, Paquot A, Muccioli GG, Lison D. Diesel exhaust particles alter the profile and function of the gut microbiota upon subchronic oral administration in mice. Part Fibre Toxicol 18(1): 7, 2021.

PHD THESES

Date: 03/02/2021 Name: **COLLIN Amandine** Lab: PNEU
Thesis: Impaired airway immunoglobulin A and epithelial differentiation in cystic fibrosis
Promotor: GOHY Sophie Copromotor: PILETTE Charles

Date: 22/02/2021 Name: **FONKOUE Loïc** Lab: NMSK
Thesis: Genicular nerves anatomy. From accuracy of anatomical landmarks to the treatment of knee osteoarthritis pain by genicular nerve blockade and radiofrequency ablation
Promotor: CORNU Olivier

Date: 23/02/2021 Name: **ASSOGBA Todègnon Franck** Lab: NMSK
Thesis: How to improve the care in hip osteoarthritis in low income countries as Benin? Orthopaedic manual therapy as a new alternative
Promotor: MAHAUDENS Philippe Copromotor: DETREMBLEUR Christine

Date: 26/02/2021 Name: **ASIABI KOHNEH SHAHRI Parinaz** Lab: GYNE
Thesis: Shedding light on recruitment and differentiation of human theca interna cells
Promotor: ANDRADE AMORIM Christiani Copromotor: DOLMANS Marie-Madeleine

Date: 04/03/2021 Name: **ANGÉ Marine** Lab: CARD
Thesis: New insight in sepsis pathophysiology: α1AMPK, from the comprehension of key molecular mechanisms to the exploration of a new therapeutic approach
Promotor: HORMAN Sandrine Copromotor: CASTANARES ZAPATERO Diego

Date: 09/03/2021 Name: **ORSI Micaela** Lab: LTAP
Thesis: Characterization of a new intermediate macrophage subpopulation: SDC-1 positive SPM-like macrophages possess immunosuppressive functions in early mesotheliomagenic responses to carbon nanotubes
Promotor: HUAUX François

Date: 28/04/2021 Name: **HOUARD Laura** Lab: CARD
Thesis: Prognosis of right ventricle systolic function parameters with heart failure and reduced ejection fraction
Promotor: GERBER Bernhard Copromotor: POULEUR Anne-Catherine

Date: 26/05/2021 Name: **FERTE Laura** Lab: CARD
Thesis: Deciphering the role of SGLT1 and SMIT1 in the heart
Promotor: BEAULOYE Christophe Copromotor: BERTRAND Luc

Date: 01/06/2021 Name: **GAUTHEY Anaïs** Lab: CARD
Thesis: Cardio-neuromodulation using auricular transcutaneous vagus nerve stimulation
Promotor: BEAULOYE Christophe Copromotor: LE POLAIN DE WAROUX Jean-Benoît

Date: 21/06/2021 Name: **MORALES Natalia** Lab: PEDI
Thesis: Functional exercise capacities and lung function in children with Congenital Heart diseases: evaluation tools and clinical assessment
Promotor: MONIOTTE Stéphane Copromotor: REYCHLER Grégory

Date: 23/06/2021 Name: **KOUASSI Kouame Jean Eric** Lab: NMSK
Thesis: Locally-developed external fixators and their impact on the stability of long bone diaphyseal fractures after osteosynthesis
Promotor: CORNU Olivier

Date: 01/07/2021 Name: **NKAMBA MUKADI Dalau** Lab: EPID et UNIKIN-ESP
Thesis: Prevention of hypertensive disorders in pregnancy in the Democratic Republic of Congo: challenges and perspectives
Promotor: ROBERT Annie

Date: 09/07/2021 Name: **OUNI Emna** Lab: GYNE
Thesis: From in-depth human ovary characterization toward a biomimetic artificial ovary
Promotor: ANDRADE AMORIM Christiani Copromotor: VERTOMMEN Didier

Date: 09/09/2021 Name: **MASIMANGO IMANI Mannix** Lab: NEFR
Thesis: Prevalence and risk factors of Chronic Kidney Disease in South Kivu, a large scale population study
Promotor: JADOUL Michel Copromotor: SUMAILI KISWAYA Ernest (Université Kinshasa)

Date: 14/09/2021 Name: **AUDAG Nicolas** **Lab: PNEU**
Thesis: Oropharyngeal Dysphagia in Patients with Neuromuscular Diseases. Validation of new tools and screening process.
Promotor: REYCHLER Grégory Copromotor: TOUSSAINT Michel (Inkendaal hosp.)

Date: 20/09/2021 Name: **POILVACHE Hervé** **Lab: NMSK**
Thesis: In-vitro and in-vivo study of biofilm disruption strategies for the treatment of Prosthetic Joint Infections
Promotor: CORNU Olivier Copromotor: VAN BAMBEKE Françoise

Date: 21/09/2021 Name: **LOUMAYE Audrey** **Lab: EDIN**
Thesis: Role of Activin A in human cancer cachexia
Promotor: THISSEN Jean-Paul

Date: 21/10/2021 Name: **STEENHAUT Patricia** **Lab: OBST**
Thesis: Cervical insufficiency : role of cerclage and changes in fetal membranes
Promotor: DEBIEVE Frédéric Copromotor: HUBINONT Corinne

Date: 08/11/2021 Name: **MOURAD Charbel** **Lab: IMAG**
Thesis: Contribution of multidetector computed tomography in the detection of epiphyseal collapse in osteonecrotic femoral heads
Promotor: VANDE BERG Bruno Copromotor: GANGJI Valérie (ULB-Erasme)

Date: 18/11/2021 Name: **NACHIT Maxime** **Lab: GAEN**
Thesis: Skeletal Muscle and NAFLD: preclinical and clinical studies to decode a muscle-to-liver axis
Promotor: LECLERCQ Isabelle Copromotor: THISSEN Jean-Paul

Date: 09/12/2021 Name: **DANWANG Celestin** **Lab: EPID**
Thesis: Fine scale analysis of symptomatic malaria incidence in children under-five in Cameroon: Hierarchical Bayesian spatio-temporal models and meta-analysis for morbidity assessment
Promotor: ROBERT Annie

Date: 14/12/2021 Name: **CARLIER François** **Lab: PNEU**
Thesis: Exploring the plasticity of the airway epithelium in chronic obstructive pulmonary disease
Promotor: PILETTE Charles

PHD DAY

PROGRAM

8th IREC PhD Day
Auditorium Maisin, UCL-Bruxelles.

FRIDAY, SEPTEMBER 17TH, 2021

8h50-9h10 Registration and poster installation

9h00-10h20 First session

Welcoming words

Camille Hossay (GYNE) - Can frozen-thawed human ovary withstand refreezing-rethawing in the form of cortical strips?

Arthur Colson (GYNE) - Use of the Hypoxia-Inducible Factor (HIF)-2α Inhibitor PT2385 in Placental Dysfunction: New Intervention Addressing Fetal Growth Restriction and Preeclampsia

Julien De Poortere (CARD) - The role of AMPK (alpha 1) in hemostatic dysfunctions induced by sepsis. Sibille Lejeune (CARD) - Nitric Oxide imbalance and Endothelial Dysfunction in Heart Failure with Preserved Ejection Fraction

10h20-10h50 Coffee Break, Posters & Sponsors

10h50-11h50 Second session

Luciana Cacciottola (GYNE) - Modulating hypoxia and oxidative stress in human ovarian tissue xenografts using adipose tissue-derived stem cells

Thu Yen Thi Nguyen (GYNE) - Safety of ovarian tissue cryopreservation and transplantation in patients with central nervous system tumors

Julien Van Damme (IMAG) - Comparison of PSMA PET-CT and WB-MRI with diffusion sequences in the staging of advanced prostate cancer

Sponsor talks (Sarstedt, Labconsult)

AM moderators: Laura Orioli (EDIN), Nicolas Huyghe (MIRO), Leo Aubert (FATH), Emeline Dierge (FATH)

11h50-12h20 Posters & Sponsors

12h20 Lunch bags distributed

13h30-14h45 Third session

Justine Gillard (GAEN) - Bile acids contribute to the development of nonalcoholic steatohepatitis Luca Maccioni (GAEN) - Increased apoptosis in duodenal CD8+ T resident memory cells contributes to gut barrier dysfunction and associates with alcohol-associated liver disease in humans

Céline Khalifa (Anesthesiology) - Predicting postoperative delirium (POD) after cardiac surgery using intraoperative EEG frontal alpha wave spectral analysis

Elena Borderias Villarroel (MIRO) - Performance of dose restoration in head and neck cancer for adaptive proton therapy

IREC platforms part I (Imaging, Flow Cytometry, Animal facility, Molecular Technologies)

14h45-15h15 Coffee Break, Posters & Sponsors

15h15-16h30 Fourth session

Louise Declerck (NMSK) - Adaptive sports in French-speaking Belgium

Arsene Kabamba (MBLG) - Epidemiological aspects and molecular characterization of the hepatitis B virus among blood donors in Lubumbashi, Democratic Republic of Congo

Olivier Pollé (PEDI) - Plasmatic proteomic in new-onset type 1 diabetes children: toward the identification of partial remission biomarkers

IREC platforms part II (Imaging, Flow Cytometry, Animal facility, Molecular Technologies)

PM moderators: Marine Blackman (FATH), Nicolas Audag (PNEU), Luca Zampieri (FATH)

16h30 Public vote & Awards

POSTERS

1- Stevens Philippe (MIRO) The microbiome in colorectal metastases: nature and impact on local immune and inflammatory response, disease evolution and response to therapy.

2- Nicolas Dubuisson (EDIN) Inflammasome inhibitors for the treatment of muscular dystrophies

3- Simon Beyaert (MIRO) Activity and safety of an anti-IDO long peptide vaccine in a randomized open-label multicentric window-of-opportunity phase II study in patients with squamous cell carcinoma of the head and neck (SCCHN): preliminary results on 7 patients.

4- Finoula Maestre (MIRO) Reappraisal of HLA class I antigen presentation alterations in melanoma

5- Loïc Vander Veken (MIRO) Voluntary vs. mechanically induced DIBH for left breast cancer: a randomized trial

6- Celestin Danwang (EPID) Fine scale analysis of malaria incidence in under-5: Hierarchical Bayesian spatio-temporal modelling of routinely collected malaria data between 2012-2018 in Cameroon

7- Françoise Derouane (MIRO) Identification of new biomarkers to better predict and improve response to neoadjuvant chemotherapy in breast cancers

8- AnhPhong Nguyen (NMSK) Perceptions and attitudes towards running shoes between runners and non-runners participants.

9- Maxime De Rudder (GAEN) Hypoxia-induced liver angiogenesis rescues survival upon small for size hepatectomy in mice

10- Evelyne Harkemanne (PNEU) Randomized controlled non-inferiority trial comparing skin tumor triage competences of general practitioners after short and long training in dermoscopy for skin tumor diagnosis.

11- Christina Anna (GYNE) Identifying common pathogenic features in deep endometriotic nodules and uterine adenomyosis

12- Gauthier Everard (NMSK) Concurrent validity of an immersive virtual reality-based version of the Box and Block Test to assess manual dexterity among patients with stroke.

13- Valentin Van den Bossche (FATH) Tumor microenvironment-mediated lipid metabolism and anti-EGFR therapy resistance in head and neck squamous cell carcinoma

14- Saeid Moghassemi (GYNE) Oncological photodynamic therapy based on AlPc/ZnPc for the selective elimination of malignant cells from ovarian tissue

15- Lucie Ruiz (EDIN) Mechanisms of pancreatic δ-cell regulation by glucose

16- Arezoo Dadashzadeh (GYNE) Evaluation of PEGylated fibrin as a 3D biodegradable scaffold for ovary tissue engineering

17- Sophie Wuyckens (MIRO) Development of a new optimization algorithm for Arc Proton Therapy treatment planning

18- Natasha Honoré (MIRO) Circulating tumor DNA as a marker of Minimal Residual Disease in squamous cell carcinoma of the head and neck: an agnostic approach

19- Alba Sánchez (PNEU) Impaired secretory IgA production in chronic rhinosinusitis: role and regulatory mechanisms

20- Firas Khattab (EDIN) The pancreatic α-cell: how is it influenced by β- and δ-cells

21- Seydou Nakanabo Diallo (MBLG) Investigation of antifungal susceptibility profile of clinical yeast isolates using Sensititre YeastOne YO10

22- Brieuc Van Nieuwenhuyse (PEDI) Phage therapy to allow liver transplantation in a toddler infected by an extensively drug-resistant Pseudomonas aeruginosa

23- Camille Pichon (GAEN) Glutamine synthetase Knock-Out in liver impacts NAFLD progression

24- Julien Cumps (CARD) Understanding the role of myo-inositol and its transporter SMIT1 in cardiac fibrosis

JURY

Cécile Dufeys (CARD) & Thomas Planté-Bordeneuve (PNEU) for 1 to 8,
Marie Octave (CARD) & Marie Cohilis MIRO) for 9 to 16,
Catherine Vander Linden (FATH) & Nina Van Goetem (EPID) for 17 to 24

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PHD DAY

FACULTY OF MEDICINE AND DENTISTRY
INSTITUTE OF EXPERIMENTAL AND CLINICAL RESEARCH

INVITATION

Doctor Honoris Causa Ceremony

May 19th, 2021 - 4:30 PM

UCLouvain YouTube Channel

Professor Vincent Blondel, Rector of the Université Catholique de Louvain
Professor Frédéric Houssiau, Vice-Rector of the Health Sciences Sector
Professor Françoise Smets , Dean of the Faculty of Medicine and Dentistry
Professor Jean-Luc Balligand, President of the IREC Institute,
Have the pleasure to invite you on Wednesday, May 19th, 2021
at the ceremony awarding the doctor honoris causa title to:

Amit Nathwani is Professor of Haematology, Senior NIHR Investigator, and Head of Department of Haematology at UCL Royal Free Campus. His internationally competitive translational research program has focused on the development of gene therapy for monogenetic disorders. Prof. Nathwani's team was responsible for the first successful trial of gene therapy in a bleeding disorder – haemophilia B and pioneered the technology that led to successful gene therapy of haemophilia A. Feeding into these successes are a diverse range of translational gene transfer approaches focused on inherited disorders such as Fabry's and Gaucher's disease. Prof. Nathwani is the recipient of the Ham Wasserman Award, ESGCT Outstanding Achievement Award, Human Gene Therapy Award, and UCL Enterprise Award for his pioneering work in gene therapy and authored >100 peer-reviewed scientific papers.

Marc Pfeffer is Distinguished Dzau Professor of Medicine at Harvard Medical School, and Cardiovascular Physician at the Brigham and Women's Hospital in Boston. He is credited with the translational and clinical studies underpinning the use of angiotensin-converting enzyme inhibitors in myocardial infarction. He is a leading investigator in prominent cardiovascular trials and has the Distinguished Scientist Award from both the American Heart Association and the American College of Cardiology; The Lifetime Achievement Award from both the Heart Failure Society of America and the Heart Failure Association of the European Congress of Cardiology. Dr Pfeffer is a Gold Medal Awardee of the European Society of Cardiology.

Bruno Crestani is Professor of Pneumology at the Université de Paris, head of the Reference center for rare pulmonary diseases in Bichat hospital in Paris, and the director of the Inserm research group "Inflammation and pulmonary fibrosis" at the Université de Paris. His research interests include the genetics of pulmonary fibrosis and the pathophysiology of fibrotic lung disorders with the aim to identify new therapeutic targets.

On the following day, you are very welcome to join a special online scientific event celebrating the 10th anniversary of IREC.

20 MAY 2021 - 9 AM / 5:30 PM

IREC

10 YEARS ANNIVERSARY
ONLINE SCIENTIFIC EVENT

with the participation of our Honorary Doctors:
***Pr Bruno Crestani**, Université de Paris*
***Pr Amit Nathwani**, University College London*
***Pr Marc Pfeffer**, Harvard University*

PROGRAM

9:00 Introduction

9:30 - 11:00 Haematology Masterclasses + Q&A:
Gene therapy of haemophilia: profiling the candidates - *Evelien Krumb*
Pain and haemophilic arthropathy: exploring the underlying mechanisms - *Valérie-Anne Chantraint and Anthe Foubert*

11:15 - 12:45 Pulmonology Masterclasses + Q&A:
Role of pIgR in idiopathic pulmonary fibrosis - *Antoine Froidure*
ACE2/ACE disbalance in the severe COVID-19 lung - *Ludovic Gérard*
ALI cultures reveal airway epithelial memory in COPD - *François Carlier*
Role of GCN2 pathway in combined pulmonary fibrosis and hypertension - *Diana Santos*

14:30 - 15:00 Intervention by IREC President - *Jean-Luc Balligand*

15:00 - 17:00 Cardiology Masterclasses + Q&A:
Introduction - *Anne-Catherine Pouleur*
Novel concept integrating metabolism and post translational modifications in the diseased heart - *Justine Dontaine*
Prognosis of right ventricle systolic function parameters in patients with heart failure with reduced ejection fraction - *Laura Houard*
Connecting platelets and myocardial fibrosis during post myocardial infarction remodeling - *Julie Badard*
Heart failure with preserved ejection fraction. The road from comorbidities to myocardial fibrosis - *Sibille Lejeune*
Conclusions & perspectives - *Anne-Catherine Pouleur*

17:00 - 17:30 Closing Remarks

REGISTRATION MANDATORY by May 18th, 2021
via the Registration Button here below
Registered participants will receive a Zoom invitation.

IREC SEMINARS 2021

DATE	SPEAKER	INSTITUTION	TITLE/THEME
02.12.21	Miriam Cnop	ULB Center for Diabetes Research	iPSC-derived beta cells for the study of rare monogenic forms of diabetes
26.11.21	Thomas Baumert	Université de Strasbourg	Single-cell genomics and spatial transcriptomics: Discovery of novel cell states and cellular interactions in liver physiology and disease biology
11.10.21	Thomas Marichal	GIGA Liège	Lung neutrophils: regulators of immune-mediated disorders and homeostasis
14.06.21	Marcel den Hoed	Uppsala University and SciLife Lab	Translational genomics in dyslipidemia and early-stage atherosclerosis using zebrafish model systems
07.06.21	Karim Bouzakri	Université de Strasbourg	The skeletal muscle, an essential actor in health : impact in the context of diabetes
31.05.21	Jérome Feige	École polytechnique fédérale de Lausanne & Nestlé	Mitochondria in muscle aging
26.04.21	Maria-Pia Di Campli	ULB	The origins of myofibroblasts in airways fibrosis
12.04.21	Khuloud T. Al-Jamal	King's College London	Exosomes for Therapeutics Delivery to Pancreatic Cancer
22.02.21	Mathieu Vinken	VUB	Liver-based in vitro models for toxicity testing and drug development
25.01.21	Aernout Luttun	KULeuven	Transcriptional regulation of vascular bed-specific molecular and functional properties of endothelial cells

** Webinar*

Design: www.acg-bxl.be

SCAN TO WATCH IREC VIDEO:

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