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

Albert Szent-Györgyi, 1937 Nobel Prize for Medicine
Introduction by the President

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

The year 2017 was pivotal in the life of the Institute, as we implemented this strategic re-orientation. In particular, we re-organized the research Poles of the Institute into Thematic groups, as reflected in the present report, 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.

We further developed our technological platforms as key elements to provide accessibility to state-of-the-art research tools 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.

Two new “Logisticiens de Recherche”, both senior PhD scientists, were recruited on UCLouvain permanent positions in 2017 to manage and develop these platforms.

We have worked (and still are working) on improving the visibility of our activities both internally and to external (including international) partners, through invitation of prominent scientists at our monthly Seminars, re-designing our Website and organizing networking events, such as the “IREC lunch” and “IREC PhD day”. Our recently appointed Research Coordinator, Nancy Van Overstraeten as well as our Administrative Director, Michel Van Hassel and his team (particularly our “CLC” –financial managers) have been instrumental in implementing all these initiatives.

In the next years, we will face more challenges, but also benefit from opportunities, such as the progressive renovation of all our research buildings, and installation into the new Tour Laennec, with a state-of-the-art new animal facility, open for collaborative experiments.

But the “engine and soul” of the Institute is its people. Through this year 2017, we have enjoyed the company and collaboration of many international young scientists, a number of whom defended their PhD thesis, others competitively obtained research Fellowships and more senior ones were promoted to permanent –including academic- positions. 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.
**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 at 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

**IREC RESEARCH GROUPS**

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Scientific Advisory Board

The Institute has constituted an external Scientific Advisory Board composed of prestigious international scientists from the various disciplines represented within the Institute.

This Scientific Advisory Board was chaired by Prof. J. Loscalzo, chair of the Department of Medicine and Hersey Professor of the Practice of Medicine at Brigham and Women’s Hospital, Harvard medical school, Boston, USA, and composed of:

- **Prof. B. Vanhaesebroek**, Professor at the University College of London, London, UK
- **Prof. B. Wouters**, Executive Vice-President, Science and Research at University Health Network, Toronto, Canada
- **Prof. H. Vidal**, Professor at Claude Bernard University, Lyon, France
- **Prof. P. Ferre**, Professor at the Faculty of Medecine Pierre et Marie Curie, Paris, France
- **Prof. M. Goldman**, Institute for Interdisciplinary Innovation in healthcare, ULB, Brussels, Belgium

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

The SAB will regularly visit the Institute to monitor the progress and update the evaluation.
NEW RESEARCH AGREEMENTS AND CONTRACTS CONCLUDED 2017

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Clinical importance

The importance of cardiovascular disease in terms of public health is well established. Indeed cardiovascular diseases, mainly following atherosclerosis, are responsible for about 50% of deaths in western countries. Therefore, a better understanding of their pathophysiology and treatment is fundamental.

Cardiovascular research within IREC

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: Pole of Cardiovascular Research (or CARD) and the Pole of Pharmacology and Therapeutics (or FATH). The basic and clinical research within this thematic group is led by principal investigators who are qualified researchers of the FNRS, cardiologists and cardiac surgeons.

POLE CARD

• Sylvain BATTAULT, Postdoctoral Fellow
• Laurent BULTOT, Postdoctoral Fellow
• Evangelos P DASKALOPOULOS, Postdoctoral Fellow
• Christophe DE MEESTER, Postdoctoral Fellow
• Mihaela AMZULESCU, PhD student
• Marine ANGE, PhD Student
• Jamila BOULIF, PhD student
• Justine DONTAINE, PhD Student
• Cécile DUFÉYS, PhD Student
• Laura FERTE, PhD Student
• Shakeel KAUTBALLY, PhD student

• Sophie LEPROPRE, PhD Student
• Florence MAILLEUX, PhD Student
• Marie OCTAVE, PhD Student
• Matteo PETTINARI, PhD Student
• Edith RENGUET, PhD Student
• Clothilde ROY, PhD Student
• Carole VERHAEGEN, PhD Student
• Audrey GINION, Research Scientist
• Delphine THIBOU, Animal Technician
• Emmanuel VANDENHOOF, Animal Technician
Basic cardiovascular research investigated 6 major areas

**Platelet biology.**

Given the increased focus on the role of lipid species in platelet function, it is imperative to understand the molecular basis of their regulation during platelet activation.

Our findings highlight the AMPK-activated protein kinase (AMPK)/Acetyl-CoA carboxylase (ACC) signalling as a novel metabolic regulatory pathway in platelets that influences thrombus formation by modulating the content of specific phospholipids which generate key mediators of platelet activation.

**Heart failure**

- **Cardiac metabolism.** Glycogen has been considered as a critical player in the adaptation of the heart to metabolic stress. However, data on the exact function of glycogen during acute ischaemia/reperfusion and post-ischemic remodelling are very limited. Hence, our research aims to shed light onto the intricate roles of glycogen utilization in the acute ischemia context and understand more about its potential as a target to attenuate the deleterious effects of ischemia for the myocardium.

- **Cardiac fibroblasts.** The plasma levels of collagen markers, which correlate with ongoing cardiac fibrosis, are emerging as predictive markers for heart failure in humans. However, cardiac fibroblasts (CFs) are still considered to play a secondary role in adverse cardiac remodelling and heart failure. We performed CF-specific gene targeting in order to investigate the impact of this cell type on global cardiac function after myocardial infarction.

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

- **Cardiac progenitor cells:** We identified an epigenetic regulation of cardiac progenitor cells differentiation through miR-29 and Dnmt3a regulation of canonical Wnt signalling.

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Implantation of cardiac progenitors with downregulated Dmnt3a around the infarcted myocardium resulted in improved contractility and reduced adverse remote remodelling. 2

Cardiac hypertrophy

AMPK is known to inhibit cardiac hypertrophy. We demonstrated that AMPK activation blocks cardiac hypertrophy by reducing protein O-GlcNAcylation both in vitro and in vivo3. AMPK inhibits O-GlcNAcylation by controlling the phosphorylation of GFAT, the rate-limiting enzyme of O-GlcNAcylation pathway, thereby reducing O-GlcNAcylation of proteins such as troponin T.

Diabetic cardiomyopathy

- **Molecular mechanisms of glucotoxicity.** Hyperglycemia (HG) stimulates the production of reactive oxygen species in the heart through activation of NADPH oxidase 2 (NOX2). This production is independent of glucose metabolism but requires sodium/glucose cotransporters (SGLT). This research investigated the expression and function of cardiac SGLT isoforms (SGLT1 to 6 and sodium-myoinositol cotransporter-1, SMIT1). We demonstrated that heart SMIT1 senses HG and triggers NOX2 activation4. This could participate in the redox signalling in hyperglycemic heart and contribute to the pathophysiology of diabetic cardiomyopathy.4

- **Protein acetylation and reduced glucose uptake.** Type 2 diabetes is characterized by elevated plasma levels of leucine and ketone bodies. We showed that both are catabolised into acetyl-CoA, inducing an increase in protein acetylation. Concomitantly, ketone bodies and leucine inhibit glucose uptake by reducing translocation of glucose transporter Glut4. Pharmacological inhibition of protein acetylation prevents this decrease in glucose uptake. We conclude that leucine and ketone bodies reduce glucose uptake by inducing acetylation of proteins involved in the translocation of Glut.5

**Endothelial dysfunction**

- **Probiotics:** Lifestyle and food choices dramatically impact cardiovascular health. Our research focuses on the impact of inulin type fructans (an example of probiotics) enriched diet on endothelial dysfunction in a mouse model of hypercholesterolemia6. Our current work proposes to further document the mechanisms underlying the improvement in endothelial function.

- **Nitric oxide (NO) bioavailability:** We developed a method to measure the circulating concentration of bioavailable NO, a major regulator of endothelial and vascular homeostasis, by quantifying a paramagnetic form of nitrosylated hemoglobin using Electron Paramagnetic Resonance spectroscopy in venous erythrocytes. We have applied this in rodent models of endothelial dysfunction and adapted the technique in human blood7.

**Circulation failure**

Sepsis is a serious healthcare problem recognized as the most common cause of mortality in intensive care units. It is characterized by a systemic inflammatory response that occurs during severe infection. Pathogen-induced inflammation impacts various organs leading to multi-organ(s) failure.

The cardiovascular system is targeted by the onset of a severe sepsis. A reversible depressed left ventricular function is frequently observed and is called septic cardiomyopathy. Besides, endothelial dysfunction is a common feature of severe sepsis and plays a major role in its pathogenesis. This research focuses on the role of endothelial α1AMPK signalling in defence against septic injury, notably through the identification of new endothelial (cytoskeletal or junctional) targets.
Clinical research

Translational clinical cardiovascular research investigated 5 major areas.

Atherosclerosis and Intervention
In a translational study the respective roles of inflammation and neovascularization in human carotid plaques were investigated using non-invasive F-18 PET and contrast echocardiography in comparison with histology. Other studies evaluated outcomes after percutaneous interventions for left atrial appendage closure and vascular disease.

Endothelial dysfunction
We have correlated endothelial dysfunction, measured by digital microtonometry (ENDOPAT) with altered concentrations of nitrosylated hemoglobin (HbNO) in young women taking contraceptive pills. We found that oral contraceptives induce plasma oxidant stress and endothelial dysfunction, which is detected by low HbNO even in absence of any other classical cardiovascular risk factors.

Cardiac Imaging
Research in cardiac imaging involves development and validation of new techniques for quantification of myocardial deformation and of automated algorithms for quantification of heart chambers by echocardiography. Moreover we performed translational work for validation of cardiac function assessment by high field cardiac MRI in mice.

Heart Failure
In order to subsequently study the role of extracellular volume expansion in heart failure with preserved ejection fraction, we evaluated normal values and age related changes of myocardial tissue times and extracellular volumes by cardiac MRI in healthy volunteers. Other works evaluated the value of myocardial deformation imaging and the role of vitamin D supplementation in heart failure with reduced ejection fraction. We are studying the effect of the beta3-adrenergic agonist mirabegron, in patients with structural heart disease (Stage B, AHA) to prevent the progression of myocardial remodeling and development of heart failure with preserved ejection fraction. This investigator-initiated, European multicentric RCT, subsidized by a Horizon2020 grant, is coordinated at UCLouvain.

Hypertension
Research in hypertension consisted in evaluating the efficacy and effects of myocardial denervation techniques for treatment resistant hypertension on management of hypertension in patients with dialysis or after renal transplantation, as well as on exploring genetic mutations in hypertension caused by pheochromocytoma and paraganglioma.

Valvular Heart Disease
Research evaluated mechanisms and outcome in aortic and mitral valve disease. In the large MIDA database, involving 1922 patients using propensity score matching. We compared long-term outcome after mitral valve repair than replacement. Other studies aimed at better understanding mechanisms of paradoxical low gradient aortic stenosis using CT calcium scoring and cardiac MR. Further work evaluated the efficacy of different new surgical techniques for repair of aortic and mitral valve regurgitation, aortic valve replacement as well as minimal invasive robotic lobectomy.

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Pain, Quality of Life, and Clinical Outcomes after Robotic Lobectomy. The Thoracic and Cardiovascular Surgeon. (2017);65:344-350.
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IMAG is the medical imaging research group of the Université catholique de Louvain originating from and embedded within the Radiology Department of the Cliniques Universitaires Saint-Luc.

IMAG supports 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 involving 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:

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

2. 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.

Pediatric imaging

Performance of chest ultrasound in pediatric pneumonia.
Claes AS, Clapuyt P, Menten R, Michoux N, Dumitriu D.

OBJECTIVE:
The objective of this study was to evaluate the performance of ultrasound in detecting lung consolidation in children suspected of pneumonia, in comparison to the current gold standard, chest X-rays.

MATERIALS AND METHODS:
From September 2013 to June 2014, a monocentric prospective study was performed on all children between 0 and 16 years-old, referred for chest X-ray for suspected pneumonia. Each child was examined by chest ultrasound by an examiner blinded to the chest X-ray. The presence or absence of areas of consolidation, their number and location were noted for each technique. The size of the consolidations identified only on ultrasound was compared with the consolidations visible on both techniques.

RESULTS:
143 children (mean age 3 years; limits between 8 days and 14 years) were included. Ultrasound detected at least one area of consolidation in 44 out of 45 patients with positive X-rays. Of the 59 areas of consolidation on X-ray, ultrasound identified 54. In the 8 patients with negative X-ray, ultrasound revealed 17 areas of consolidation. The mean size of consolidations visible only on ultrasound was 9.4 mm; for consolidations visible on both techniques the mean size was 26 mm (p<0.0001). The sensitivity and specificity of ultrasound were calculated at 98% and 92%. PPV and NPV were 85% and 99%, respectively.

CONCLUSION:
Chest ultrasound is a fast, non-ionizing and feasible technique. With its high negative predictive value, it can replace X-rays in order to exclude lung consolidation in children, thus reducing radiation exposure in this population.

Neurosciences
Topic: optimization of diffusion weighted (DWI) MRI.
A comparative study of the sensitivity of diffusion-related parameters obtained from diffusion tensor imaging, diffusional kurtosis imaging, q-space analysis and bi-exponential modelling in the early disease course (24 h) of hyperacute (6 h) ischemic stroke patients.
Duchêne G, Peeters F, Duprez T.

This project is developed in collaboration with A. Peeters (Neurology department, CUSL)

OBJECTIVES: To compare the sensitivity and early temporal changes of diffusion parameters obtained from diffusion tensor imaging (DTI), diffusional kurtosis imaging (DKI), q-space analysis (QSA) and bi-exponential modelling in hyperacute stroke patients.

MATERIALS AND METHODS:
A single investigational acquisition allowing the four diffusion analyses was performed on seven hyperacute stroke patients with a 3T system. The percentage change between ipsi- and contralateral regions were compared at admission and 24 h later. Two out of the seven patients were imaged every 6 h during this period.

RESULTS:
Kurtoses from both DKI and QSA were the most sensitive of the tested diffusion parameters in the few hours following ischemia. An early increase-maximum-decrease pattern of evolution was highlighted during the 24-h period for all parameters proportional to diffusion coefficients. A similar pattern was observed for both kurtoses in only one of two patients.

CONCLUSION:
Our comparison was performed using identical diffusion encoding timings and on patients in the same stage of their condition. Although preliminary, our findings confirm those of previous studies that showed enhanced sensitivity of kurtosis. A fine time mapping of diffusion metrics in hyperacute stroke patients was presented which advocates for further investigations on larger animal or human cohorts.

Musculoskeletal imaging: rheumatologic diseases
Topic: optimization of MRI screening for rheumatoid arthritis.

Fat suppression at 2D MR imaging of the hands: Dixon method versus CHESS technique and STIR sequence.
Kirchgesner T, Perlepe V, Michoux N, Larbi A, Vande Berg B.

OBJECTIVE:
To compare the effectiveness of fat suppression and the signal-to-noise ratio (SNR) of the Dixon method with those of the CHESS (Chemical Shift-Selective) technique and STIR (Short Tau Inversion Recovery) sequence in hands of normal subjects at 2D MR imaging.

MATERIAL AND METHODS:
14 healthy volunteers (mean age of 29.4 years) consented to have both hands prospectively imaged with SE T1 Dixon, T1 CHESS, T2 Dixon, T2 CHESS and STIR sequences in a 1.5T MR scanner. Three radiologists scored the effectiveness of fat suppression in bone marrow (EFSBM) and soft tissues (EFSST) in 20 joints per subject. One radiologist measured the SNR in 10 bones per subject. Statistical analysis used two-way ANOVA with random effects, paired t-test and observed agreement to assess differences in effectiveness of fat suppression, differences in SNR and inter-observer agreement.

RESULTS:
EFSBM was statistically significantly higher for T1 Dixon than for T1 CHESS and for T2 Dixon than for T2 CHESS (p<0.0001). EFSBM was significantly higher for T2 Dixon than for STIR in the coronal plane (p=0.0020). The SNR was significantly higher for T1 Dixon than for T2 CHESS (p<0.0001).

CONCLUSION:
The Dixon method yields more effective fat suppression and higher SNR than the CHESS technique at 2D T1-weighted MR imaging of the hands. At T2-weighted MR imaging, fat suppression is more effective with the Dixon method while SNR is higher with the CHESS technique.

Whole body MRI in spondyloarthritis (SpA): Preliminary results suggest that DWI outperforms STIR for lesion detection.
Lecouvet FE, Vander Maren N, Michoux N, Triqueneaux P, Malghem J, Denis ML, Larbi A.
Collaboration with Collette L (European Organization for Research and Treatment of Cancer, Brussels), Stoenuiu M, Houssiau F and Nzeusseu Toukap A (Rheumatology, CUSL).

PURPOSE:
To compare the diagnostic accuracy of DWI and STIR sequences in Whole body (WB) MRI of SpA patients.

MATERIALS AND METHODS:
Twenty consecutive patients with confirmed active SpA and 20 controls were investigated with identical WB MRI protocols, including DWI and STIR images. Two observers recorded ‘lesions’ (high signal intensity foci on STIR and high b-value DWI) in 17 anatomical areas, making a 17-point ‘area score’ and a 40-point ‘lesion score’. ROC performance, inter-observer agreement, correlation with clinical parameters and spine and sacro-iliac joints (SIJ) MRI scores were assessed.

RESULTS:
SpA patients had significantly higher lesion scores on DWI than on STIR (p<0.025). The lesion score area under the curve was significantly higher with DWI (99.9) than with STIR (95.8, p=0.02). DWI lesion score ≥5 had both sensitivity and specificity ≥85 %. With STIR the best threshold ≥3 yielded sensitivity ≥85 % and specificity ≥60 %. DWI area score ≥3 yielded sensitivity ≥85 % and specificity ≥80 %. With STIR the best threshold ≥4 yielded sensitivity ≥70 % and specificity ≥80 %. CONCLUSIONS: DWI is a promising alternative to STIR in WB MRI to detect active SpA lesions.

KEY POINTS:
• DWI is a robust alternative to STIR in WBMRI in SpA.
• DWI might be superior in discriminating relevant inflammatory and degenerative changes. • Positive correlations exist between WB MRI, clinical, biological, local MRI data. • Distribution and frequency of abnormal MRI findings in SpA are highlighted.

Patients with oligometastatic disease (OMD) often have controllable symptoms, and cures are possible. Technical improvements in surgery and radiotherapy have introduced the option of metastasis-directed ablative therapies as an adjunct or alternative to standard-of-care systemic therapies. Several clinical trials and registries are investigating the benefit of these therapeutic approaches across several cancer sites.

This requires that patients are correctly included and followed with appropriate imaging. This article discusses the evidence and offers recommendations for the implementation of standard-of-care (Response Evaluation Criteria in Solid Tumours measurements on computed tomography [CT], magnetic resonance imaging [MRI] and bone scintigraphy) and advanced imaging modalities (functional, metabolic and radionuclide targeted) for identifying and following up patients with OMD.

Imaging requirements for recognising OMD vary with tumour type, metastatic location, and timing of measurement in relation to previous treatment. At each point in the disease cycle (diagnosis, response assessment and follow-up), imaging must be tailored to the clinical question and the context of prior treatment. The differential use of whole-body approaches such as 18F-FDG positron emission tomography (PET)/CT, diffusion-weighted imaging (DWI), and sequence combinations to detect bone involvement in prostate cancer (PCa) and multiple myeloma (MM) patients.

Quality assured and quality controlled imaging data included in databases such as the European Organisation for Research and Treatment of Cancer Imaging platform for the Oligocare trial (a prospective, large-scale observational basket study being set up to collect outcome data from patients with OMD treated with radiation therapy) will establish a large and high-quality imaging warehouse for future research.

**Topic: optimization of metastatic screening in prostate cancer and multiple myeloma.**

Whole-body MRI to assess bone involvement in prostate cancer and multiple myeloma: Comparison of the diagnostic accuracies of the T1, short tau inversion recovery (STIR), and diffusion-weighted imaging (DWI) sequences. Larbi A, Omoumi P, Pasoglu V, Michoux N, Triqueneaux P, Tombal B, Cyteval C, Lecouvet F.

Project developed in collaboration with The University Hospitals from Montpellier and Lausanne

**PURPOSE:** To compare the diagnostic accuracy of whole-body T1+, short tau inversion recovery (STIR), diffusion-weighted imaging (DWI), and sequence combinations to detect bone involvement in prostate cancer (PCa) and multiple myeloma (MM) patients.

**MATERIALS AND METHODS:** We included all patients with PCa at high risk for metastasis and with a histologically confirmed diagnosis of MM who received whole-body MRI at two institutions from January to December 2015. Coronal T1, STIR, and reconstructed coronal DWI were obtained for all patients. Two musculoskeletal radiologists read individual sequences, pairs of sequences (T1-DWI, T1-STIR, and STIR-DWI) and all combined (T1-STIR-DWI) to detect bone involvement. Receiver operating characteristic curve analysis was used to assess diagnostic performance according to a "best valuable comparator" combining baseline and 6-month imaging, clinical and biological data. Interobserver agreement was calculated.

**RESULTS:** Fifty PCa patients and 47 MM patients were included. Interobserver agreement for individual and combined MRI sequences ranged from good to very good; agreement was similar in the PCa and MM groups (0.76–1.00). In PCa patients, T1-DWI, T1-STIR, and T1-STIR-DWI showed the highest performance (sensitivity=100% [95% CI=90.5–100%], specificity=100% [75.3–100%]). In MM patients, the highest performance was achieved by T1-STIR-DWI (sensitivity=100% [88.4–100%], specificity=94.1% [71.3–100%]). T1-STIR-DWI significantly outperformed all sequences (p<0.05) except T1-DWI (p=0.49).

**CONCLUSION:** In PCa patients, a combination of either T1-DWI or T1-STIR sequences is not inferior to a combination of three sequences to detect bone metastases. In MM, T1-STIR-DWI and T1-DWI had the highest diagnostic performance for evaluating bone involvement. Eur Radiol, in Press
**Topic:** optimization of prostate cancer detection and diagnosis.

Prospective comparison of a fast 1.5T biparametric to the 3.0T multi-parametric ESUR magnetic resonance imaging protocol as triage test for men at risk of prostate cancer. has now been submitted to BJU International. Van Nieuwenhove S, Trefois P, Annet L, Michoux N, Lecouvet FE

**Collaboration with Saussez T, Thiry S and TombalB (Urology department, CUSL)**

**OBJECTIVE:** To prospectively compare the diagnostic performance of a biparametric (T2 and DWI) fast 1.5T magnetic resonance imaging protocol (fMRI) to the standard multi-parametric 3.0T ESUR (mpMRI) protocol in men referred for a prostate biopsy.

**SUBJECTS AND METHODS:** Ninety patients with a PCA risk ≥10% on SWOP calculator 4 underwent first the fMRI and then the reference mpMRI. Patients with Pi-RADS v.2 lesions ≥3/5 on the mpMRI were scheduled for MRI/US fusion-guided prostate biopsy. Performance of fMRI using ROC curve analysis and mpMRI as reference. Calculation of inter-technique agreement on Pi-RADS v.2 score by Cohen’s Kappa.

**RESULTS:** fMRI diagnostic accuracy on the lesion-based analysis is excellent: AUC 0.961 (p <0.001), sensitivity 95%, specificity 97%, positive predictive value 99%, negative predictive value 89%. On the patient-based analysis, fMRI AUC is 0.975 (p <0.001), sensitivity 98%, specificity 97%, positive predictive value 98%, negative predictive value 97%. Agreement on the PI-RADS score between both protocols was found to be good (Kappa = 0.78 [0.57; 0.99]).

**CONCLUSION:** In the triage of men with a high risk of prostate cancer for prostate biopsy, a fast MRI protocol (1.5T magnet, T2 + DWI, < 15 minutes) may safely replace the traditional ESUR 3.0T mpMRI protocol, saving time and contrast injection.

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**Topic:** Can texture analysis predict NonSmall Cell Lung Cancer recurrence after surgery?

Michoux N, Guillet A, Ghaye B

**Project in collaboration with the SMCS (Support en Méthodologie et Calcul Statistique) from UCL.**

**Purpose:** To predict the aggressiveness of NSCLC (in terms of recurrence) using morphology and texture analysis on a pre-surgical CT.

**Materials and Methods:** In this retrospective study, 46 consecutive patients with NSCLC (T1 or T2 N0 M0) exclusively treated by surgery were included. A preoperative acquisition obtained using the same reconstruction parameters on the same CT scanner was used (i) to extract tumor morphological properties, (ii) to assess intra-tumoral texture parameters from the Grey Level Co-occurrence and Run-Length matrices. All patients underwent a thoraco-abdominal CT every 6 months and an 18FDG PET-CT in case of recurrence suspicion. Eight patients (17%) presented with tumor recurrence during a mean follow-up of 4.5 years (2.5-8) after surgery. Different predictive models either based on individual parameters (morphology and texture) or on a small set of parameters embedded in a logistic regression were reconstructed. Receiver operating characteristic analysis was performed to assess the predictive performance of these models. Then, the best multiparametric models were submitted to a leave one-patient out cross-validation (LOOCV) for assessing how accurately they will perform on an independent data set.

**Results:** Individual morphological parameters Surface Area (in mm2) and Aspect Ratio (major axis/ minor axis of the tumor’s fitted ellipse) displayed a good performance in identifying patients with tumor recurrence (Area: Se = 88%, Sp = 88%, AUC = 0.86, Aspect Ratio: Se = 88%, Sp = 60%, AUC = 0.73). After LOOCV, models based on 4 texture parameters (Homogeneity, Sum Variance, Grey-Level Nonuniformity, Run Percentage) or on (Sum Average, Grey-Level Nonuniformity, Run Percentage, Short Run Low Grey-Level Emphasis) displayed a very good performance in identifying patients with tumor recurrence (Se = 100%, Sp = 91%, Acc = 91% for both models).

**Conclusion:** These preliminary results confirm the growing evidence that lung cancers have texture features related to their tumoral aggressiveness. Combining morphological and texture parameters may allow improved tumor recurrence prediction. Further work is required to understand how to optimally implement texture analysis of these CT images.
Tissue-specific or systemic dysregulation of the immune system leads to several diseases or disease complications across all fields of medicine. Auto-immune or auto-inflammatory disorders, hypersensitivities/allergies, inflammatory responses, and graft rejection represent major clinical manifestations indicative of a disruption in the homeostasis of the innate and/or adaptive immune system.

Clinical care of patients with such disorders requires the intervention of qualified rheumatologists, pulmonologists, nephrologists, and others according to the affected system.

By contrast, understanding mechanisms of disease and finding innovative strategies in order to stratify patients (and thereby personalize medical decisions) takes advantage of pooling diverse scientific and technological expertise in a translational platform that aims at scaling up ambitions and results.

In this context, the scientific competitiveness of the IREC clinical and translational immunology platform is promoted by specific strengths. In particular, access to large collections of biological samples from well-characterized patients with immune-related disorders, shared high-throughput and imaging technological platforms, development of appropriate animal models and, last but not least, numerous interactions in national and international research networks gave rise to significant advances in the field, as described below.
Very much in contrast to a common belief, rheumatologists take care not only of elderly patients suffering from the consequences of aging of their musculoskeletal system but also – and nowadays mainly – of (very) young adults with inflammatory and autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis, which may considerably impact not only their quality of life but also their life span.

Over the last decade, our interest has moved towards translational and clinical research in these diseases. Clues to success have been our databases, the systematic use of an appropriate clinimetrics, the possibility to harvest synovial tissue by mini-arthroscopy or PBMC from active patients through leucopheresis and the set-up of an European network of clinical researchers willing to collaborate in investigator-initiated randomized trials.

Disease severity of proliferative lupus nephritis in Maghrebians
Farah Tamirou, Séverine Nieuwland-Husson, Frédéric Houssiau

Many factors negatively impact the prognosis of LN among which unfavorable socio-economic status, uncontrolled hypertension, renal impairment at baseline, first-line treatment failure, non-adherence to therapy, renal relapses and, last but not least, ethnicity. Indeed African-American and Hispanic patients experience a poorer renal outcome because of both genetic and socioeconomic factors. Whether this conclusion can be extrapolated to other ethnic groups more commonly represented amongst current European populations, such as Maghrebians, is unknown.

In Europe, especially in France and Belgium, universal access to health care is provided to patients, irrespectively of socio-economic status, thereby blunting confounding factors. Since Belgium and France have a significant proportion of inhabitants originating from Maghreb, lupus expert centers from these two countries are ideally placed to address the question whether LN is more severe in Maghrebians living in Europe (ME patients) compared to native Europeans (E patients). Moreover, thanks to a collaboration with a Moroccan expert center located in Casablanca, we were also able to compare disease severity at LN onset in Maghrebians living in Maghreb (MM patients) with E and ME patients.

In this study, we assessed the influence of Maghrebian ethnicity on i) the clinical and pathological presentation of LN; ii) the renal relapse rate; iii) the renal and overall survival; and iv) the predictive value of an early proteinuria decrease for good long-term renal outcome.

We retrospectively reviewed the files of an inception cohort of 194 patients with proliferative LN followed in 7 lupus centers belonging to three groups: Europeans living in Belgium/France (E; n=111), Maghrebians living in Europe, in casu Belgium/France (ME; n=43) and Maghrebians living in Morocco (MM; n=40). Baseline presentation was compared between these 3 groups but complete long-term outcome data were available only for E and ME patients.

At presentation, clinical and pathological characteristics of LN did not differ between E, ME and MM patients. Renal relapses were more common in ME patients (54%) than in E patients (29%) (p<0.01). Time to renal flare and to ESRD was shorter in ME patients compared to E patients (p<0.0001 and p<0.05, respectively) (Figure 1). While proteinuria measured at month 12 accurately predicted a serum creatinine value <1 mg/dl at 7 years in E patients, this was not the case in the ME group, in whom serum creatinine at month 12 performed better (9).

Despite a similar disease profile at onset, the prognosis of LN is more severe in Maghrebians living in Europe compared to native Europeans, with a higher relapse rate. The reasons why Maghrebian LN patients living in Europe experience almost twice more renal relapses remain speculative. First, we could not unmask differences in the initial immunosuppressive treatment, except that ME patients received more oral GC, which should, at least in theory, be associated with a lower risk of early renal relapse. Second, non-adherence to treatment, a major cause of relapses in SLE might be more prevalent in Maghrebians for different reasons such as fear of side-effects, disease denial, chronic nature of the disease requiring long-term treatment well beyond initial symptoms improvement, cultural beliefs, language barrier, etc. None of these hypotheses could be tested here. Last but not least, the higher renal relapse rate observed in Maghrebians might be explained by genetic factors. Even though it has been shown that Moroccans are genetically closer to Europeans than to sub-Saharan Africans, the distribution of G1 and G2 alleles of the APOL1 gene, which encodes the trypanolytic L1 apolipoprotein, has never been studied in Maghrebians suffering from LN. These alleles indeed confer an increased risk of developing renal impairment in African-Americans with various kidney diseases, not only LN, but also focal segmental glomerulosclerosis, HIV-associated nephropathy and even hypertensive nephropathy.
Renal markers of disease severity in lupus nephritis

Aurélie De Groof, Gaëlle Tilman, Pauline Montigny, Sylvie Goletti, Joëlle Marchandise, Anne-Lise Maudoux, Christine Galant, Bernard Lauwerys

Lupus Nephritis (LN) is caused by the deposition of anti-double stranded DNA antibodies on the glomerular basal membrane, resulting in complement activation and recruitment of inflammatory cells. LN is a severe complication of systemic lupus erythematosus (SLE) and requires therapy with high doses glucocorticoids and other immunosuppressive agents. One of the most frequently used treatment strategy is the Euro-Lupus Nephritis Regimen, developed and validated by our center, which uses lower doses intravenous cyclophosphamide in the induction phase, thereby reducing side effects (amenorrhea, infections). Despite these therapeutic advances, LN still leads to the development of end-stage renal disease in 15% of the patients at 10 years, and permanent impairment of renal function in a larger proportion, a major source of concerns in a population of mostly young women (1-5).

We recently performed high-throughput transcriptomic experiments on kidney biopsies from 32 LN patients and 8 controls (cadaveric donors). We found that molecular profiles in kidney biopsies were strongly associated with renal function and renal outcomes in LN samples. In particular, we found that local activation of $T$ and $B$ cells in the kidney interstitium is associated with renal tubular cell damage and decreased renal function at the time of biopsy, but also during follow-up. Taken together, our data indicate that the lupus kidney is not just a target of systemic autoimmunity, but also hosts secondary activated immune effectors that play a determining role in disease progression and response to therapy. (Figure 2)

In order to confirm the role of intra-renal adaptive immune effectors in the pathogenesis of LN, we are presently cloning and expanding renal CD8$^+$ T cells, in order to test their reactivity against renal tubular antigens. We are also evaluating whether urinary $T$ and $B$ cell populations reflect intra-renal activation patterns, in order to develop non invasive methods of assessing LN disease severity and progression.

In this work, we are also taking advantage of mouse models of SLE presently bred in the laboratory. B6.Sle1.Sle2.Sle3 mice are C57Bl/6 mice congenic for three lupus susceptibility loci. These mice spontaneously develop anti-nuclear antibodies, and lupus nephritis. Using flow cytometry panels, we showed how systemic adaptive immune cells become activated from the age of 5 months, resulting in end-stage differentiation of $B$ cells into plasma cells (11). Similar to what we did in human kidney biopsies, we are presently focusing on intra-renal adaptive immune effectors in these mice, and their role in renal disease progression, independently of the systemic activity of the disease.

Clinical effects of new rheumatoid arthritis therapies and studies on synovial biopsies

Clément Triaille, Isabelle Faille, Aleksandra Avramovska, Laurent Meric de Bellefon, Maria Stoienoiu, Adrien Nzeusseu Toukap, Frédéric A. Houssiau, Bernard Lauwerys, Patrick Durez

Our constant recruitment of new patients, our systematic registration of clinical and biological parameters of disease activity, and our large repository of biological samples (in particular synovial biopsies) put us in a central position in the development of research activities in the field of rheumatoid arthritis (RA).
In 2017, we kept recruiting patients in numerous international sponsored clinical trials. In addition, we run several academic protocols in early and refractory RA. Thus, we developed a medical research program in which young patients with early arthritis, lupus or scleroderma are included in a prospective cohort (collaborative project with Ulg and ULB, supported by CAP48 and the RTBF). In 2017, CAP48 and RTBF decided to support this program until 2023. The clinical information collected up to 10 years on the activity of the disease, joint destruction, and functional capacity will serve as a basis for the development of new molecular biomarkers, using synovial biopsies collected in these patients prior to initiation of therapy. In this perspective, we are presently analyzing more than 120 synovial tissue samples in early RA to evaluate how histopathological and transcriptomic patterns correlate these with disease activity, severity and clinical responses.

Synovial biopsies are obtained from small and large joints from patients with arthritis by ultrasound-guided biopsies, a minimally invasive and very well tolerated procedure that is routinely performed in the Department of Rheumatology of the Cliniques Universitaires Saint-Luc. We demonstrated how molecular patterns in synovial tissue from patients with arthritis are informative not only about diagnosis, but also about disease severity and response to therapy (6-8). Our findings led to the development of a diagnostic kit, aiming at early diagnosis of RA in patients with undifferentiated arthritis, using a low-density transcriptomic platform (in association with DNAlytics, a spin-off company of the Université catholique de Louvain). More importantly, our work fits in the development of a molecular taxonomy of systemic and inflammatory rheumatic diseases, in which diagnostic categories developed in the 19th or 20th century matter less than molecular profiles associated with prediction of disease progression and/or response to therapy. We are participating at several multi-centric protocols (R4RA, MatuRA) aiming at validating the use of synovial biopsies in predicting response to several therapies in RA, and we are coordinating the multicentric PantheRA trial, investigating synovial markers of response to TNF blockade in RA patients. In our capacity as chair of the European Synovitis Study Group inside EULAR (European Society of Rheumatology), we are also working at the harmonization of techniques and protocols involving synovial biopsies. The first international course on synovial biopsies will be organized in Brussels in September 2018.

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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:

1. **Physiology and pathology of breathing and sleep.**
2. **Mucosal immunobiology and inflammation of the lungs and skin.**
3. **Biology of lung cancer.**

### Physiology and pathology of breathing and sleep:

**(a) pitfalls of CPAP treatment in sleep apnea**

*B. Mwenge, G. Desuter & Ph. Rombaix*

**Support: external funding (Imthera).**

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

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

Currently neuropsychological determinants of compliance with CPAP in patients with OSAS are studied.

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

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

This year we are studying a prosthetic device allowing a muscles tongue training in order to counteract the bad compliance to the exercises.

We are also assessing 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.

(b) Drug delivery by nebulization


Support: SSS-IREC (mandate G. Reychler).

Drug delivery to the lung has been mainly studied in spontaneously breathing patients and in patients. New indications are emerging. A recent international consensus stated about the aerosol delivery combined with tracheostomy. To combine nebulization with invasive or non-invasive ventilation and with high flow nasal cannula was investigated by our group during this year.

We showed that:

Volume-controlled ventilation was associated with higher lung deposition of nebulized particles as compared to pressure support ventilation (4).

During NIV with a single-limb circuit bilevel ventilator, the use of inspiratory synchronized vibrating mesh nebulization improves respirable dose and reduces drug loss compared with continuous vibrating mesh nebulization (5).

A new system combining a vibrating-mesh nebulizer with a valved holding chamber to deliver nebulized particles into the lungs is superior to a constant-output jet nebulizer with a corrugated tube (6).

Finally, new exercise field tests were investigated in children and questionnaires useful in clinical practice were validated (7).

Mucosal immunology and inflammation in the airways and the skin: altered function of the respiratory epithelium and dendritic cells


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.

Dendritic cells (DC) are professional antigen presenting cells that play a crucial role in initiating allergic responses. We previously showed that myeloid DC (mDC) from patients with allergic rhinitis and allergic asthma are skewed for signals promoting Th2, Th9 and Th17 immune responses (8). This DC dysregulation has also been associated with disease persistency in patients with occupational asthma that persists despite cessation of exposure to the offending allergen (9). In addition, our findings about local IgE responses in the lung provide novel insights into the pathophysiology of asthma phenotypes, which is of particular interest in view of the precision medicine in severe asthma with the arrival of biotherapies targeting IgE or IL-5 (10).

Besides DCs, our first focus was the bronchial epithelium and studying its integrity during chronic lung diseases, including expression of the plgR (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 plgR 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 (11-13) (Fig. 2). This IgA/plgR axis is now studied in cystic fibrosis and IPF.

Patients with allergic contact dermatitis to corticosteroids have been reclassified, with important consequences for clinical management. In addition, detailed tissue immunophenotyping has been 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 current further investigations with other contact allergens.
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 (14).

In a previous work (15), 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 (16), we also showed that PF-573,228 increased apoptosis, induced cell cycle arrest in G2/M phases, and decreased proliferation, DNA synthesis, and motility in SCLC cell lines. We then evaluated the effects of FAK genetic inhibition through stable transduction with FAK shRNA and/or FAK-related non-kinase (FRNK), a splice variant lacking the N-terminal and kinase domains. While FAK shRNA transduction decreased total and phospho-FAK (Tyr397) expression, it did not affect proliferation, DNA synthesis, or progression through cell cycle. However, restoration of FAK-targeting (FAT) domain (attached to focal adhesion complex where it inhibits pro-proliferative proteins such as Rac-1) by FRNK transduction inhibited proliferation, DNA synthesis, and induced apoptosis.

Moreover, while FAK shRNA transduction increased active Rac1 levels, FRNK re-expression in cells previously transduced with FAK shRNA decreased it. From this work, we concluded that FAK is central in SCLC biology and that targeting its kinase domain may have a therapeutic potential, while targeting its FAT domain should be avoided to prevent Rac1-mediated pro-tumoral activity.

Currently, we attempt to further investigate the role of FAK and address its potential as a targeted therapy in SCLC by pursuing the following specific aims.

1/ To evaluate the antitumoral potential of FAK inhibition in an orthotopic SCLC mouse model.

2/ To investigate signaling events downstream of FAK contributing to its pro-tumoral functions.

3/ To quantify the expression/activation of proteins involved in the FAK pathway in human SCLC tissues and establish correlations with clinical outcomes.

4/ To identify and characterize the role of FAK mutations in tissues from SCLC patients. Understanding the role of FAK in SCLC may provide greater insight into the molecular steps leading to SCLC progression and, ultimately, may justify the development of FAK-targeted therapeutic strategies to reduce mortality from SCLC.
Novel therapies in nasal, lung and skin diseases: clinical research program.

M Baecck, J Bousata, C Colbrant, Ph Collard, C Dahlqvist, F Duplaquet, M Durry, Ph Eloy, V Erculisse, E Marchand, G Liistro, B Mwenge, S. Ocak, Th Pieters, Ch Pilette, F Pirson, C Sohy, Ph Rombaux, Y Sibille, O Vandenplas, S Viart.

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.

SELECTED PUBLICATIONS


The «acute medicine thematic group» comprises physicians conducting research in the three acute medicine units of the UCL Cliniques Universitaires Saint-Luc and CHU UCL Namur site Mont-Godinne: anesthesiology, intensive care, and emergency medicine.

Our primary research work is devoted to clinical research, from local original studies to international multicenter studies, either academic or industry-sponsored. Our research pole does not currently have its own experimental lab, so that some acute medicine themes are shared with IREC poles (CARD and PNEUMO) according to a translational research.

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

Most of the researchers of this group belong to international collaborative groups, resulting in national or European leading board coordination and some co-authoring studies published in the highest impact factor journals.

One of the challenges of this research sector focused on acutely-ill patients is developing fundamental aspects of clinical studies, participating in preliminary phases of drug developments, and including patients outside working hours (at nights and weekends).

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- Marie-France DJARDIN, study nurse
- Ayhan FINDIK, study nurse
- Leslie GIELENS, study nurse
- Suzanne RENARD, study nurse
- Agnès CHAIGNAUX, study nurse
Here are our main contributions for the year 2017

1. 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.

In 2017, PF. Laterre co-authored a study devoted to selepressin, a selective vasopressin type 1a receptor agonist which increases arterial pressure and has the potential to reduce vascular leakage and pulmonary edema. This trial showed promising results for selepressin by rapidly replacing norepinephrine while maintaining adequate blood pressure, and by improving fluid balance and shortening the time of mechanical ventilation (1).

He also improved the knowledge on the field of combatting hospital-acquired infections with a vaccine: a new, recombinant vaccine against the opportunistic pathogen Pseudomonas aeruginosa has been tested in a phase-II randomized, placebo-controlled, study in mechanically ventilated ICU patients. This vaccination produced a significant immunogenic effect without safety or mortality concerns (2). The ICU team also measured the impact of early exercise on signaling pathways in muscle metabolism in patients with sepsis: the objective of this project was to demonstrate that maintaining muscle activity at an early stage in patients with severe sepsis, restored the balance of skeletal muscle protein (3).

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

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

In 2017, F. Verschuren participated in a new international phase Ib, randomized, double-blind, placebo-controlled, multi-center study to assess the safety and efficacy of a new Thrombin-activatable fibrinolysis inhibitor (TAFI) in subjects with acute pulmonary embolism. He also co-authored a study on the rationale for using Dabigatran (one of the DOAC) early after the diagnosis of intermediate-risk pulmonary embolism (4).

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

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

In 2017, S. Lessire and M. Gourdin published several papers on the validation of bedside guidelines for help during the anesthesiology consultation for the perioperative management of DOACs, on the monitoring of hemorrhagic and thromboembolic events, on the validation of biological tests in cases involving low DOAC concentrations, and on the validation of the interruption of DOAC prior to loco-regional anesthesia (5,6,7,8).

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

3. Improvement of the perioperative management

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

In 2017, Ph. Baele published an original paper on twenty years of collaboration between Belgium and Benin in training anesthesiologists for Africa: he explained how this collaboration allowed 123 graduates from 15 African countries to succeed in reversing the trend of a decreasing anesthesiology workforce in those countries, thus improving the quality of anesthesia and patient safety (10).

4. Cardiovascular and hemodynamic failure

Sepsis is one of the world’s 10 leading causes of death. The cardiovascular system is directly affected by the occurrence of sepsis.

On one hand, a myocardial depression, defined as a reversible impairment of cardiac function, occurs in 50% of cases, on the other hand, an endothelial dysfunction, characterized by an increase of the permeability of the vessels and an increase in the expression of adhesion
and coagulation molecules, induces a prothrombogenic state.

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

5. 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.

In 2017, A. Dive, P. Bulpa and X. Wittebole participated in a Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE). In particular, they showed that the use of noninvasive ventilation in patients with ARDS was associated with higher ICU mortality when the patient is severely hypoxemic (11). The St-Luc ICU team reviewed the effect of aerosol delivery during mechanical ventilation, by performing a systematic review. They showed that lung deposition was as low as 20% (12). P. Bulpa was leader in the reflection on which algorithm diagnoses invasive pulmonary aspergillosis best in ICU patients with COPD (13). Ludovic Gerard also participates in collaborative and transversal research activities between the two IREC poles PNEU and MEDA, devoted to acute medicine thematic. Ludovic is a resident in the ICU and current PhD student. He has recently published a paper on the interest of open lung biopsy to identify a steroid-sensitive pathology in case of non-resolving acute respiratory distress syndrome patients (14).

6. 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.

In 2017, Ph. Hantson and X. Wittebole confirmed their expertise in the management of severe poisoning with calcium channel blocker allowing us to be part of an international consensus experts panel for establishing a management consensus. We offered recommendations for the stepwise management of calcium channel blocker toxicity. For all interventions, the level of evidence was very low (15,16).

Selected publications in 2017:


Advances in immunosuppression therapy have led to the successful transplantation of allogeneic tissues and organs, and have improved the management of various ailments including end stage organ failure and metabolic disorders. However, the increasing demand for organ transplantation is confronted to a shortage of donors. Regenerative medicine aims at alleviating the burden of these unmet medical needs by repairing the affected organs or replacing them with bioengineered organs displaying similar functionalities. The regenerative medicine research group of IREC is active in the areas of fertility preservation (gynecology department), liver and pancreatic disease (pediatric research department), and tissue engineering (vascularized composite tissue engineering group).

**Gynecology department**

- **Maria Costanza CHITI**, postdoc
- **Emna OUNI**, PhD-student
- **Rossella MASCANGELO, MD**, PhD-student
- **Parinaz ASIABI**, PhD-student
- **Diego MANAVELLA, MD**, PhD-student
- **Ellen LEONEL**, visiting researcher
- **Luciana CACCIOTTOLA, MD**, visiting researcher

**A. Ovarian tissue cryopreservation and transplantation**

1. **Restoration of endocrine function**

   Ovarian tissue cryopreservation is offered to young women at risk of premature menopause and sterility after gonadotoxic treatments like chemo- and radiotherapy (1). Cryopreservation (2) and transplantation of ovarian tissue is a promising approach to preserve ovarian function in young cancer patients (3). Transplantation of frozen-thawed ovarian tissue allowed restoration of ovarian function in more than 95% of the cases, with a graft life span of 6-7 years.

2. **Restoration of fertility**

   Fertility is restored after transplantation in 40% of the patients. Worldwide, so far, 130 babies were born with this technique, including 15 babies in the Cliniques Universitaires Saint-Luc (3). There is still place for improvement as there is a huge follicle loss after transplantation, mainly due to ischemia, since initiation of graft reperfusion takes place only on day 5 (4). The goal of one of our projects is to improve early revascularization of grafted ovarian tissue using adipose tissue-derived stem cells (ASCs) delivered inside a fibrin implant using a two-step transplantation procedure, to ultimately increase follicle survival rates (5-6). We have already demonstrated that high concentrations of ASCs enhance vascularization in peritoneal grafting sites. Also, in human ovarian tissue grafted to SCID mice, follicle survival rates were increased by enhanced vascularization and shortened hypoxic exposure. The potential mechanisms responsible for the proangiogenic behavior of ASCs is differentiation of these cells into endothelial cells and secretion of proangiogenic factors like VEGF and FGF2.

3. **Restoration of hormone secretion at menopause**

   At the dawn of humanity, it was rare to live beyond the age of 35 years, so the ovary was intended to function for a woman’s entire life (7). Nowadays, it is not unusual for women to live into their 80s. This means that many of them spend 30-40% of their life in the menopause, at increased risk of various conditions associated with an absence of estrogens (cardiovascular disease, bone mineral density loss, etc). Reimplantation of frozen-thawed ovarian tissue is able to restore long-term ovarian endocrine function, which may persist for
6-7 years (12 years if the procedure is repeated) (8). If ovarian tissue reimplantation is capable of restoring ovarian activity after menopause induced by chemotherapy, radiotherapy and/or surgery, why not propose it to recover sex steroid secretion after natural menopause and prevent menopause-related conditions in the aging population? Freezing ovarian tissue at a young age followed by reimplantation upon reaching menopause, could well become a new option for regenerative medicine, or the anti-aging therapy of the future.

**B. THE ARTIFICIAL OVARY**

### 1. Risk of transplanting malignant cells

In case of acute lymphoblastic leukemia, our experimental studies have shown that ovarian tissue reimplantation is not safe because of the risk of reintroducing the disease. Other diseases have also been tested for safety in the context of ovarian tissue reimplantation, by both molecular analyses with disease-specific markers and by xenografting experiments (9). One option to restore fertility in these patients may be grafting of isolated preantral follicles inside a specially constructed artificial ovary.

### 2. The transplantable artificial ovary

The aim of this project is to develop a bioinspired artificial ovary that offers an environment in which isolated ovarian follicles can survive and grow after transplantation (10).

There are three essential aspects to develop: (i) safe isolation of ovarian follicles; (ii) combination with ovarian (endothelial and stromal) cells; and (iii) creation of a biomimetic extracellular matrix where follicles and cells can be encapsulated together, mainly to give them structural support and facilitate handling during transplantation (11-12).

Improvement to our follicle isolation procedure allowed to personalize the procedure (13) and to obtain a safe suspension of follicles without any residual leukemic cells and ready to be grafted (14).

Regarding the matrix, a fibrin-based one composed of fibrinogen and thrombin appears to be the best option (15), and most closely resembling human ovarian cortex in terms of ultrastructure and rigidity (16-17).

Finally, multi-dimensional label-free mass spectrometry allowed us to chart the most complete representation so far of the human ovarian ECM with more than 1500 proteins identified, opening the door to improved bioengineering techniques for creation of better biomimetic matrices (18).

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**Publications in 2017:**

1. **Dolmans MM.** Expert Rev Anticancer Ther. (2018); 18:115-120.


The research pole PEDI, historically dedicated to pediatric research, is focused on liver and pancreatic diseases in general, and more deeply on stem cell-based regenerative medicine, including translational clinical application thanks to the liver and liver cell tissue bank. The target diseases include inborn metabolic liver diseases as well as acquired diseases of the liver, and pancreatic endocrine diseases. By accumulating and combining significant expertise in cell/stem cell biology, cell isolation/banking as well as in liver and pancreatic disease mechanisms, the unit aims at developing advanced therapy medicinal products.

In 2009, PEDI launched its spinoff “Promethera Biosciences” which has become a key biotech player in the field of liver regenerative medicine using stem cell technology, using candidate stem cells identified by PEDI.

Liver Cell Transplantation (LCT) using a suspension of isolated liver cells aims to restore liver function deficiencies, be they congenital or acquired, and consists in injecting a liver cell suspension to the patient. If conditions are favorable, the cells will either engraft, proliferate, spread, and restore parenchymal structure and function. Liver stem cells are obtained by a specific culture and purification process of the liver cell suspension. Our team has identified a proprietary progenitor cell population within the adult human liver, which emerges in vitro following culture of the parenchymal fraction is issued from a two-step collagenase digestion of the organ. These cells, coined ADHLSCs (adult-derived human liver stem/progenitor cells), exhibit both mesenchymal and hepatic characteristics. They are capable of proliferating in vitro and acquiring hepatocyte-like morphology and function in vitro when subjected to a specific differentiation protocol.

ADHLSCs have a potent paracrine function and act through the production of cytokines and growth factors. These cells are in clinical development phase for urea cycle disorders, for the treatment of acute-chronic liver failure, and other fibro-inflammatory liver diseases. The unit’s research activity focuses on the mechanisms of action of ADHLSC’s against fibrosis and inflammation, and the mechanistic pathways that govern liver parenchymal regeneration. The unit develops alternatives for culture and/or delivery of the cells such as microcarriers and cell sheets. Furthermore, our research unit is working on:

- the development of the best stem cell candidate displaying high expansion stability, hepatogenic differentiation, Beta cell differentiation, and immuno-modulatory properties, assessing the experimental conditions that allow the 3D reconstitution of the stem cells niche and their interactions with neighbouring cells in vitro developing methods to isolate the various cell populations present in the liver investigating the potential use of stem cell derived extracellular vesicles as therapeutic tools.

- In addition, the unit is also tackling the safety issues related to the development of clinical stem
cell therapy including in situ bio-distribution, the modulation of host immune functions, and the potential effect of the cells on the coagulation cascade in healthy and cirrhotic patients.

Finally, the team is working on developing methods to protect the β-cell mass against inflammation and glucolipotoxicity in type 1 diabetes using genome editing techniques such as CRISPR/Cas9 to target key molecular pathways such as IL-1β, IFN-γ and TNF-α.

Publications in 2017


Vascularized Composite tissue Engineering research group (VCE)

Principal collaborators:
- Chantal DESSY, PhD (FATH Lab, IREC)
- Caroline BOUZIN, PhD (2IP, IREC)
- Benoît HERMAN, PhD (Ecole Polytechnique de Louvain, UCL)
- Thomas PARDOEN, PhD (Ecole Polytechnique de Louvain (UCL)
- Giuseppe ORLANDO, MD PhD FACS (Wake Forest Institute for Regenerative Medicine, USA)
- Adeline DEDRICHE, Technician
- Hadrien AMIEL, Master student
- Donovan DEBLUTS, Master student
- Louis MAISTRIAUX, Master Student.
For two decades, Vascularized Composite tissue Allotransplantation (VCA) has represented a true revolution in the field of reconstructive surgery. However, the indications for such transplants remain very limited (fewer than 200 cases for limbs, less than 40 years for the face, worldwide) because of the need for an immunosuppressive treatment, burdened with significant systemic complications. In addition, recent results from long-term follow-up have shown a limited lifespan of the graft, due to chronic vascular rejection.

Aiming to overcome these limitations, new solutions must be found: 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 has been known for a long time for simple tissues, such as the dermis or the valves: it allows to remove cells and antigens of a native tissue, by physical and / or chemical agents, while preserving the extracellular matrix and associated growth factors, the complexity of which is currently impossible to be reproduced, even with the most advanced synthesis techniques (i.e. 3D bioprinting).

The major limitations are the size and complexity of the treated tissues, restricted by the passive diffusion of the products, and the absence of an accessible vascular tree.

The so-called «perfusion-decellularization / recellularization» (PDR) technique, previously described for solid organs (i.e. heart, kidney, lung), represents a variant of conventional bath-stirring techniques: by infusing the products directly by the arterial pedicle, it thus enables the production of very complex matrices, with a preserved, accessible and transplantable vascular system.

In a new paradigm, the approach is to take the graft from the donor, transfer it to the laboratory where it will be decellularized, then recellularized into a bioreactor, partially or totally, with the recipient’s cells. Thus, transplantation in the recipient will be performed with a totally immunologically compatible graft, removing current allotransplantation barriers.

Our work initially hypothesized that the PDR technique could be applied to composite tissues, despite their great variability and tissue associations, characteristic of the body part’s grafts. This required the development of a multi-purpose protocol, and developing strategies specific recellularization and necessary bioreactors.

In order to simplify our approach, we have surgically divided the face and hands into soft motor (lip, eyelid), non-motor (ear, nose), or skeletal (finger/hand) subunit models. Indeed, the VCE approach required a strategy in the tissue association choices, rather than their anatomical location.

By this mean, we were able to describe the bioengineering of porcine and human ears, as well as the extension of VCE to the face and hand in humans, demonstrating the quality of the matrix produced, their cyto-compatibility, as well as the integrity of vascular accesses and network (through in vitro imaging, and by performing short in vivo reperfusion tests).

We have also been able to develop and patent a new generation of bioreactors, adapted to the multi-compartmental aspect of composite grafts and their regeneration specificities. This work paves the way for further developments and, ultimately, the clinical use of VCE: the decellularization path will already allow the first applications; it will also provide the technology and know-how of matrix regeneration, as well as their understanding, which can be translated to future synthetic matrices of the same complexity, when the accurate technologies will be available.
Publications 2017:

Patent:
The topic «Metabolism, obesity and diabetes» gathers MD and PhD scientists from different IREC Poles who are active in two translational lines of research with fundamental, translational and clinical aspects.

The «Hormones and Metabolism» section focuses on the mechanisms of action of hormones and their therapeutic use or inhibition in human diseases, with a large array of research on the causes and consequences of obesity and diabetes mellitus.

The «Cancer and Metabolism» section investigates the mechanisms of metabolic plasticity in tumors in order to identify innovative anticancer targets to fight cancer, and addresses the mechanisms that lead to cachexia and the associated increase in mortality in cancer patients.

These lines of research are briefly presented in the following pages. They extend well beyond the topic. The «Cancer and Metabolism» section is indeed closely related to the «Oncology» theme (on pages 57-61), and the «Hormones and Metabolism» section is connected to the «Cardiovascular» and «Regenerative Medicine» themes (on pages 9-15 and 36-41).
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The Pole of Endocrinology, Diabetes and Nutrition (EDIN), the team of Philippe Lysy at the Pole of Pediatrics (PEDI), the team of Isabelle Leclercq at the Pole of Gastro-Enterology (GAEN), the team of Pierre Gianello at the Pole of experimental surgery (CHEX), and the team of Marie-Christine Many at the Pole of Morphology (MORF) focus on the mechanisms of action of hormones and their therapeutic use in human diseases, with a large array of research on the causes and consequences of obesity and diabetes mellitus in different tissues.

Among several achievements of the thematic group in 2017 were the scientific awards attributed to Sonia Brichard’s team for its work on the treatment of Duchenne’s muscular dystrophy, high impact publication on tumor acidosis in Nat. Rev. Cancer by Olivier Feron, a patent about “Transgenic pig islets and uses thereof for treating diabetes” by the team of Pierre Gianello, and a patent by Pierre Sonveaux reporting on a radiolabeled tracer of lactate for PET scan. The reader is referred to the “Research highlights” pages of our website for further information.

Most research programs include translational aspects, with the aim of identifying new anticancer approaches targeting tumor metabolism. The team of Jean-Paul Thissen at the Pole of Endocrinology, Diabetes and Nutrition (EDIN) focuses on cancer cachexia.

The central role of metabolism and hormones in human diseases 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.

The teams of Olivier Feron and Pierre Sonveaux 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 (eg, hypoxia and acidosis), tumor progression to metastasis, and cancer-host cells relationships.

Most research programs include translational aspects, with the aim of identifying new anticancer approaches targeting tumor metabolism. The team of Jean-Paul Thissen at the Pole of Endocrinology, Diabetes and Nutrition (EDIN) focuses on cancer cachexia.

The teams of Olivier Feron and Pierre Sonveaux 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 (eg, hypoxia and acidosis), tumor progression to metastasis, and cancer-host cells relationships.
P Gilon (EDIN)
The team of P Gilon studies the dialogue between cells of the endocrine pancreas and other organs to identify new targets to combat certain metabolic diseases including diabetes.

Publications 2017-2018


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

Publications 2017-2018


P Lysy (PEDI)
The team of P Lysy focuses on the natural evolution of type 1 diabetes in children and their tolerance to physical activity.

Publications 2017-2018


I Leclercq (GAEN)
The activities of the laboratory of hepatogastroenterology (GAEN) are divided into 4 main themes. The first one is the study of non-alcoholic steatohepatitis and its progression to liver fibrosis and cirrhosis with a specific interest for the cross-talks between the liver and peripheral organs in the context of metabolic syndrome. The second one explores derangements of the gut-brain-liver axis in the context of alcohol consumption. The third one is the study of the mechanisms enabling maintenance of hepatic metabolic functions in context of acute or chronic liver diseases. The last one is the study of pancreatic and neuro-endocrine malignancies.

Publications 2017-2018


SM Brichard (EDIN)

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.

Publications 2017-2018


MC Many (MORY)

The team of MC Many is mainly involved in the study of oxidative stress (ROS source vs. antioxidant defenses) in the pathogenesis of iodine-deficient goiter, of Th1 autoimmune Hashimoto’s thyroiditis, and of Th2 autoimmune Graves’ disease and associated ophthalmopathy.

Publications 2017-2018


J Donckier (EDIN/CHU UCL Namur)

The Service of Endocrinology and Diabetes at the CHU UCL Namur (Godinne) 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.

Publications 2017-2018


D Maiter (EDIN/UCL Saint-Luc University Hospital)

The Division of Endocrinology and Nutrition provides a wide range of services for patients with any endocrine pathology and is conducting several clinical studies on type 2 diabetes, metabolic syndrome, bariatric surgery, Grave’s ophthalmopathy and pituitary tumours.

Publications 2017-2018

CANCER

The research programs of the following teams focus on metabolism and hormones in cancer in order to identify and validate new therapeutic targets. Their expertise covers microenvironmental cancer hallmarks (such as hypoxia, acidity and nutrient resources), cancer cell metabolomics (in particular around pathways related to glutamine, serine and lipid metabolism) as well as local and systemic consequences of tumor bioenergetics (including metastasis and cachexia). Their publications in 2017 are listed after a brief description of the research project of each team.

O Feron (FATH)

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.

Publications 2017-2018


D Gruson (EDIN)

Emerging Biomarkers and mobile Health.

We are investigating the added value of biomarkers for risk stratification in conditions like diabetes and heart failure. 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 of patients with chronic diseases.

Publications 2017-2018


**P Sonveaux (FATH)**

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

**Publications 2017-2018**


**Sonveaux P.** (2017) ROS and radiotherapy: more we care. Oncotarget 8:35482-35483


**JP Thissen (EDIN)**

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.

**Publications 2017-2018**


**JP Thissen (EDIN)**

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.

**Publications 2017-2018**


COLLABORATIVE PROJECTS in 2017

Action de Recherche Concertée ARC 12/17-047 to S Brichard, P Cani, I Leclercq and JC Jonas: «Inflammatory and cellular stress in metabolic syndrome and other disorders»

Action de Recherche Concertée ARC 13/18-051 to C Beauloye, D Dufrane and P Gilon: «Glucose homeostasis: from its physiological control to the consequences of its dysregulation in diabetes»

Action de Recherche Concertée ARC 14/19-058 to P Sonveaux, O Feron, R Frédérick, B Gallez, V Grégoire and BF Jordan: «Understanding the contribution of mitochondrial metabolism to cancer progression and resistance to treatments»
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.

Bone and cartilage diseases

Catherine Behets

Osteogenesis imperfecta (OI), or brittle bone disease, is a kind of osteoporosis due to a congenital defect in type 1 collagen. Its main features are small stature, bone fragility and numerous fractures. Using oim/oim mice, a validated model of human OI, we demonstrated a significant decrease in the number of long bone fractures after 10 weeks of treatment with sclerostin-antibody, a potent stimulator of osteoblastic Wnt pathway.

OI mice were also crossed with Cathepsin K KO mice. The resulting Oim(-/-)CatK(-/-) mice showed no fracture. These results suggest that such treatments could be useful in human OI patients in order to prevent the huge disabilities related to fractures.

In osteoarthritis (OA), stress- and inflammation-induced signaling pathways promote articular cartilage degradation. Hyaluronidases 1 and 2 cleave hyaluronan (HA) into small fragments that increase osteoclastic differentiation and trigger inflammatory signaling. Preliminary data suggest that hyaluronidase Spam1 is up-regulated in human OA chondrocytes. We assessed the effect of Spam1 deficiency in vitro on chondrocytes cultured in the presence of IL-1β and TNF-α.

Murine spam1/- chondrocytes treated with IL-1β and TNF-α expressed significantly less adams-5 and mmp13 (matrix degrading enzymes) and more has2 (enzyme synthesizing HA) than WT chondrocytes exposed to same conditions. These results suggest that Spam1 could play a role in osteoarthritis pathogenesis.

Bone implants and biomaterials

Olivier Cornu

Orthopedic implants (prostheses) were assessed in order

- to optimize hip arthroplasty surgery by quantifying functional improvement using gait analysis and by searching the transfusion risk factors after Hip Arthroplasty;
- to diagnose and manage bone and joint infections; we launched a fundamental experience on the treatment of bacterial biofilms associated to orthopedic implants;
- to improve the technique of osteosynthesis in trauma by developing a protocol for measuring joint penetrations; this project was associated with development of an accessible technology in developing countries.
An anatomical study focused on innervation of the knee in order to develop a technique for effective analgesia in disabling knee arthrosis, either in the absence of access to modern surgical techniques, or after failure of these latter.

**Surgical bone models**  
*Xavier Banse, Olivier Cartiaux, Raphael Olszewski*

The skeletal structure of patients was also modeled. For example, spine surgery planning involves many decisions for which the surgeon has not enough information, and for which biomechanical models might be helpful. Therefore, a biomechanical model for spine surgery planning might be useful in giving the surgeon sufficient information to propose the best treatment. In this context, the intervertebral efforts represent an essential input to help in the diagnosis and subsequently to guide surgical planning of scoliosis.

We also assessed the accuracy of surgery using an intraoperative cone beam computed tomography system, and we analyzed the factors potentially influencing this accuracy. In craniofacial surgery, three-dimensional Frankfort horizontal plane was studied for 3D cephalometry. Virtual implant planning was studied in order to define new original sites of implantation to the maxilla. Finally, in the open-access approach, we realized a systematic review on the open-access software in dentistry.

**Patient mobility evaluation**  
*Christine Detrembleur, Philippe Mahaudens*

Patient mobility is evaluated before and after treatments, such as osteosynthesis, joint replacement, transplant, etc. The outcomes are the ultimate measure of success in health care. When seeking treatment, patients want to know what their life will be like after treatment: will I return to work, will I be able to take care of myself, and will my symptoms improve? Helping patients answer these questions is very important. We developed standardized protocol based on biopsychosocial approach as the use of International Classification of Functioning, Disability and Health model. This model provides an internationally accepted conceptual framework to understand functioning and disability associated with health and illness. We used this approach to evaluate the effect of total hip replacement or slipped capital femoral epiphysis treated with in situ fixation, for example.

**Neurorehabilitation**  
*Thierry Lejeune, Gaëtan Stoquart*

Rehabilitation is designed to improve the functional activities of disabled people. Our team is conducting various projects to better assess and rehabilitate people with a neurological disorder (stroke, multiple sclerosis, Parkinson’s disease). In particular, we study the interest of new technologies (robotics, e-health). We also develop close collaboration with Benin to validate new practices of rehabilitation in line with the local healthcare system. During 2017 year, Didier Niama Natta presented his PhD thesis entitled: “Neurorehabilitation in Benin: efficacy of a self-rehabilitation program for the upper limb”. Thibault Warlop presented his PhD thesis entitled: “Can long-range autocorrelations be a clinical tool for assessing dynamic stability?” Maxime Valet published two papers about fatigue and physical fitness among multiple sclerosis patients.

We welcomed two new colleagues. Clara Selves obtained a clinician-researcher grant from the Fonds de Recherche Clinique (FRC). She will study the efficacy of high doses of botulinum toxin to treat simultaneously the upper and lower limbs of spastic stroke patients. Alexis Lheureux will study the efficacy of gait training in virtual reality on gait pattern and quality of life in parkinsonian patients.

**Exercise, aerosol and physiotherapy**  
*Gregory Reychler*

The research projects of the group « Exercise, aerosol and physiotherapy » were based on the nasal deposition of nebulized particles and on the lung deposition of nebulization combined with non-invasive and invasive ventilation. 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. Exercise training programs and telemedicine were tested in new indications (cancer, congenital heart disease, sleep apnea, Ehlers-Danlos). Physiological effects were studied by the group in relationship with airway clearance techniques. Original tools of evaluations (electrical impedance tomography, lung clearance index) were used as outcomes in these studies.
Selected references


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
- Lab Gait: instrumented treadmill fitted with 3D force sensors, 8 infrared 3D cameras, 16 channels of Wifi EMG, ergospirometer
- Stiffness muscle apparatus
- Calcified tissue histology, pQCT, microradiography
- Animal facility (mice)
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 renal diseases.

Transport mechanisms are also relevant for **water and solute transport across the peritoneal membrane, sustaining peritoneal dialysis (PD) - a therapeutic modality for patients with end-stage renal disease.** 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 depicted 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 worldwide. The disease leads to relentless development of cysts causing progressive kidney enlargement associated with hypertension, pain, cyst hemorrhage, kidney stones, cyst infections, and reduced quality of life. ADPKD is a systemic disorder with potentially serious complications such as massive hepatomegaly and intracranial aneurysm rupture. Mutations in the PKD1 (80-85%) and PKD2 (15-20%) genes account for the overwhelming majority of ADPKD cases. Until recently, there was no 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 participated in the TEMPO and REPRISE international randomized controlled trials which evaluated the effect of tolvaptan, a vasopressin V2 receptor antagonist, on ADPKD disease progression. Based on the findings of these pivotal studies, tolvaptan has been approved as the first disease-modifying therapy in ADPKD on a global scale.

Our investigations are based on a multidisciplinary approach including studies on patients, human and mouse genetics, and analyses 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)
- Fondation Roi Baudouin, Fonds Alphonse et Jean Forton, Fondation Horlait-Dapsens
- Fondation Saint-Luc et Fonds de Recherche Clinique
- Fonds National de la Recherche Scientifique - FNRS et FRSM
- Région Wallonnie
- Baxter Extramural Grant Program
- 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
- Manipulation of gene expression in cell lines and primary cultures
- Promoter analysis (in silico, in vitro)
- In situ hybridization, advanced quantitative RT-PCR
- Immunoblotting, immunoprecipitation, and immunohisto-/cyto-chemistry
- Intracellular distribution studies: subcellular fractionation, immunogold, biotinylation
- Transport studies in cells and native tissues (Ussing chamber)
- Mouse phenotyping: metabolic cages, special diets, pharmacology interventions
- Multisystemic phenotyping: cardiovascular, osmoregulation & thirst
- Biochemical profiling on dedicated platform optimized for rodent samples
- Development and automation of ELISA
- Water and solute transport in mouse model of peritoneal dialysis
- Biobanking: end-stage kidney samples (300+); 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


The Oncology thematic brings together laboratories with basic and clinical research activities. Regular interactions between 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/or optimize new cancer treatments and biomarkers. A brief survey of the main lines of research is presented in the following pages.

Among several achievements of our research groups in 2016-17 are high impact publications by the FATH pole in Cell Metabolism and Nature Rev. Cancer documenting how fatty acid metabolism -as driven by the acidic tumor microenvironment- is a critical determinant of cancer progression, and in Cancer Cell identifying LDHB as a major driver of autophagy in cancer cells. The contribution of the MIRO pole was also instrumental in clinical studies related to targeted therapies (afatinib) and immunotherapy (nivolumab), published in Annal Oncol and JAMA Oncol, respectively.

RESEARCH HIGHLIGHTS

OLIVIER FERON Team:
- Cyril CORBET, PhD (FNRS)
- Estelle BASTIEN, PhD
- Natalia TREMPOLEC, PhD
- Joao SANTIAGO, PhD student (Télévie)
- Bastien DOIX, PhD student (ITN Marie Curie)
- Catherine VANDER LINDEN, PhD student (Télévie)
- Emeline DIEGUE, PhD student (Télévie)
- Quentin SPILLIER, PhD student (Télévie)
- Marine DESKEUVRE, PhD student
- Céline GUILBAUD, Techn
- Laureen PETIT, Techn
- Charline DÉGAVRE, Techn

Pierre SONVEAUX Team:
- Ilias KATSOULIERIS, PhD
- Joanna KRZYSTYNIAK, PhD
- Amanda CAÑAS RODRIGUEZ, PhD
- Pierre DANNIER, PhD
- Valérie MARCHAND, PhD student
- Vincent VAN HEE, PhD student
- Martina SBOARINA, PhD student
- Valéry L PAYEN, PhD student
- Bjorn BASELET, PhD student
- Debora GRASSO, PhD student
- Samantha SCHEINOK, PhD student
- Léopold THABAULT, PhD student
- Marine BLACKMAN, PhD student
- Thibault VAZELLE, Techn
- Loic HAMELIN, Techn
- Emmanuel VANDENHOOF, Techn
- Claude REMACLE, Research Assistant

Pole of Pharmacology and Therapeutics (FATH)
https://uclouvain.be/fr/instituts-recherche/irec/fath/
Two 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, 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. This 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.

The group of P Sonveaux currently investigates metabolic remodeling during metastasis and metabolic changes associated with acquired radio- and chemoresistance in cancer, and is also collaborating with chemists to develop new drugs targeting the oxidative pathway of lactate in cancer.

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): lactate, glutamine and fatty acids**
- **Mitochondria at the crossroad of metastasis and resistance to anticancer therapy**
- **How acidosis and hypoxia independently and coincidentally influence tumor metabolic preferences**
- **Development of a hypoxia-related prognostic biomarkers and lactate tracers for PET scan**
Pole of Molecular Imaging, Radiotherapy & Oncology (MIRO)

The pole of Molecular Imaging, Radiotherapy and Oncology includes two independent laboratories, the lab of Molecular Imaging and Radiation Oncology led by Prof. V. Grégoire, 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 treatment - 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 improving the radiation delivery,
- at a better understanding of the role of tumour microenvironment in radiation response,
- at integrating molecular imaging with various PET tracers in the radiation treatment process. This laboratory includes various scientists with as different background as physicians, biologists, physicists, radio-chemists and engineers.

Here below is a non-exhaustive list of ongoing projects in the lab.

- **Mechanisms of cancer radiosensitization by human papilloma-virus (HPV)**
- **Robust planning and adaptive treatment in proton therapy**
- **Calorimetry in hadron beams**
- **Automatic segmentation of CT images using a registration-free atlas**
- **Preclinical in vivo imaging**
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, 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
- Expression and immuno-suppressive role of IDO1 in colorectal cancer
- Neoadjuvant combination of chemoradiotherapy and anti-PD-L1 antibody for patients with locally advanced rectal cancer

### Selected publications 2016-2017

**Schneider K, Bol V, Grégoire V.**

**Differding S, Sterpin E, Hermand N, Vanstraselen B, Nuys S, de Patoul N, Denis JM, Lee JA, Grégoire V.**


**Van Hée, V., Labar, D., Dehon, G., Grasso, D., Grégoire, V., Muccioni, G., Frédérick, R., Souveaux, P.**
Radiosynthesis and validation of (±)-[18F]-3-fluoro-2-hydroxypropionate ([18F]-Flac) as a PET tracer of lactate to monitor MCT1-dependent lactate uptake in tumors. Oncotarget (2017) 8: 24415-24428.
Selected publications 2016-2017

Biomarkers predict enhanced clinical outcomes with afatinib versus methotrexate in patients with second-line recurrent and/or metastatic head and neck cancer. Annal Oncol (2017); 28:2526-2532.


El Baroudi M, Machiels JP, Schmitz S.


Galot R, Machiels JP.


Schmitz S, Machiels JP.

Machiels JP, Galot R, Schmitz S.


Schmitz S, Duhoux F, Machiels JP.

Phase II study of dual phosphoinositol-3-kinase (PI3K) and mammalian target of rapamycin (mTOR) inhibitor BEZ235 in patients with locally advanced or metastatic transitional cell carcinoma. BJU Int. (2016) Sep;118(3):408-15.
Our research activities on reproductive medicine focus on topics related to human reproduction, both male and female aspects:

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

A pluridisciplinary team (gynecologists, molecular biologists, clinical biologists and veterinary surgeons) investigate reproductive tissue physiology at the molecular and cellular level, both on patient biopsies and in experimental animal models. The teams involved in these projects work in close cooperation with the gynecology, hematology and oncology departments of the Cliniques Universitaires Saint-Luc.

**GYNECOLOGY**
- Jean SQUIFFLET, MD, PhD
- Pascale JADOUX, MD
- Mathieu LUYCKX, MD
- Maria Costanza CHITI, postdoc
- Guillaume COURTOY, PhD-student
- Diego Daniel MANAVELLA, MD, PhD-student
- Javier GARCIA-SOLARES, PhD-student
- Parinaz ASIABI KHOBEH SHAHRI, PhD-student
- Emna OUNI, PhD-student
- Rossella MASCANGELO, MD, PhD-student
- Luciana CACCIOTTOLA, MD, Visiting researcher
- Ellen LEONEL, visiting researcher
- Ana Vetrina LAI MABIWAHAB, MD, visiting researcher
- Francesca BONESI, PhD-student
- Maria Dolores GONZALEZ, Technician
- Olivier VAN KERK, Technician
- Mira HRYNIUK, ba, English language editor
- Dora OURIVES SERENO, logistics and finance
- Deborah CODEFROLD, secretary

**ANDROLOGY**
- Jonathan POELS, PhD
- Federico DEL VENTO, MD, PhD-student
- Francesca DE MICHELE, MD, PhD-student
- Maxime VERMEULEN, PhD-student
- Maria-Grazia GIUDICE, MD, PhD-student

**CONTACT**

**SENIOR SCIENTISTS**

**Gynecology:**
- Marie-Madeleine DOLMANS
- Christiani Andrade AMORIM

**Andrology:**
- Christine WYNS

**WEB SITE (S)**
- http://www.isfp-fertility.org/
A. CRYOBANKING

**MM. Dolmans, P. Jadoul, C.A. Amorim**

Ovarian tissue cryopreservation is offered to young women at risk of premature menopause and sterility after gonadotoxic therapies such as chemo- and radiotherapy. Cryopreservation and transplantation of ovarian tissue is a promising approach to preserve fertility in young cancer patients undergoing gonadotoxic treatment and the only option for prepubertal patients and patients who have no time to undergo stimulation for embryo or oocyte cryopreservation. Transplantation of cryopreserved ovarian tissue allowed restoration of ovarian function, and fertility in more than 130 patients so far worldwide, with 15 babies for Saint-Luc.

The ovarian tissue bank at Cliniques Universitaires St Luc (one of the first and largest in the world) contains tissue from 700 patients, with around 100 patients having donated their tissue for research purposes and 600 for fertility preservation and long-term cryopreservation. Pathologies are various and include both malignant and benign diseases requiring chemotherapy. The most frequent indications are hematological malignancies and breast cancer.

The clinical results of our ovarian tissue bank activities were recently published. Premature ovarian failure rate is as high as 31.5%, proving a good referral from the oncologists. So far, the return rate for autotransplantation is estimated at 4.4% and the pregnancy rate after autotransplantation is 40%, in line with the top 3 world best centers. Each year, a workshop “Course on cryopreservation and transplantation of human ovarian tissue and preantral follicle isolation and in vitro culture” is organized in close collaboration between the research laboratory and the Clinics.

B. MINIMAL DISSEMINATED DISEASE IN THE OVARY

**R. Masciangelo, M.C. Chiti, C.A. Amorim, M.M. Dolmans**

C. Developping A TRANSPLANTABLE ARTIFICIAL OVARY

**C.A. Amorim, M.C. Chiti, P. Asiabi, E. Ouni, M.M. Dolmans**

D. IMPROVING HUMAN OVARIAN GRAFTING OUTCOME WITH ADIPOSE-DERIVED STEM CELLS

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

For sections B-D, please refer to the report of Regenerative Medicine.

E. IN VIVO CHARACTERIZATION OF METABOLIC ACTIVITY AND OXIDATIVE STRESS IN GRAFTED HUMAN OVARIAN TISSUE

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

Other mechanisms besides ischemic damage are thought to be involved in follicle loss after ovarian tissue transplantation, such as oxidative stress triggered by the release of reactive oxygen species (ROS) once the tissue becomes reoxygenated.

Oxidative stress in grafted human ovarian tissue has only been studied indirectly, by investigating as ROS scavenger expression and lipid peroxidation through malondialdehyde levels, for example, but no data have been reported in the literature on direct ROS levels in human ovarian tissue, their production profiles, or timing post-transplantation.

To better understand the metabolic behavior of grafted ovarian tissue, a dynamic in vivo method must be used. Microdialysis is a tool for continuous sampling of drugs and metabolites present in the extracellular space, acting like capillaries and allowing passage by simple diffusion.

We were able to characterize metabolic activity and oxidative stress for the first time by direct detection and quantification of glucose, lactate and ROS in grafted human ovarian tissue within the first 21 days of transplantation (Cacciottola, Manavella et al, 2018 [in press]). The ultimate goal is to provide descriptive information upon which we can base other research projects aiming to identify potential targets to further improve grafted ovarian tissue quality and life span.

SELECTED PUBLICATIONS 2017

**Dolmans MM.** Recent advances in fertility preservation and counseling for female cancer patients. Expert Rev Anticancer Ther. (2018); 18:115-120.


Institut de Recherche Expérimentale et Clinique REPRODUCTIVE MEDICINE


Partnership

- Inter-university: ULg, ULB, UCL, University of Brasilia (Brazil), University of Sevilla (Spain), University of Valencia (Spain), University of Nottingham (UK)
- Entreprises: Baxter and SMI

Fundings

- Mécénats
- FNRS
- Fondation contre le Cancer
- Fondation Saint Luc
- Wallonie-Bruxelles International (WBI)
- Région Wallonne (Pôle BioWin)

Main Equipment

- Programmable freezers
- Facilities for cell and follicle culture
- Facilities for cryopreservation of isolated cells and tissue

Key words for r&d

- Cryopreservation
- Vitrification
- Transplantation
- Fertility preservation
- Post-chemotherapy
- Follicle isolation
- Artificial ovary
- Scaffold
- Ovarian tissue

Products and Services

- Scaffold for human ovarian follicle grafting
Endometriosis: collective cell migration and innervation in the development of deep nodular endometriosis

J. García-Solares, J. Squifflet, M.M. Dolmans

Endometriosis is one of the most commonly encountered gynecological diseases. Three different forms of pelvic endometriosis have been identified: peritoneal, ovarian and deep endometriotic nodules of the rectovaginal septum.

In 2013, our team developed an in vivo baboon model, recreating deep nodular endometriosis and allowing to investigate its invasion process. Results obtained from this animal study suggested the involvement of collective cell migration (CCM) and nerve development in the invasiveness of the disease. CCM occurs when groups of cells that retain their cell-cell junctions move together to invade other tissues.

In human nodules, the invasion and innervation phenomena were never studied before. To investigate that, we collected tissue samples from 17 patients presenting with deep nodular endometriosis. All lesions were divided into two sites, depending on anatomical location: front (most invasive area of lesions approaching rectal infiltration) or center (area situated close to the posterior part of the cervix) (Figure 1).

Our results suggested that the mechanism of invasion of deep nodular endometriosis is dominated by CCM. During this process, connection between the center and the invasive front is essential to promote gland migration, therefore when the center is removed, residual glands may be unable to evolve. This could explain the low rates of recurrence observed after conservative surgery, further supporting use of a more conservative approach as first-line surgery in case of type III nodules.

We also found significantly higher expression levels of the nerve growth factor (NGF) in glands and stromal cells located at the invasion front of lesions than in those located in the center. Innervation was also significantly greater at the front. These findings may further endorse the role of NGF as a nerve recruiter from surrounding organs.

SELECTED PUBLICATIONS 2017


SELECTED PUBLICATIONS 2017


Uterine fibroids: evaluation of the mechanism of action of ulipristal acetate in myoma treatment

Our study aims to elucidate the molecular action of UPA producing myoma volume reduction. We previously established that UPA treatment (i) reduces proliferation, (ii) increases apoptotic index and (iii) a crucial reduction in the fibrotic extracellular matrix. It was suggested that proteases like matrix metalloproteinase 2 (MMP-2) may participate in ECM resorption. In vitro studies suggested a number of key factors to explain the mechanism of action of UPA, including the PR and its isoforms, PR nuclear cofactors, the prosurvival factor Bcl-2, and Akt. Unexpectedly, no difference was observed in their expression, distribution and ratios, hence tempering possible extrapolations based on in vitro findings. To identify gene regulations associated to myoma volume regression after UPA treatment, expression of apoptosis-associated and ECM-related genes was investigated in myomas that decreased in size (responsive) or not (non-responsive).
This comparison identified several new factors that are differently expressed according to response. Furthermore, shrinkage of UPA-responsive myomas implies fibrosis resorption. The contribution of MMPs and of tissue inhibitors of metalloproteinases (TIMPS) to myoma volume reduction was investigated by immunohistochemistry and gel zymography (Figure 1). Increased MMP and decreased TIMP expression and activity correlate with responsiveness to UPA treatment. This provides a legitimate explanation for the long-term volume reduction of myomas and their softening in texture, as clinically observed.

Casein zymogram. Compared to untreated (Unt) and non-responsive (NR) samples, myomas responsive to short-term (ST-R) or long-term (LT-R) treatment exhibited higher level of MMP-1, -3, -10 or -11 activity. No MMP-7 activity was detected in the myomas (samples, 100 ng DNA per well; reference layer, conditioned medium obtained from endometrial cultures).

SELECTED PUBLICATIONS 2017

Courtoy GE, Donnez J, Luyckx M, Marbaix E, MM Dolmans. Progesterone receptor isoforms, nuclear cofactors NCoR1 and SRC1, and Bcl-2 and Akt/p-Akt in uterine myomas after ulipristal acetate treatment: a systematic immunohistochemical evaluation. Gynecol Obstet Invest (2017); Epub ahead of print.


Fundings

- PreGlem/GedeonRichter;
- FNRS-FRIA (FC005053)

ANDROLOGY

Due to remarkable advances in cancer therapies, the survival rates of pediatric male patients had seen great improvements. Gonadotoxic therapies also cure a variety of non-malignant disorders. Unfortunately, fertility in adult life might be severely impaired by these treatments.

Our research focuses on four main axes:

- Optimization of fertility preservation methods by cryopreservation of immature testicular tissue (ITT).
- Development of fertility restoration techniques
- Creation of a bioengineered artificial testicle
- Optimization of the transplantation technique of ITT

Fertility preservation and restoration from cryopreserved ITT

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

After developing a slow-freezing protocol for ITT yielding good structural integrity of tissue we were allowed to start banking of ITT from prepubertal boys undergoing gonadotoxic treatments. Cryopreserved human ITT in an in vivo xenotransplantation model showed seminiferous tubule integrity and ability of spermatogonial cells to proliferate, but not complete spermatogenic differentiation.

A high proportion of spermatogonial cells were lost. The potential of vitrification was evaluated, and in non-human primates it allowed survival and proliferation of spermatogonia. In humans vitrification is quite promising. The grafting method played a role in spermatogonial loss and incomplete differentiation, stressing on the need to develop a robust controlled environment before autotransplantation.

Successful fertility restoration with frozen-thawed ITT in humans has not yet been reported. Our current research focuses on three different fertility restoration strategies from cryopreserved ITT:
1) Autotransplantation of ITT for patients in whom there is no risk of contamination by cancer cells. Avascular transplantation showed limited spermatogonial survival (14.5% and 3.7% three weeks and 6 months after transplantation, respectively). To improve the transplantation outcome, we aimed at reducing tissue hypoxia occurring before revascularization of the graft.

We demonstrated that encapsulation of mice ITT in hydrogels supplemented with VEGF nanoparticles improved vascular density, VEGFR2 activation, and endothelial proliferation. However, vascular density was not maintained after 21 days of grafting suggesting a lack of neovessel stabilization. Further studies will focus on improvement of angiogenesis and spermatogonial survival, via the supply of vascular factors and antinecrotic agents.

2) In vitro maturation of the spermatogonial stem cells yielding haploid gametes available for ICSI, circumventing the risk of reintroducing malignant cells. We reported an organotypic culture system allowing Sertoli cell maturation and testosterone production during a 139 day period. This is the first time that human ITT was studied in a long-term organotypic culture, deepening the understanding of the SSC molecular niche in the pre and peripubertal phase.

3) Elaboration of a porcine bioengineered testicular scaffold to incorporate sorted human testicular cells with a view to be transplanted and achieve differentiation of spermatogonia. By comparing different decellularization protocols of pig ITT, we designed a testicular tissue scaffold allowing Sertoli cell attachment and functionality. Further studies will compare the testicular cell behavior in a solid and in a gelified scaffold to obtain organoids with a potential of spermatogonial renewal and differentiation.

SELECTED PUBLICATIONS 2017


The pole of microbiology includes the virology and the bacteriology groups and is devoted to clinical microbiology research. It acts as a Belgian National AIDS Reference Laboratory (ARL), and houses the National Reference Centers for Clostridium difficile, Yersinia and Borrelia. Recently, the group has developed important activities in the fields of Mycobacteriology and rapid diagnosis of septicemia.
Diagnosis and epidemiology of \textit{C. difficile} infections (CDI).

\textit{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 \textit{C. difficile} infections and is the National Reference Center (NRC) for this pathogen, a contract with the national Institute of Public Health (IPH) which was renewed in 2015 for the next 4 years. A national epidemiological survey was pursued in 2017 in collaboration with the IPH and 30 Belgian hospitals. This prospective study aimed at collecting and typing all strains isolated in those hospitals over a one-year period in order to better understand the mode of transmission of the disease. More than 1200 isolates have been collected and typed so far. In addition to ribotyping, strains that were considered as possibly epidemiologically linked have been sub-typed by MLVA (multilocus variable number tandem repeats analysis). The results strongly suggest a wide diversity in the sources of contamination in hospital settings, which is at the opposite of a patient-to-patient epidemic transmission which has always been considered as the main way of transmission.

Microbiological diagnosis of septicemia

Septicemia is the association of sepsis and the presence of a pathogen in the blood of the patient. This infection is associated with high morbidity and mortality rates and the rapid instauration of an appropriate antimicrobial treatment is crucial.

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

Two projects are currently performed in our laboratory. The first project consists in the evaluation of a MALDI-TOF MS (Matrix Assisted Laser Desorption Ionization Time-of-Flight) software for the rapid identification of all bacteria and yeast in polymicrobial septicemia. The second project is based on the use of a molecular technique for the identification of pathogens directly from the blood of a positive blood culture. The FilmArray BCID panel© is performed 24/7 on positive blood cultures of intensive care patients. We aim at evaluating the impact of this tool on the clinical outcome of the intensive care patients with septicemia.

Additional work is in the pipeline including the use of NGS (next generation sequencing) for the diagnosis of septicemia.

MALDI-TOF MS and outbreak typing

MALDI-TOF MS is challenged as a rapid and easy typing tool in acute hospital-outbreaks. MALDI-TOF MS was used for typing multiresistant \textit{Corynebacterium striatum} strains at the origin of an outbreak in an intensive care unit and for typing methicillin resistant \textit{Staphylococcus aureus} strains at the origin of an outbreak in a neonatal intensive care unit. MALDI-TOF MS showed good concordance with the standard typing tools.

Currently MALDI-TOF MS is evaluated for the typing of strains isolated from two nosocomial outbreaks, i.e. carbapenemase (OXA-48) producing \textit{Klebsiella pneumonia} and multi-resistant \textit{Pseudomonas aeruginosa} strains.

Tuberculosis and Mycobacteriology

Within a few years, the Tuberculosis and mycobacteria research group has gained important national and international visibility.

The laboratory has developed a series of innovative assays for the phenotypic and genotypic rapid detection of tuberculosis drug resistance and the identification of non-tuberculosis mycobacteria. Very recently, the laboratory contributed to the detection of an outbreak of multi-drug resistant tuberculosis undetected by commercial methods in South-Africa.

Our laboratory is among the two first teams in the world to use the Deeplex MycTB assay (Genoscreen, France), which is the first commercial kit based on the next-generation sequencing technology.

The Laboratory further works on the development of connectivity solutions for laboratory networks and electronic medical records dedicated for epidemic situations in under-resourced environments. Savics (www.savics.org) is a spin-off company based in Belgium but with activities in several countries that was created following the development of proof of concept IT solutions developed by our research team.
The laboratory participates to international research studies that focus on TB under-detection and the social consequences of this disease.

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.

**Borrelia burgdorferi**

In 2017, the *Borrelia* NRC contributed to the publication of 4 articles (see selected publications).

We participated to a study evaluating the seroprevalence of *Borrelia* in 310 Belgian forest workers that are exposed to tick bites and tick-borne diseases in Wallonia, Belgium, including the integrated landscape approach, the individual and environmental factors associated with the seroprevalence. Data were analysed and the manuscript is submitted for publication. The screening and the confirmatory tests for the detection of IgG were conducted by the NRC-UCL.

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. This study is coordinated by the service ‘Epidemiology of infectious diseases’ of the OD Public Health Surveillance of the Scientific Institute of Public Health (Sciensano) in collaboration with some national and international institutions including the NRC for Lyme borreliosis.

The *Borrelia* NRC is involved in an ongoing study in collaboration with CODA-CERVA, the veterinarian lab, and the Earth and Life Institute (ELI) of the UCL aiming to detect pathogens such as Borrelia in collected ticks in the “Bois de Lauzelle” in Louvain-la-Neuve (Belgium).

**Yersinia**

Acting as the NRC *Yersinia* together with the KULeuven, an increase of incidence of *Yersinia pseudotuberculosis* in 2015 has been studied by MLVA typing. This led to the identification of a specific epidemic clone which was shown to be similar to strains isolated recently in Scandinavia. In collaboration with the university of Ghent, the study of the prevalence of *Yersinia* in animals led to two publications.
factor that interferes with the viral replication. Particularly, we focus on the interaction between a viral envelope glycoprotein (gpTM) and the cell protein BST-2 or tetherin, interfering with virion release. Site-directed mutagenesis, viral culture replication and protein interactions studies are performed at the lab. These results were published by Dufrasne F. et al. in Nov2016. Protein modeling studies are also conducted in collaboration with the LIH in Luxembourg.

Moreover, our research focus to identify genetic variability in bst-2 gene. Results should relate to the story of patients, to the viral load and classify according to the course of the disease (controllers or not).

LARGE EQUIPMENT

Nucleic acid sequencing facilities
Safety laboratory (BL3)
digital PCR technology

SELECTED PUBLICATIONS

Neely, F; Lambert, M-L; Van Broeck, J; Delmée, Michel.
Clinical and laboratory features of the most common Clostridium difficile ribotypes isolated in Belgium. In: Journal of Hospital Infection, Vol. 95, p. 394-399 (2017).

André, E.; Goeminne, L.; Colmant, A.; Beckert, P.; Niemann, S.; Delmée, M.


De Keukeleire M, Vanwambke S, Kabamba B, Belkhir, Pierre P, Luyasu V, Robert A.


Leen I, Bruynseels P, Mukadi BK, van Oort M, van den Akker M.


Neely F, Lambert ML, Van Broeck J, Delmée M.

Dauby N, Libois A, Van Broeck J, Delmée M, Vandenberg O, Martiny D.

André E, Goeminne L, Colmant A, Beckert P, Niemann S, Delmee M.
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Anne-Catherine Lantin
Quality Assistant for the Ethics Committee
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1.1 Development of clinical research at the CUSL

**Ethics Committee (EC) submissions**
Academic studies versus total studies submitted to the Ethics Committee.
In 2017, academic studies represented 48% of the total submissions.

1.2 Research mandates

**NEW «FRC» STARTING GRANTS SINCE 2017**

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL:</td>
<td>4</td>
<td>4</td>
<td>8</td>
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</table>

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

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>TOTAL: Clinical researchers (ST-LUC)</td>
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<td>9</td>
<td>13</td>
<td>3</td>
<td>8</td>
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<td>Of which renewals:</td>
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<td>0</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>24</td>
<td></td>
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<tr>
<td>TOTAL: Researchers (UCL)</td>
<td>12</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>12</td>
<td>11</td>
<td>8</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>Of which renewals:</td>
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<td>7</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>22</td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<tbody>
<tr>
<td>TOTAL:</td>
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<td>8</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>12</td>
<td>11</td>
<td>64</td>
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</table>

**FNRS MANDATES SINCE 2012 (NEW APPOINTMENTS AND RENEWAL)**

<table>
<thead>
<tr>
<th></th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>Total</th>
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<tbody>
<tr>
<td>Clinicians (Clinical service)</td>
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<td>11</td>
<td>11</td>
<td>9</td>
<td>13</td>
<td>13</td>
<td>63</td>
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<td>Researchers (Poles)</td>
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<td>4</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>23</td>
</tr>
</tbody>
</table>

2. THE CLINICAL TRIAL CENTER

2.1 Tasks and activity report of each CTC component

During 2017, the CTC FTE increased from 9.5 to 11.2.

2.1.1 BOARD OF DIRECTORS

The Board of Directors is composed of the Medical Director of the CTC (Prof JL Vanoverschelde), the Administrative Director (Mrs D Van Ophem) and the Associate Administrative Director who is also the Administrative Coordinator of «IREC» (Dr M Van Hassel).

The mission of the CTC is to professionalize the organization and coordination of biomedical research at the CUSL. To accomplish this mission, the positions were reorganized in 2017 in order to cover the two pillars, namely the contractual, financial and reporting aspects on the one hand, and regulatory and quality management on the other.
2.1.2: CONTRACTS, FINANCING AND REPORTING

A: CONTRACTS AND FINANCING

Signed commercial contracts:

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
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<td>120</td>
<td>159</td>
<td>141</td>
<td>140</td>
<td>144</td>
<td>153</td>
<td>146</td>
<td>139</td>
</tr>
</tbody>
</table>

Signed academic contracts:

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL contracts</td>
<td>34</td>
<td>25</td>
<td>31</td>
<td>35</td>
<td>37</td>
</tr>
</tbody>
</table>

B: REPORTING AND ACADEMIC INDICATORS

Credits/Departments

GROUPED H-INDEX
(2017 career managerial physicians) BY AGE

C: COMMERCIAL CENTRAL DESK
An administrative support person was recruited in October 2017 to develop the «commercial central desk» and to be the single institutional entry point for the Ethics Committee for the submission of commercial studies files.
2.1.3 : QUALITY MANAGEMENT AND REGULATORY AFFAIRS

A : QUALITY AND ACCREDITATION
Preparation of the AAHRPP re-accreditation with the objective of submitting the file in September 2017 and an accreditation site-visit in July 2018.

B : ACADEMIC CENTRAL DESK AND SUPPORT
This new function was formalized in July 2017. The academic central desk and support officer is responsible for giving regulatory and administrative support to the Ethics Committee submission and for the implementation of academic research at the CUSL. Support provided in a 6-month period from July to December 2017:

Ethics Committee submissions

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Prospective non-interventional</th>
<th>Prospective interventional without IMP</th>
<th>Prospective interventional with IMP</th>
<th>Prosp. with a medical device</th>
<th>Retrospective</th>
<th>Residual Human Body Material</th>
<th>FAHMP submissions</th>
<th>CUSL Sponsor</th>
<th>UCL Sponsor</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>22</td>
<td>5</td>
<td>6</td>
<td>24</td>
<td>9</td>
<td>2</td>
<td>63</td>
<td>7</td>
<td>76</td>
</tr>
</tbody>
</table>

Study coordinators at the CUSL on 31 December 2017:
101 employees: 79.2 FTE allocated to 25 medical services.

C : OPERATIONAL SUPPORT FOR THE STUDY COORDINATORS
The operational support for the study coordinators is responsible for coordinating the hiring and training of the study coordinators.

18 study coordinators were hired in 2017:
7 with a permanent contract; 10 with a fixed term contract and 1 with a replacement contract

D : ACADEMIC H2020 EUROPEAN PROJECTS SUPPORT

*The European projects support officer implements institutional procedures together with the various components of the CTC: quality and regulatory affairs, academic support, contracts and finances;*

Nine European projects were ongoing on December 31, (2017)
- Types of projects: 1 ERC (European Research Council), 6 H2020/RIA (Research Innovation Action), 2 IMI (Innovative Medicine Initiative)
- Types of contracts: 3 where the CUSL are a linked third party and 6 where the CUSL are direct contractors.
The objectives targeted by the technological platforms are:

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

In 2017, a floor (55+2) dedicated to the IREC platforms (except for CTMA) has been renovated and devices have been centralized together with their respective logisticians and technicians.
Proposed services

The 2IP multi-user platform was created in 2011 thanks to the sharing of imaging equipment present among the IREC research groups. 2IP gradually acquires new equipment and is recognized as a UCL platform. 2IP is composed of a research logistician (Caroline Bouzin) and two technicians (Aurélie Daumerie and Michele de Beukelaer).

2IP offers access to:

Sample preparation services:
- Paraffin & cryo-sectioning
- Histological stainings
- Immunostainings (chromogenic-fluorescence-TSA multiplex)

Image acquisition:
- Slide digitalization in brightfield with a 384 slides capacity scanner (Leica SCN400)
- Structured illumination fluorescence microscopy (Zeiss AxioImager.z1 + ApoTome1 module) which allows optical sections and 3D reconstruction
- Polarized light microscope (Zeiss AxioPlan)
- Histological scanner (FF-OCT technology; LLTech Light-CT scanner)

Image analysis:
- Author (Visiopharm)
- TissueIA (Leica)
- ImageJ support

In 2017, a « Histo-lab » has been setup on the platform floor and is accessible to researchers since June either through 2IP services or in "self-service". A new microtome station, a 3-head microscope, an additional license of the Author analysis software with a TissueAlign add-on completed the platform, respectively acquired thanks to 2IP, IREC and Health Science Sector investments.


The following technological seminars and demonstrations have been organized:

- Tissue clearing presentation (Thomas Guyon, Westburg, 21/03/2017) and X-Clarity demonstration (19-30/06/2017, 9 tested tissue types/7 research poles involved),
- IREC seminar "FFPE samples, multiplex immunofluorescence staining and quantitative analysis: lung cancer illustration" (Caroline Bouzin (2IP) & Frank Aboubakar (pole PNEU), 25/09/2017);

Selected publications

Through sustained collaborations, 2IP has been involved in the following projects published in 2017:


Cao-Pham TT, Joudiou N, Van Hul M, Bouzin C, Cani PD, Gallez B, Jordan BF.


van Steenberghe M, Schubert T, Guiot Y, Bouzin C, Bollen X, Gianello P.


Varma S, Stéphenne X, Komuta M, Bouzin C, Ambroise J, Smets F, Reding R, Sokal EM.
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 researchers (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), and microarrays facilities (Affymetrix, Agilent, custom glass slide arrays...).

This support integrates the experimental design (technological choice, experimental workflow, sample size), the pre-analytical (DNA and RNA quantification and Quality control) and analytical steps, as well as the bioinformatic and 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)
- mRNA sequencing
- Targeted RNA sequencing

Since 2016, CTMA participated to the MinION Access Program from Oxford Nanopore. Ever since, CTMA has acquired a steadily larger expertise in the preparation, use, and analysis of the MinION long reads sequencer

- Resequencing of Bacterial, viral and protist whole genome.

In late 2017 CTMA also acquired on his own budget a new 8 capillaries Sanger sequencing machine (Beckman Coulter : GenomeLab GeXP).

CTMA has been involved in a series of projects leading to specific publications

1. TP53 mutations in p53-negative dysplastic urothelial cells from Belgian AAN patients: New evidence for aristolochic acid-induced molecular pathogenesis and carcinogenesis
   S Aydin, J Ambroise, JP Cosyns, JL Gala
   Mutation Research/Genetic Toxicology and Environmental Mutagenesis 818, 17-26

2. Salvage surgery in recurrent head and neck squamous cell carcinoma: Oncologic outcome and predictors of disease free survival
   M Hamoir, E Holvoet, J Ambroise, B Lengelé, S Schmitz
   Oral oncology 67, 1-9

3. The histological quantification of alpha-smooth muscle actin predicts future graft fibrosis in pediatric liver transplant recipients
   S Varma, X Stéphenne, M Komuta, C Bouzin, J Ambroise, F Smets, R Redings, E Sokal
   Pediatric transplantation 21 (1)

4. Blood-testis barrier organization in a prepubertal and peripubertal boys’ cohort: correlation with Sertoli cell maturation, clinical puberty and testicular anatomopathol...
   F De Michele, MG Giudice, J Poels, F De Smedt, J Ambroise, C Wyns
   Human Reproduction 32, i7
The platform was created at the beginning of the year but only in middle June it moved in the current renovated location. In November 2017, we presented the request for the recognition of the platform to UCL. The platform is composed by a logistician (Davide Brusa), supervised by the IREC coordinator (Jean-Luc Balligand).

The Flow Cytometry Platform offers the following services:

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

The platform is equipped with the following instrumentations:

- FACSCalibur, analyzer, 2 lasers, 4 fluorescences;
- FACSCantoll, analyzer, 3 lasers, 8 fluorescences;
- FACSARiaIII, cell sorter, 4 lasers, 16 fluorescences;
- Analysis workstation, equipped with FACSDiva and FlowJo softwares.

The following technological seminars have been organized:

- Multicolor Flow Cytometry, presented by Biolegend, 23/11/2017
The animal experimentation, integrated physiology and Proteomics & Metabolism platforms are currently under development. They currently provide the following support:

### Animal experimentation platform

Coordinated by Solveig Mouterde, this platform will be set up in the new Laennec building in 2018. Located on the bottom two floors, the facility will be dedicated to animal experimentation.

- **on the level 0**, the platform will house rodents in two confinement areas: SPF-like and Linné-like, with up to 560 mice cages and 105 rats cages in each area.
- **on the level -1**, the platform will house rodents in a Conventional area (up to 480 mice cages and 140 rat cages), as well as large animals (mostly pigs).

The main goals of this new platform are to procure improved living conditions for animals, as well as give access to high-end equipment for researchers, in an effort to mutualize equipment, skills and knowledge within the institute.

The facility housing large animals will be connected to a surgery room. This facility will be implemented in a later stage.

For the facility housing rodents, each confinement area will be serviced by the same type of high-level equipment: individually ventilated cages (IVC) for animals, bedding disposal stations, cage washers and autoclaves for the washing areas, dry showers for the personnel entrance, air pressure differential between rooms, hydrogen peroxide disinfection rooms etc. Each confinement area will also contain laboratories, where animal-related research can be conducted within the corresponding sanitary status. Here is a non-exhaustive list of procedures that can be conducted in each area:

- **SPF-like area**: surgery, cell therapy, tumor induction, inhalation cages
- **Linné-like area**: surgery, laser Doppler, intravital microscopy, tumor induction, viral infection, metabolic cages
- **Conventional area**: surgery, laser Doppler, intravital imagery, tumor induction, ultrasonography, telemetry, metabolic cages.

Animal-related activities in the platform will be recorded into a dedicated software, which will be made available to all research teams (in and out of the platform), in order to harmonize the follow-up of animals and comply with regulatory requirements. A team of animal technicians will be at work in the platform to take care of the animals.

### Integrated physiology:

This platform is installed on the 2d floor of the Harvey Tower (55). Other equipments will be transferred in 2018 within the animal experimentation platform.

### Proposed services

**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, to be transferred in the animal facility platform.):**
Surgery, Haemodynamic profiling (HR/P), Variability evaluation

*Technical support: H Esfahani (FATH)  
Scientific support: JL Balligand/C Dessy (FATH)*

**Electronic paramagnetic resonance (55+2):**
Quantitative evaluation of nitric oxide (NO, HbNO); ROS (with DMPO, CAT-1, CP-H or CMH); thiol-containing molecules in biological samples (cultured cells, Blood and tissues); and metal-containing proteins (methemoglobin, ceruloplasmin etc).

*Technical and scientific support : I Lobysheva (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 Perfusion (55+2):**
The platform is equipped with 6 chambers of perfusion 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)*
Recent Publications

Vascular Endothelium-Dependent and Independent Actions of Oleoanic Acid and Its Synthetic Oleane Derivatives as Possible Mechanisms for Hypotensive Effects.

Madlala HP, Metzinger T, van Heerden FR, Musabayane CT, Mubagwa K, Dessy C.

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, Cani PD, Dessy C, Delzenne NM.

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.

Targeting the gut microbiota with inulin-type fructans: preclinical demonstration of a novel approach in the management of endothelial dysfunction.

Catry E, Neyrinck AM, Lobysheva I, Pachikian BD, Van Hul M, Cani PD, Dessy C, Delzenne NM.

Ongoing Collaborations

UCL : IREC (LTAP); IREC (CARD); LDRI (MNUT)
KUL : Pneumology
UNAMUR : URPhyM

Proteomics & Metabolism:

Coordinated by Olivier Feron, this platform will be installed in dedicated rooms at the second floor of Building 55 (Tour Harvey) in the Fall 2018. The platform will be initially equipped with instruments previously bought by Profs O. Feron and P. Sonveaux (with the help of other co-promoters when grants were obtained from the FRS-FNRS).

The «Proteomics» equipment will initially include:

- 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)

The «Metabol.omics» equipment will initially include:

- hypoxia worstation (Ruskinn In Vivo 400) [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)]
- Iscus-flex CMA400 (Microdialysis) for metabolites monitoring [eg, lactate, pyruvate, urea, glutamate]

Besides the facilitated access to the above instruments (and associated expertise), the platform aims to act as an interface with external academic and non-academic resources (through privileged interactions, - some being already available), in particular for 13C metabolomics studies and MS peptide identification.

The facilities will also accommodate other proteomics and metabol(om)ics instruments from different IREC poles willing to share them with other users from the Institute.

In 2018, the CTMA platform activities will move to 55+1.
"The Centre de Technologies Moléculaires Appliquées (CTMA - Centre for Applied Molecular Technologies)" is a mixed academic-clinical-military biotechnological platform mutualizing the resources of three partners:

**UCL/IREC** (Université catholique de Louvain/Institut de recherche expérimentale et clinique). CTMA is the IREC-reference biotechnological platform (genetics and molecular genetics); it therefore directly supports IREC-related research activities while also developing proprietary research.

CTMA carries out clinical routine analysis and clinical research in the field of genetics and molecular genetics to support the medical activity of the academic hospital “Cliniques universitaires Saint-Luc” (CUSL).

**MOD** (Ministry of Belgian Defence). CTMA hosts several research projects and activities for the MOD to improve the detection and identification of biological threats in the CBRN domain (Chemical, Bacteriological, Radiological & Nuclear threats) spectrum. As such, CTMA is the “Biothreat control unit of the Defence Laboratory Department (DLD)” and is therefore specifically named DLD-Bio; from there its full acronym CTMA/DLD-Bio.

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

---

- **BADIR Jamal**, Technological Logistician CUSL
- **BOUYER Michèle**, Technician MOD
- **CARLIER Elodie**, Technician MOD
- **CRUZ MITJANS Denny**, Technician IREC
- **CRUZ MITJANS Olga**, Technician IREC
- **DECCACHE Yann**, Research Assistant MOD
- **DELCORPS Cathy**, Technician MOD
- **DELHEZ Huguette**, Technician CUSL
- **DEMARET Christelle**, Director Assistant IREC
- **DILLEMBOURG Marc**, Technical Manager IREC
- **DUBOIS Nicolas**, Research Assistant IREC
- **DUMONT Catherine**, Research Assistant MOD
- **DURANT Jean-François**, Research Assistant IREC
- **ELMIOUZI Maimouna**, Account Manager IREC
- **LADANG Auxane**, Research Assistant IREC
- **LAKCHER Oumaima**, Technician MOD
- **LINERO Florencia**, Postdoctoral Fellow MOD
- **MARCEL Jean-Paul**, Technological Platform Manager CUSL
- **MARTIN Christian**, Logistics Assistant CUSL
- **MINEEVA-SWANGO Olga**, Research Assistant IREC
- **PIETTE Anne-Sophie**, Postdoctoral Fellow MOD
- **SMITS Benjamin**, Technician IREC
- **VAN CAUWENBERGHE Stéphane**, Technician MOD
- **VAN EYCKEN Anne**, Clinical Administrative Assistant CUSL
- **VERBERCKMOES Steven**, Manager Defence Bio-Lab MOD
- **VYBORNOK Aleksandr**, Research Assistant IREC

The cooperation between UCL/CTMA and the Belgian Defense has been formalized in a convention framework signed on 30 August 2016. https://uclouvain.be/fr/scientetoday/actualites/une-convention-de-recherche-inedite-entre-la-defense-et-lrsquo-ucl.html
Research Thematics and 2017 Results

CTMA/DLD-Bio is active in microbial research (bacteria, viruses, helminths...) particularly in the diagnostic field, the characterization of virulence and resistance genomic determinants and the relationship with environment.

Through its involvement in several previous EC FP7 and current HORIZON 2020, the unit has developed a rapidly deployable bio-laboratory capacity thanks to the ESA funded B-LiFE project and used it as an operational capacity in case of health crisis or as testbed (technological incubator) for developing and/or testing emerging technologies for use under field conditions. The design and validation of new emerging technologies, including nanotechnologies, encompass multiplex immuno-chromatographic lateral flow assay and 3d generation sequencing for a better detection and protection against known and unknown biological agents, DNA- and RNA-based profiling of biomarkers in malignant and inflammatory diseases, genome characterization by re-sequencing and related signal processing, machine learning and bio-statistical analysis. CTMA/DLD-Bio is also developing decontamination methods.

As pictured here below the R&D activities imply multidisciplinary resources (Bio-medical genomics, -statistics, -informatics and engineering).

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

CTMA/DLD-Bio is developing and continuously improving its rapidly deployable bio-laboratory for many years. This mobile lab can be scalable from a light version packed in a few flight cases to a fully autonomous and self-sufficient assembly with 2 fully equipped operational tent labs working simultaneously.

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

The B-LiFE system integrates space technologies, i.e. satellite telecommunications to communicate with the distant reach back home base laboratory, stakeholders and end users, GNSS (Global Navigation Satellite System) for geo-location and Earth Observation for site selection and monitoring. B-LiFE is also equipped with management tools (LIMS, decision support software...). B-LiFE has been involved in many exercises (Clueless Snowman in Munich with the German Defence Bundeswehr in February 2016 and EC MODEX in Revinge, Sweden in April 2017). The last operational deployment was the support of an Ebola Treatment Unit in Guinea (N'Zerekore) during the last Ebola outbreak in West-Africa (2014-2015).

B-LIFE:
Biological Light Fieldable Laboratory for Emergencies
Phase II /Demonstration

Mostafa BENTAHIR, Nicolas DUBOIS, Jean-Luc GALA, Jean-Paul MARCEL, Leonid IRENCE, Alexander VYBORNOV, Olga VYBORNOVA

In 2017 B-LIFE has successfully passed the EU certification as autonomous module belonging to the European Emergency response Capacity (EERC) and part of the European Medical Corps (EMC) (also known as voluntary pool), established under the EU Civil Protection Mechanism (EUCPM). Through EERC/EMC, teams and equipment from the EU Member States can be rapidly deployed to provide worldwide medical assistance and public health expertise in response to national and international emergencies.
Between two deployments, CTMA/DLD-Bio is continuously developing new diagnostic tools for sample analysis usable under field conditions in the B-LiFE laboratory.

HFM14/8: Novel multiplex method for identification of genetically modified or acquired bacterial resistance mechanisms

Yann DECACCHE

Several assays previously developed and validated in the framework of research studies are now integrated in a multiplex, single, simple, rapid and sensitive method for assessing the antimicrobial resistance of clinical pathogens involved in nosocomial infections. The study enters its final stage in late 2017 – early 2018 by issuing a new method which targets a fast and reliable identification of resistance markers in bioterrorism-related class III infectious agents (i.e., B. anthracis, Y. pestis, F. tularensis, B. melitensis and B. Mallei): the complete process between sample receipt and genetic characterization of resistance markers lasts about 3 hours. The DNA purification of the bacteria present in the sample is followed by PCR-specific amplification of the targeted resistance markers and then a search by pyrosequencing for mutations causing resistance.

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

Funding: Belgian Defense Research Program (2017-2021)
Catherine DUMONT, Oumaima LAKCHER

Started in mid-2017, this study aims to circumvent the limitations of current identification assays, i.e. the need for multiple targeted diagnostic tests to cover clinical syndromes and all related differential diagnoses and the limiting use of tiny parts of target genomes. To do so, a shotgun metagenomic sequencing approach is used for the identification of “unknown viral and bacterial agents” using the bench-top MiSeq-Illumina Next Generation Sequencing (NGS) platform and a pre-analytical enrichment step. We aim to optimize the identification workflow and to adapt it to the pocket sized MinION® (Oxford Nanopore) NGS in order to enable us to carry out NGS analysis in the B-LiFE fieldable bio-laboratory in case of public health issues requiring the B-LiFE laboratory deployment.

HFM 17-3: Development of innovative methods for ultra-fast amplification and specific detection of high pathogenic bio-agents (CBRN) on Operation Theater

Funding: Belgian Defense Research Program (2017-2022)
Mostafa BENTAHIR

The study started in late 2017. A panel of assays based on high-speed isothermal genomic amplification will be used to rapidly identify highly pathogenic biological agents in a field setting. Lyophilized reagents will be tested and validated for use under field conditions in the B-LiFE laboratory.

ALLERT: Handheld Allergens Detector

Jamal BADIR, Benjamin SMITS, Bertrand BEARZATTO, Jérôme AMBROISE, Olga MINEEVA-SWANGO, Auxane LADANG, Nicolas DUBOIS

The study developed a portable, multiplex, qualitative food allergen detection system ("yes/ no" response) usable in field conditions by food industry and patients. This low-cost assay enables unexperienced users to quickly (results within 15 min) and simultaneously assess the presence of several key allergens. The Chromatographic Lateral Flow ImmunoAssay (LFIA) is embedded into a casing and analysed by an electronic reader fitted with a high resolution camera, an algorithm for analysis and image processing and an automatic transfer of results. 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. In 2017 the LFIA passed the proof-of-concept of multiplexing 6 antigens.

TOXINE-ID: Specific multiplex and immuno-lateral flow detection of a well-defined panel of toxins inside a representative food sample

Funding: WALInnov (2017-2021)
Jamal BADIR, Mostafa BENTAHIR, Auxane LADANG, Benjamin SMITS, Florencia LINERO, Olga MINEEVA-SWANGO

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 (saxitoxin, okadaic acid, and domoic acid); myco-toxins (aflatoxin, ochratoxin).
The EU faces growing security and health threats, e.g. an intentional use of CBRN agents, large external crises, and pandemics due to the convergence of risk factors driving disease emergence, amplification and dissemination of pathogens with pandemic potential. Protecting the health and security of EU citizens against these threats requires a coherent response by all stakeholders.

For several years, CTMA/DLD-Bio has actively contributed by addressing those challenges as coordinator, end user or as operator of the B-LiFE laboratory on EC projects.

**MSP 16-4: Development of procedures for biological agent inactivation to enhance biosafety conditions during the procedure of identification under field conditions**

*Funding: Belgian Defense Research Program (2016-2019)*
*Cathy DELCORPS, Stéphane VAN CAUWENBERGHE*

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

**Risk Assessment for chemical and biological exposure after decontamination (RACED) - European Defense Agency (EDA), 2d Joint Investment Programme on CBRN Issues (JIP-CBRN2).**

*Funding: EDA (2015-2018)*
*Mostafa BENTAHIR, Florencia LINERO*

In military protection against chemical and biological (CB) warfare agents, decontamination is a crucial step. For ensuring a successful response to an attack involving CB agents, it is essential to clean contaminated surfaces well enough to avoid users’ contamination.

RACED took the following staged approach: (1.) Decontaminate a representative number of CB agents / surfaces by standard means and procedures. (2.) Apply state-of-the art analytical and micro/molecular biological assays to identify and quantify residual agent. (3.) Simulate and understand transport from decontaminated surface to exposure of human airways and skin. (4.) Relate exposure to toxicity and infectiousness, respectively.

In late 2017 – early 2018 the study outcome, a risk management tool, has been written which will enable operational decision makers either to rationally and confidently declare an asset clean, or to re-launch a decontamination step, or to clear away asset that remain dangerous for use.

**PANDEM - Pandemic Risk and Emergency Management – Phase 1**

*Funding: EU 7FP (2015-2017)*
*Anne-Sophie PIETTE*

PANDEM Phase 1 assessed current pandemic preparedness and response tools, systems and practice at national, EU and global level in priority areas including risk assessment and surveillance, communication and public information, governance and legal frameworks. End of 2017 PANDEM identified gaps and improvement needs leading to the development of viable innovative concepts focused on the needs and requirements of users and first responders across the spectrum of pandemic risk management.

**Horizon2020 eNOTICE: European Network Of CBRN Training Centers**

*Funding: EU H2020 (2017-2022)*
*Olga VYBORNOVA, Aleksandr VYBORNOV*
*Project coordinator*

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. Since late 2017 CTMA is preparing an exercise to be held in June 2018 involving the Belgian Crisis Centre, Civil Protection and the Scientific Police, an Hungarian Bio lab and CTMA B-LiFE bio Laboratory.

**Horizon2020 ENCIRCLE: EuropeaN CBRN Innovation for the maRket ClustEr**

*Funding: EU H2020 (2017-2021)*
*Olga Vybornova, Anne-Sophie PIETTE, Nicolas DUBOIS*
*Project coordinator*

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

Related Publications 2016-2017

Publications 2017

**Irenge L, Dindart JM, Gala JL.**

**Mahy P, Collard JM, Gala JL, Herman P., De Groofs D, Quoilin S, and Sneyers M.**

**Palich R, Irenge L, Barte de Sainte Fare E, Augier A, Malvy D, Gala JL.**


Selection of Publications 2016 with CTMA/DLD-Bio as first and/or last authorship


The Prize Pr C. Coërs 2016 was attributed by the Académie Royale de Médecine to Michel Abou Samra, Raphaël Bousereau and Sophie Lecompte for their work, under the supervision of Sonia Brichard, on « The anti-inflammatory properties of adiponectin in the dystrophic skeletal muscle ».

The Prize Fonds Cremers-Opdebeeck 2018 was attributed by the "Fondation Roi Baudouin pour la Recherche en Santé" to Sonia Brichard for her work on "Adiponectin mimics or targets: a brake on muscle inflammatory disorders and Duchenne muscular dystrophy?"

The Prize Matthys Bove 2017 was attributed by UCL Health Sciences Sector to Jean-Christophe Jonas for his work on the « Molecular mechanisms of the phenotypic plasticity of pancreatic β-cells under metabolic stress conditions: nutrient-induced changes in β-cell redox state at the subcellular level ».

The Prize Alexandre et Gaston Tytgat 2017 was awarded to Olivier Feron for his work on the influence of acidosis on tumor metabolism.

The Award of the AstraZeneca Foundation – Oncology 2016 was attributed to Pierre Sonveaux for his work on “Cancer metabolism: an innovative target for therapy”

The Young Investigator Award 2017 of the European Society for Pediatric Endocrinology was attributed to Philippe Lysy for his work on diabetes cell therapy, type 1 diabetes remission, and gigantism.

The Prix Suzanne et Jean Pirart 2017 of the Association Belge du Diabète was awarded to Philippe Lysy for his work on the study of β-cell mass evolution during type 1 diabetes.

The STEM CELLS Translational Medicine Young Investigator Award 2017 was attributed to Philippe Lysy for the best scientific paper in the Journal during 2016 : "V-Maf Musculoaponeurotic Fibrosarcoma Oncogene Homolog A Synthetic Modified mRNA Drives Reprogramming of Human Pancreatic Duct-Derived Cells Into Insulin-Secreting Cells".
PHD Theses

DUGERNIER Jonhatan
(prom: Prof. Pierre-François LATERRE and Prof. Grégory REYCHLER)
March 31, (2017)

HICKMANN Cheryl
Impact of early physical therapy on skeletal muscle wasting during critical illness
(prom: Prof. Pierre-François LATERRE and Prof. Marc FRANCAUX)
June 21, (2017)

NAMIA NATTA Didier
(prom: T. Lejeune et G. Stoquart)

WARLOP Thibault
The temporal organization of stride duration variability for assessing gait stability: clinical application to Parkinson’s disease
(prom: C. Detrembleur et T. Lejeune)

PONCIN William
Lung clearance index from nitrogen washout in patients with cystic fibrosis and non-cystic fibrosis bronchiectasis: from a comparison of two devices to the assessment of chest physiotherapy.
(prom: P. Lebecque)

TERRANOVA Lisa
Matrices tridimensionnelles pour la régénération osseuse.
(prom: D. Chappard (Univ. Angers) et C. Behets)

FATAKANWA Claver
Développement et validation in vitro de nouvelles prodrogues sélectives de l’hypoxie tumorale.
(prom: O Feron; co-prom: O Riant)

DROZAK Xavier
Design, synthesis and biological evaluation of new glutaminase inhibitors.
Promotors: O Feron; co-prom: O Riant

VAN STEENBERGEN Anne
SMIT1 mediates the production of reactive oxygen species induced by hyperglycemia in the heart
(prom: BEAULOYE Christophe; co-prom: BERTRAND Luc)

VAN HEE Vincent
Functional characterization and imaging of oxidative lactate metabolism in cancer
(prom: SONVEAUX Pierre)
31/03/2017  SBOARINA Martina
Metabolic regulation of cancer cell proliferation and resistance to temozolomide chemotherapy
(prom: SONVEAUX Pierre; co-prom: LEFRANC Florence)

07/04/2017  REZZOUG Nawel
Prevalence and Prognostic impact of Valvular Heart Disease
(Echocardiographic studies in the very elderly)
(prom: VANOVERSCHELDE Jean-Louis; co-prom: PASQUET Agnès)

15/05/2017  VARMA Sharat
Study of Liver allograft - Immune mediated Fibrosis post-Transplant (LIFT),
predicting fibrogenesis and digital quantification of histological characteristics
(prom: SOKAL Etienne)

14/06/2017  POEKES Laurence
Brown adipose tissue in metabolic syndrome, NAFLD progression and management
(prom: LECLERCQ Isabelle; co-prom: HORSMANS Yves)

16/06/2017  BELKHIR Leïla
Pharmacogénétique et antirétroviraux: le cas du Darunavir et du Raltegravir
(prom: HAUFROID Vincent; co-prom: VANDERCAM Bernard)

05/07/2017  VAN DEN EYNDE Marc
Characterization of the tumour immune microenvironment in metastatic colorectal cancer
(prom: MACHIELS Jean-Pascal; co-prom: RASCO Javier)

07/07/2017  BARBÉ Caroline
Identification of mediators involved in the Follistatin actions on skeletal muscle
Proteomic and Transcriptomic approaches
(prom: THISSEN Jean-Paul)

30/08/2017  BASELET Bjorn
Molecular characterization of endothelial cell response in the context
of radiation-induced atherosclerosis
(prom: SONVEAUX Pierre; co-prom: AERTS An (SCK-CEN))

01/09/2017  ANDRE Emmanuel
Complementing TB control strategies with end-user innovations in Sub-Saharan Africa
(prom: DELMEE Michel)

11/09/2017  MOSALA NEZHAD Zahra
Outcome of patch materials used in aortic valve repair.
Examining CorMatrix bioscaffold as suitable cardiac tissue substitute.
Outcome of patch materials used in aortic valve repair.
(prom: EL KHOURY Gebrine; co-prom: GLANELLO Pierre)

25/09/2017  MAILLEUX Florence
AMPK prevents cardiac hypertrophy development by inhibiting O-GlcNAcylation
(prom: BERTRAND Luc; co-prom: HORMAN Sandrine)
19/10/2017  CHITI Maria Costanza
Fertility preservation in cancer patients:
Development of a transplantable artificial ovary prototype
(prom: DOLMANS Marie-Madeleine; co-prom: ANDRADE AMORIM Christiani)

06/11/2017  BARRAGAN MONTERO Ana Maria
Robust, accurate, and patient-specific treatment planning for proton therapy
(prom: LEE John; co-prom: STERPIN Edmond)

23/11/2017  SHINDANO AKILIMALI Bernard
Hépatite B en République Démocratique du Congo: aspects génotypiques, sociologiques
et effets de la vaccination chez les nouveau-nés du Kivu
(prom: HORSMANS Yves; co-prom: NKONDI NSENGA Jacqueline (UNIKIN))

13/12/2017  MAES Frédéric
Paradoxical low-gradient aortic stenosis: characterization and natural history of a complex
and heterogeneous entity
(prom: VANOVERSCHELDE Jean-Louis; co-prom: PASQUET Agnès)

18/12/2017  BOURSEREAU Raphaël
Novel muscular anti-inflammatory mechanisms of adiponectin and their implication
in Duchenne Muscular Dystrophy
(prom: BRICHARD Sonia)

20/12/2017  DE BRAUWER Isabelle
Optimizing the care of older patients hospitalized through and as soon as the emergency department
(prom: CORNETTE Pascale; co-prom: D’HOORE William)
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<th>DATE</th>
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<td>21 November 2016</td>
<td><strong>S Hernot</strong></td>
<td>Immuno-imaging using nanobodies</td>
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<td>Symposium of the « OMEDIAB » research group</td>
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<td><strong>Adipose Tissue Hormone-sensitive Lipase and Insulin Sensitivity</strong></td>
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<td><em>D Langin</em>, CHU Rangueil, Toulouse</td>
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<td><strong>A conserved phosphatase destroys toxic glycolytic side products</strong></td>
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<td><strong>Role of adipose tissue inflammation and NLRP3 inflammasome in</strong></td>
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<td>the pathogenesis of metabolic syndrome and type 2 diabetes</td>
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<td><strong>Glucose metabolism and gluotoxicity in the heart:</strong></td>
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<td><em>identification of SMIT1, a new glucose sensor</em>*</td>
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<td><strong>Translational research in lipidology: from PCSK9 to</strong></td>
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<td><strong>B Cariou</strong>, CHU Nantes</td>
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<td><strong>Treating cardiometabolic diseases by using gut microbes:</strong></td>
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<td><em>focus on the translational development of Akkermansia</em>*</td>
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<td><strong>H Plovier</strong>, LDRI/MNut</td>
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<td><strong>Connexion between lipid metabolism and platelet function</strong></td>
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<td><strong>Use of modified RNA in beta-cell regeneration strategies</strong></td>
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<td><strong>Manipulation of the pancreatic islet vasculature as a strategy for</strong></td>
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<td>12 December 2016</td>
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<td>FlowCyto platform/IREC</td>
<td><em>new developments and applications</em></td>
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<td>11 January 2017</td>
<td><strong>P Monga</strong></td>
<td><strong>Cellular and Molecular Basis of Hepatobiliary</strong></td>
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<td>Repair: A Wnt-beta-catenin Perspective</td>
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<td><em>what drives left ventricular remodeling in heart failure with preserved</em>*</td>
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<td>Insulin Resistance induced by alternate cardiac metabolic substrates</td>
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<td>27 March 2017</td>
<td><strong>H Heimberg</strong></td>
<td>Diabetes Research Center, Vrije Universiteit Brussel</td>
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<td>24 April 2017</td>
<td><strong>M Dubuisson</strong></td>
<td>LTTO/UCL</td>
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<td>17 May 2017</td>
<td><strong>N Lanthier</strong></td>
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<td>29 May 2017</td>
<td><strong>C BUGLI</strong></td>
<td>Platform for Statistics (SMCS)/UCL</td>
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<td>19 June 2017</td>
<td><strong>E Trepo</strong></td>
<td>Bioinformatics group, INSERM U1162, Paris</td>
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<td>25 September 2017</td>
<td><strong>C Bouzin et F Aboubakar</strong></td>
<td>Imaging platform (I2P) /IREC</td>
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<td>4 October 2017</td>
<td><strong>T Roskams</strong></td>
<td>Translational Cell and Tissue Research, KULeuven</td>
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<td>16 October 2017</td>
<td><strong>J Steykova</strong></td>
<td>Scriptorium</td>
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<td>20 October 2017</td>
<td><strong>J Lima</strong></td>
<td>Department of Medicine, Johns Hopkins School of Medicine, USA</td>
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<td><strong>O Chavez-Talavera</strong></td>
<td>Institut Pasteur, Lille</td>
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<td><strong>G Kerckhofs</strong></td>
<td>Biomechanics Lab - Institute of Mechanics, Materials, and Civil Engineering - UCL</td>
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<td>Aarhus University, USA</td>
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<td>22 December 2017</td>
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PhD DAY

KEY FIGURES

- About 100 participants in total
- 12 oral presentations
- 18 posters
- NEW: 4 presentations of the platforms (SMCS-statistics, flow cytometry, CTMA, imaging)
- 8 private sponsors

PROGRAM

8h30 Registration and installation of posters

9h00 Session «Oral I»
Jury and moderators: Raphaël BOURSEREAU (EDIN); Bjorn BASELET (FATH)

9h00 – Prognostic significance of diffuse myocardial fibrosis evaluated by cMR in patients with heart failure with preserved ejection fraction.
Roy CLOTILDE, A-C POULEUR (CARD)

9h15 – Understanding the metabolism of cardiac progenitor cells: a first step towards controlling their proliferation and differentiation?
André Emilie, Jean-Luc Balligand (FATH)

9h30 – Liver progenitor cells significantly contribute to hepatocyte pool in chronic liver injury and cirrhosis: a kinetic study in mice
Manco Rita, Isabelle Leclercq (GAEN)

9h45 – Upper Airway stability in wakefulness and during sleep

10h00 – 10h20 IREC Imaging Platform
Caroline BOUZIN

10h20 – 11h15 Coffee break + poster advertisement + sponsors booths

11h15 Session «Oral II»
Jury and moderators: Jessica VANDERSTRAETEN (MORF); Amadou SOW (NERF)

11h15 – Intraportal infusion of human liver-mesenchymal stem cells in rats lead to transient interruption of the hepatic blood flow: intravital microscopy and anapathological analysis
Coppin Louise, Stephenne X, Sokal E (PEDI)

11h35 – Intraportal infusion of human liver-mesenchymal stem cells in rats lead to transient interruption of the hepatic blood flow: intravital microscopy and anapathological analysis
Coppin Louise, Stephenne X, Sokal E (PEDI)
11h50 – Lack of differences in radiation-induced immune stimulation between HPV-positive and HPV-negative human HNSCC
Schneider Karolin, Vincent Grégoire (MIRO)

12h05 – Role of transabdominal cerclage in fetal membranes histology after term elective cesarean deliveries
Patricia Steenhaut, Fr. Debiève, C. Hubinont (OBST)

12h20 – Platelet Acetyl-CoA Carboxylase phosphorylation: a potential marker for atherothrombotic coronary artery disease
Kautbally Shakeel, BEAULOYE Christophe (CARD)

12h35 – 12h55 - Molecular Technoloigies Platform (CTMA)

12h55 – 14h30 Lunch + coffee + Session Poster + sponsors booths

Jury poster #1 to 6: Florence MAILLEUX (CARD); Ruben MARTHERUS (FATH)

P.1 Sustained inhibition of acetyl-CoA carboxylase decreases platelet dense granules secretion and aggregation
Lepropre Sophie, Horman Sandrine (CARD)

P.2 Cancer radiosensitivity under metabolic control
Grasso Debora, Pierre Sonveaux, Vincent Gragoire (FATH)

P.3 Angiogenesis enhancement in ovarian tissue grafts with adipose-derived stem cells delivered inside a fibrin matrix using a two-step transplantation approach
Manavella I. Diego D., Marie-Madeleine Dolmans (GYNE)

P.4 Reactive Oxygen Species: the hidden face of biodegradable Fe-based alloys?
Scarcello Eleonora, Dominique Lison (LTAP)

P.5 The important role of collective cell migration and nerve fiber density in the development of deep nodular endometriosis.
Garcia Solares Javier, Marie-Madeleine Dolmans (GYNE)

P.6 Role of angiotensin II transient exposure in persistent ROS production in endothelial cell: a “stress” memory?
Pothen Lucie, Jean Luc Balligand (FATH)

Jury poster #7 to 12: Lauriane MICHEL (FATH); Maria Costanza CHITI (GYNE)

P.7 Is fatigue associated with exercise tolerance among patients suffering from multiple sclerosis?
Valet Maxime, Lejeune Thierry, Stoquart Gaetan (CARS)

P.8 Towards development of an artificial testis by decellularization of pig prepubertal testicular tissue and recolonization using human cells
Vermeulen Maxime, Christine Wyns (GYNE)

P.9 Compared efficacies of Lung Delivery using Two Nebulizers in the Prophylaxis Against Pneumocystis Carinii Pneumonia
Audag Nicolas, P. Gianello, G. Rey切尔 (PNEU)

P.10 Metformin use and gastric adenocarcinoma survival in Belgium
Lacroix Lacroix, Annie Robert (EPID)

P.11 Early and sustained immunosuppressive macrophage in rat mesothelioma
Orsi Micaela, François Huaux (LTAP)

P.12 In vitro studies on differentiation of isolated human ovarian stromal cells into theca cells
Parinaz Asiabi, Kohneh Shahri, Marie-Madeleine Dolmans, Christiani Andrade Amorim (GYNE)

Jury poster #13 to 18: Estelle BASTIEN (FATH); Jamilia BOULIF (CARD)

P.13 Platelet Acetyl-CoA Carboxylase phosphorylation: a potential marker for atherothrombotic coronary artery disease
Kautbally Shakeel, Beauloye Christophe (CARD)

P.14 Genetic and phylogenetic characterisation of hepatitis B virus in the eastern part of the democratic republic of Congo
Shindano Akilimali, Yves Horsmans (ECLI)

P.15 Validation of upper limb motor assessment tasks using a rehabilitation robot in healthy children
Dehem Stéphanie, T. Lejeune (CARS)

P.16 AMP-activated protein kinase α1 controls cytosolic calcium concentration and induces calcium sensitization in resistance arteries
Metzinger Thomas, Dessy Chatal, Horman Sandrine (FATH/CARD)

P.17 Cathepsin K knockout improves vertebrae parameters in murine model of severe osteogenesis imperfecta
Roels Thomas, Behets Catherine and Manicourt Daniel (MORF)

P.18 Immunogenic cell death induced by a new photosensitizer compound supports the production of a dendritic cell-based anticancer vaccine
Doix Bastien, Olivier Feron (FATH)
14h30  **Session «Oral III»**

**Jury and moderators:** Noémie Emeriau (IONS); Charlotte FARAH (FATH)

14h30  – Twenty-Year Outcome After Mitral Repair Versus Replacement for Severe Degenerative Mitral Regurgitation. Analysis of a Large, Prospective, Multicenter, International Registry

*Lazam Siham, Jean-Louis Vanoverschelde (CARD)*

14h45  – Factors associated with late antenatal care initiation among pregnant women: a cross-sectional study in a rural area of Vietnam

*NGO Thi Thuy Dung, Annie Robert (EPID)*

15h00  – Is Myocardial Fibrosis A Hallmark of Paradoxical Low Gradient Aortic Stenosis?

*Alison Slimani Molli (CARD)*

15h15  – Is paradoxical low gradient severe aortic stenosis a more advanced form of aortic stenosis: New insights gained from valve weight and the measurement of valvular calcium content by use of 256-slice MDCT

*Boulif Jamila, Vanoverschelde Jean-Louis (CARD)*

15h30 – 15h50  – Plateforme technologique de Support en Méthodologie et Calcul Statistique (SMCS)

*Céline BUGLI*

15h50  – Award ceremony

16h15  Cocktail and award ceremony
As every year, IREC organized a festive lunch with Belgian culinary specialties, allowing PI’s, researchers, students, technicians and the administrative personnel to meet and share their experiences.
The 2017 activity report of the Institut de Recherche Expérimentale et Clinique is a publication from IREC

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