

ANNUAL REPORT 2015

2015

GIGA

Annual Report



«Le Fonds Européen de Développement Régional et la Région wallonne investissent dans votre avenir»



Université
de Liège



Published by GIGA
Avenue de l'Hôpital 1 - 4000 Liège (Belgium)
www.giga.ulg.ac.be

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Print AZ Print
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«I am convinced that these changes in the GIGA structure will reinforce its recognition as a biomedical research flagship of the University of Liège»

2015 was once again a great year for the GIGA Research Center as exemplified by its considerable number of publications in high profile journals, patents, defended PhD thesis, seminars and number of external visitors. Despite the increasing difficulty to secure research grants in Wallonia, the GIGA PIs have conducted remarkable scientific activities and they must be congratulated and supported in their continued efforts to pursue scientific excellence. I sincerely hope that these difficult times will soon be over because our society, which is based on scientific and technological advances, is in urgent need of competent and innovative young scientists. Spoiling such a potential is just not in our best interest.

Last year, the Walloon region informed us that our Feder grant application would be supported. This news came as a huge relief to the scientists and technicians working in the technology platforms and animal facilities. For the next five years this grant will support key services for the GIGA research community, the ULG researchers and our external customers. This major accomplishment is credited to the incredible joint effort of Catherine Sadzot and Christina Franssen, which was supported by the entire GIGA administration and financial teams. We should all commend them for the countless hours spent in preparing the application and negotiating with the Walloon administration. Without well-supported technology platforms and animal facilities, the future of the GIGA research center would definitely be very dark. It should also be mentioned that the Feder grant application was prepared with significant input from Eric Salmon and André Luxen from the Cyclotron Research center (CRC). This collaborative effort led us to negotiate a possible integration of the CRC research team and technologies into the GIGA, which was subsequently accomplished in the beginning of 2016. We are now very proud to have the GIGA-CRC in vivo imaging as a new thematic unit.

2015 was also my last year of service as Director of GIGA-Research, which I used as an opportunity to review the activities and future prospects of the eight thematic units of the center. Together with the PIs and the directors, we reached the conclusion that some changes were needed. The GIGA-Development and GIGA-Systems Biology thematic units were reorganized; and the GIGA-In silico Medicine unit was created. In addition, we welcomed the arrival of the COMA group in the GIGA. All these changes were done in the frame of a new vision for the GIGA research into the ULG research landscape that was prepared by our new vice-rector for research. I am convinced that these changes in the GIGA structure will reinforce its recognition as a biomedical research flagship of the University of Liège.

Therefore, having served as GIGA-Research director for the past nine years, I am very proud of the outstanding development of the research center and its facilities. The GIGA has secured a leadership role in the field of biomedical research and I am convinced that Michel Georges, who was elected to be its new Director from 2016, will be the needed propelling force to drive the GIGA to an even brighter future.

Jacques Piette
Vice-Director GIGA-Research

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Highlight **GIGA landscape revisited**

Our academic authorities are reshaping the university landscape. It will now officially include "Interdisciplinary Research Units" comprising members of several faculties. This trend, in essence, follows the example of what GIGA has been standing for since 2007. "Interdisciplinary Research Units" that are officially recognized as such will benefit from direct funding from the university starting 2017. This initiative is welcomed by GIGA as it consolidates and rationalizes research activities in our university. It is essential to maintain national and international competitiveness. Under the leadership of Director Jacques Piette, GIGA has taken advantage of this movement to further strengthen and streamline the organization of GIGA-R, our own research arm.

First of all, several new laboratories have integrated GIGA. The COMA Science Group (Dr. Steven Laureys), already joined GIGA in 2015. COMA's move will now be followed by that of the entire Cyclotron Research Center (CRC) and its 50 members. We are absolutely thrilled by this merger as COMA/CRC brings world-class and complementary expertise in neurosciences to our center. Also joining GIGA is the Biomechanics Research Unit of the ERC-laureate Liesbeth Geris. We are delighted to have the Faculty of Engineering empowering GIGA with some of its most active laboratories to mutual benefit.

Secondly, to accommodate these new arrivals, adjust to internal changes since GIGA's inception, and align our priorities with those of the emerging "Health Pole", GIGA has re-crafted its Thematic Units. Starting 2016, GIGA-R's landscape will exhibit eight such units : **Cancer, Cardiovascular Sciences, CRC-In Vivo Imaging, In silico Medicine, Immunity, Infection & Inflammation, Molecular Biology of Diseases, Neurosciences.**

GIGA's breath of expertise is now larger, its interdisciplinary composition reaffirmed, the research focus enhanced, and the stage set for closer interactions. Several initiatives to further empower the GIGA community are in the works. Catherine Sadzot's team is setting new objectives for the operation of the administrative and platform teams. Marilou Ramos Pamplona is animating a cell to support researchers in grant writing and submission. We hope to rapidly define the program and modus operandi of a new GIGA Graduate School.

Striving for excellence in biomedical sciences in the Walloon Region in 2016 is a tough, every day battle. Let us be smart and pull together to achieve our common goals. We'll need everybody's skills and talents!

Michel Georges, GIGA-Research Director

248 PhD Scientists

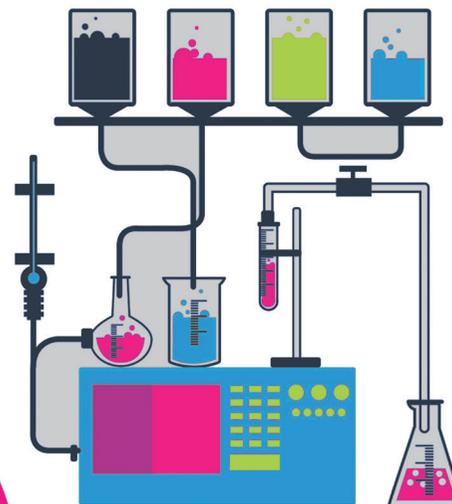
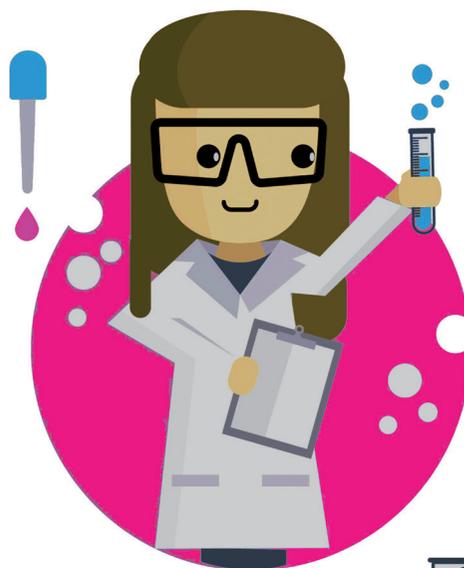
214 PhD Students

78 Technicians

22 Administratives

24 Platforms people

586
members



129 foreign researchers

45 nationalities



 44%

 56%

Highlight **ERC** **Patrizio Lancellotti**

Heart valve prostheses are currently among the most widely used cardiovascular devices. To maintain enduring optimal biomechanical properties, the mechanical prostheses, based on carbon, metallic and polymeric components, require permanent anticoagulation, which often leads to adverse reactions, i.e. higher risks of thromboembolism, hemorrhage and hemolysis.

Continuing advances in heart valve prosthesis design and in techniques for implantation have improved the survival length and quality of life of patients who receive these devices. In an ongoing effort to develop a more durable and biocompatible heart valve prosthesis, researchers have used a variety of techniques to determine the suitability of given valve materials for a given implant application. In recent years, advances in polymer science have given rise to new ways of improving artificial cardiovascular devices biostability and hemocompatibility.

To date, no polymer coated mechanical prosthetic heart valve exists.

The present research project aims to improve the hemocompatibility and long-term in vivo performance of mechanical prosthetic heart valves by reducing contact-induced thrombosis through bioactive polymer prosthetic valve surface coating.

These new coated prosthetic heart valves will be designed for hemodynamic performance and durability similar to uncoated materials, combined with a greater thromboresistance, both in vitro and in animal studies.

With these promising advances, bioactive surface coated prosthetic heart valves could replace previous generation of prosthetic valves in the near future. The utmost perspective of the current project paves the way for the development of new bioactive coating for other implantable cardiovascular devices or materials.

ERC grants

The European Research Council (ERC) has announced the 372 winners of its Consolidator Grant competition. These excellent mid-career scientists are awarded a total of €713 million, as part of the European Union Research and Innovation programme Horizon 2020. Grants are worth up to €2.75 million each, with an average of €1.91 million per grant. The funding will enable them to consolidate their research teams and to develop their most innovative ideas.

On this occasion Carols Moedas, European Commissioner for Research, Science and Innovation, said: «With every project of this calibre, we're making Europe the laboratory of the world. Our most extraordinary and creative researchers benefit from EU funding and, in turn, Europe benefits every day from its investment in knowledge and people».

The President of the ERC, Professor Jean-Pierre Bourguignon, commented: «These Consolidator Grants awarded to 372 research leaders, still in an early stage of their career, will also back some 1,500 postdocs and PhD students as team members. This is one more way in which the ERC is fostering the next generation of bright research talent, and thereby the human basis for Europe's competitiveness that conditions its economic growth».

Patrizio Lancellotti

Patrizio Lancellotti is the head of the GIGA-Cardiovascular Sciences unit.

Despite aspiring to a manual job when he was young, Patrizio Lancellotti went on to study medicine at the University of Liège. Once qualified, Patrizio Lancellotti naturally veered towards cardiology. Clinical Head of the CHU at Sart Tilman, Patrizio Lancellotti had been awarded the Inbev-Baillet Latour Prize for his clinical research in the field of cardiovascular illness and more specifically for his work on complications of coronary illnesses.

He is the first European to receive the Tajik/Seward prize from the Mayo Clinic that rewards the expertise to whom could demonstrate an exceptional competence in cardiological care.

Now, he's the winner of an ERC grant for a five-year project.



Highlight **Horizon 2020** **Edouard Louis**

Edouard LOUIS has received funding of the European Commission for his project «BIOlogical therapy CYCLEs towards tailored, needs-driven, safer and cost-effective management of Crohn's disease – BIOCYCLE ('action')».

The objective of the BIOCYCLE project is to assess long-term treatment strategies in Crohn's disease that will improve safety and control associated costs while ensuring a constant level of efficacy during maintenance therapy.

Crohn's disease is a chronic longstanding disease that can't be cured with currently available treatments. The aim of long-term treatment is to fully control the symptoms and avoid the progression of intestinal damage. Currently, the preferred strategy for moderate-severe disease is a combination therapy with anti-TNF α and anti-metabolites (immunosuppressant). This long-term treatment adversely affect cost and safety. The BIOCYCLE action will assess the efficacy, safety, effectiveness and feasibility of either anti-TNF α or immunosuppressant withdrawal in those patients.

The core of the project is a randomized controlled trial: SPARE clinical trial. Crohn's disease patients with sustained remission without steroids for at least 6 months and treated with a combination therapy (infliximab and anti-metabolites) will be randomized into three arms: a first arm where both infliximab and anti-metabolites are continued, a second arm where infliximab is stopped and a third arm where anti-metabolites are stopped. The enrollment of 300 patients is planned in France, UK, Sweden, Germany and Belgium. The primary objective of the trial is to assess the relapse rate and the time spent in remission in the three arms. Classical biomarkers (CRP, calprotectin) and new ones will also be assessed for their ability to correctly predict the risk of relapse and disease progression.

The impact on health economics of treatment cycles will be compared using comparative cost-of-illness and cost-effectiveness calculations between the three arms of the SPARE clinical study. The main factors that drive the burden on direct healthcare costs will be identified. Finally, we will generate cost models for completing specific recommendations according to the patients' characteristics and risks profiles.

Coordination and partners

CHU is the coordinator of the BIOCYCLE project. CHU has contributed to the design of the SPARE study protocol and is involved in the SPARE clinical trial with Belgian centres. CHU leads the proteomics exploratory research on new biomarkers associated with disease relapse, disease progression and mucosal healing, with the help of GIGA (ULg), as third party. CHU is also responsible for the coordination of the SPARE biobanking.

The participating members are Edouard Louis, Marie-Alice Meuwis and Marcella Chavez.

The BIOCYCLE project involves a consortium between 13 partners.

<http://biocycle-project.eu/>

Crohn's disease

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) affecting the gastro-intestinal tract. CD often begins at young age and lasts the whole life. The prevalence is 20-30% higher for women than for men.

CD is characterized by a sequence of active disease episodes (flare-ups) and remissions of variable duration. The chronicity of CD has a significant impact on patients' quality of life (QoL). Genetic susceptibility, modified composition of the gut microbiota and impaired function of the mucosal immune system are the main known contributors to the etiology of CD. However, the primary cause remains unknown.

Curative therapies do not yet exist and the current best treatments are symptoms relieving therapies. The drug of choice and treatment strategies depend on the clinical characteristics and severity of the disease.

Mild disease may be treated by mesalazine or no treatment with limited number of courses of topical steroids.

The gold standard of care for moderate to severe Crohn's disease is the Combo therapy, the uninterrupted combination of anti-TNF α monoclonal antibodies and immunosuppressant. However, this kind of treatment raises safety and costs issues.

Indeed, anti-TNF α is the most expensive medication and potential adverse effects are associated with the Combo therapy, namely cancers and possible increase of severe infections. In addition, patients are exposed to class-specific drug complications.



Highlight **Coma Science group** **Steven Laureys**

Steven Laureys and his Coma Science Group are joining GIGA early 2015.

Neurologist and Clinical Professor of the Neurology Department of the Liège University Hospital, and FNRS Research Director, Steven Laureys leads the Coma Science Group. The main part of his work is dedicated to the scientific, clinical and ethical study of alterations in consciousness in severely brain injured patients (coma, vegetative state, state of minimum consciousness, locked-in syndrome), as well as during anesthesia, sleep and hypnotic states.

The team has published more than 300 scientific articles, a lot of which have been published in the most prestigious journals such as Science, Lancet, New England Journal of Medicine. In 2005, he published a book entitled «The Boundaries of Consciousness» (Editions Elsevier). «The neurology of consciousness» was released in 2008 (a new edition is coming out this year) and his last book «Un si brillant cerveau» was published early 2015 (Editions Odile Jacob).

The multidisciplinary team of the Coma Science Group (clinicians and bio-engineers) is world renowned for this pioneer work on human consciousness and the clinical and ethical issue of «comatose» patients. It has joined GIGA in order to foster translational research (to translate the latest scientific knowledge into the clinical reality of the University Hospital) and transversal interactions with the multidisciplinary teams of the center, in accordance with the philosophy of the Pôle Santé/ULg/CHU.

Steven Laureys studies the brain of Tibetan Buddhist monk Matthieu Ricard

What happens in the brain during meditation? The neurologists are more and more interested in that subject, and, thanks to medical imaging tools (IRMf, Pet-Scan, TMS-EEG, etc...), they are trying to discover neuronal correlates of a brain in full meditation. Steven Laureys is exploring this new research path. In May, he hosted the Tibetan Buddhist monk Mathieu Ricard who underwent a series of tests on his brain at rest, during meditation.

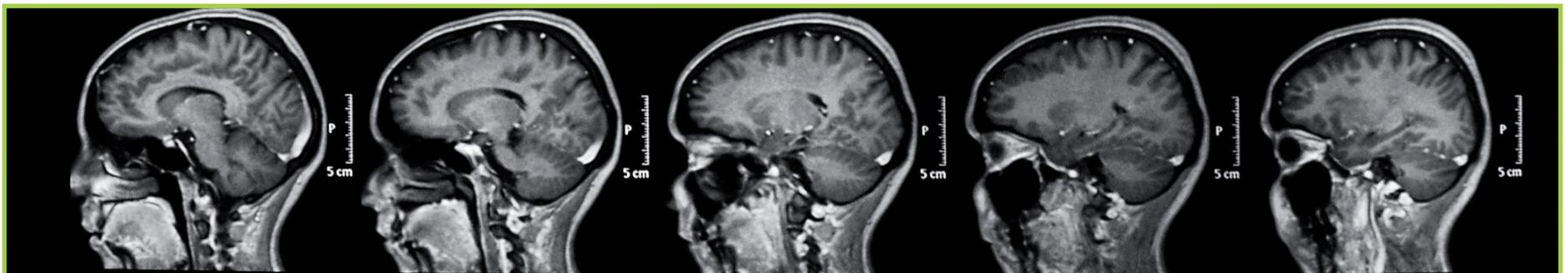
Steven Laureys explains : «Our goal is to put to the test theories previously studied about consciousness during sleep, coma, anesthesia and hypnosis. Is there a brain modification during meditation? Does meditating involves a «flat» brain? I don't think so, because meditation is a neuronal «activity» and it must be possible to set objective measures of a subjective tale with the help of medical imaging. This might show an intense activity of brain waves or a high use of glucose during meditation». A conference brought to a close this week of tests.



Wanderings of the mind and signs of consciousness

Declaring the state of consciousness of severely brain-damaged patients who are incapable of communication remains a challenge for physicians. Clinical evaluation of these people is traditionally based on examination of their motor responses with the help of behavioural scales. Interestingly, these patients can be paralysed, deaf, blind, suffering from aphasia or attention deficit disorders, which may lead to an underestimation of their level of consciousness. According to a study published in 2009 in BMC Neurology, the risk of misdiagnosis has been estimated at 40%. Nevertheless, the systematic use of the "Coma Recovery Scale-Revised" (CRS-R), a standardised and sensitive behavioural scale developed in the US by Joseph Giacino at the New Jersey Neuroscience Institute and validated in French and Dutch by Caroline Schnakers and Steven Laureys of the Coma Science Group, reduced the percentage of misdiagnosis rate to 31%.

Read the complete article (and others about Coma Science group's researches) on www.reflexions.ulg.ac.be.



GIGA-Research



GIGA-Cancer

The GIGA-Cancer unit gathers 7 teams conducting basic and translational research with the aim to unravel molecular and cellular mechanisms involved in cancer initiation, progression and metastatic dissemination. Some GIGA-Cancer researchers are conducting genomic studies on breast cancers and studying circulating nucleic acids in patient plasma. They are investigating intrinsic features of primary, metastatic and circulating tumor cells. A special emphasis is also given on virus-induced cancers (human papillomavirus or HPV and bovine leukemia virus) and how these carcinogenic viruses escape the host immune response. Other unit members are investigating the specific roles of host cells including inflammatory cells, cancer-associated fibroblasts and blood or lymphatic endothelial cells, for cancer progression. By deciphering the biology and intra-heterogeneity of different cancer types, they aim at defining new predictive, prognostic and diagnostic tools. Their ultimate goal is to develop antibody-based targeted therapies focused on accessible proteins, to design personalized treatment and to overcome tumor resistance or the metabolic adaptation of tumors during cancer development and treatment. GIGA-Cancer researchers are also extending their studies to other disorders associated with abnormal tissue remodeling and angiogenesis such as ocular diseases, lung inflammatory disorders, preeclampsia, endometriosis and embryonic implantation.



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Laboratories

- ▶ Laboratory of Tumor and Development Biology
Agnès Noel, Didier Cataldo, Jean-Michel Foidart
- ▶ Metastases Research Laboratory
Vincent Castronovo, Akeila Bellahcene
- ▶ Laboratory of Experimental Pathology
Philippe Delvenne
- ▶ Laboratory of Molecular Angiogenesis
Ingrid Struman
- ▶ Laboratory of Connective Tissues Biology
Alain Colige
- ▶ Laboratory of Human Genetics
Vincent Bours
- ▶ Laboratory of Cellular and Molecular Epigenetics
Luc Willems

People

44 Scientists

57 PhD Students

20 Technicians



39%



61%

Carcinogenic hpv infection in the cervical squamo-columnar junction

Mirkovic J, Howitt BE, Roncarati P, Demoulin S, Suarez-Carmona M, Hubert P, McKeon FD, Xian W, Li A, Delvenne P, Crum CP, Herfs M. **Journal of Pathology** 2015;236:265-271

Recent studies have suggested the involvement of a unique population of cells at the cervical squamo-columnar junction (SCJ) in the pathogenesis of early (squamous intraepithelial lesion or SIL) and advanced (squamous cell and adeno-carcinomas) cervical neoplasia. However, there is little evidence to date showing that SCJ cells harbour carcinogenic HPV or are instrumental in the initial phases of neoplasia. This study was designed to (1) determine if normal-appearing SCJ cells contained evidence of carcinogenic HPV infection and (2) trace their transition to early SIL. Sections of cervix from high-risk reproductive age women were selected and SCJ cells were analysed by using several techniques which increasingly implicated HPV infection: HPV DNA (genotyping and in situ hybridization)/RNA (PCR), immunostaining for HPV16 E2 (an early marker of HPV infection), p16(ink4), Ki67, and HPV L1 protein. In 22 cases with a history of SIL and no evidence of preneoplastic lesion in the excision specimen, HPV DNA was isolated from eight of ten with visible SCJ cells, six of which were HPV16/18 DNA-positive. In five of these latter cases, the SCJ cells were positive for p16(ink4) and/or HPV E2. Transcriptionally active HPV infection (E6/E7 mRNAs) was also detected in microdissected SCJ cells. Early squamous atypia associated with the SCJ cells demonstrated in addition diffuse p16(ink4) immunoreactivity, elevated proliferative index, and rare L1 antigen positivity. We present for the first time direct evidence that normal-appearing SCJ cells can be infected by carcinogenic HPV. They initially express HPV E2 and their progression to SIL is heralded by an expanding metaplastic progeny with increased proliferation and p16(ink4) expression. Whether certain SCJs are more vulnerable than others to carcinogenic HPV genotypes and what variables determine transition to high-grade SIL remain unresolved, but the common event appears to be a vulnerable cell at the SCJ.

Soluble factors regulated by epithelial-mesenchymal transition mediate tumour angiogenesis and myeloid cell recruitment

Suarez-Carmona M, Bourcy M, Lesage J, Leroi N, Syne L, Blacher S, Hubert P, Ericum C, Foidart JM, Delvenne P, Birembaut P, Noel A, Polette M, Gilles C. **Journal of Pathology** 2015;236:491-504

Epithelial-mesenchymal transition (EMT) programmes provide cancer cells with invasive and survival capacities that might favour metastatic dissemination. Whilst signalling cascades triggering EMT have been extensively studied, the impact of EMT on the cross-talk between tumour cells and the tumour microenvironment remains elusive. We aimed to identify EMT-regulated soluble factors that facilitate the recruitment of host cells in the tumour. Our findings indicate that EMT phenotypes relate to the induction of a panel of secreted mediators, namely IL-8, IL-6, sICAM-1, PAI-1 and GM-CSF, and implicate the EMT-transcription factor Snail as a regulator of this process. We further show that EMT-derived soluble factors are pro-angiogenic in vivo (in the mouse ear sponge assay), ex vivo (in the rat aortic ring assay) and in vitro (in a chemotaxis assay). Additionally, conditioned medium from EMT-positive cells stimulates the recruitment of myeloid cells. In a bank of 40 triple-negative breast cancers, tumours presenting features of EMT were significantly more angiogenic and infiltrated by a higher quantity of myeloid cells compared to tumours with little or no EMT. Taken together, our results show that EMT programmes trigger the expression of soluble mediators in cancer cells that stimulate angiogenesis and recruit myeloid cells in vivo, which might in turn favour cancer spread.

Circulating microRNA-based screening tool for breast cancer

Freres P, Wenric S, Boukerroucha M, Fasquelle C, Thiry J, Bovy N, Struman I, Geurts P, Collignon J, Schroeder H, Kridelka F, Lifrange E, Jossa V, Bours V, Josse C, Jerusalem G. **Oncotarget**. 2015

Circulating microRNAs (miRNAs) are increasingly recognized as powerful biomarkers in several pathologies, including breast cancer. Here, their plasmatic levels were measured to be used as an alternative screening procedure to mammography for breast cancer diagnosis. A plasma miRNA profile was determined by RT-qPCR in a cohort of 378 women. A diagnostic model was designed based on the expression of 8 miRNAs measured first in a profiling cohort composed of 41 primary breast cancers and 45 controls, and further validated in diverse cohorts composed of 108 primary breast cancers, 88 controls, 35 breast cancers in remission, 31 metastatic breast cancers and 30 gynecologic tumors. A receiver operating characteristic curve derived from the 8-miRNA random forest based diagnostic tool exhibited an area under the curve of 0.81. The accuracy of the diagnostic tool remained unchanged considering age and tumor stage. The miRNA signature correctly identified patients with metastatic breast cancer. The use of the classification model on cohorts of patients with breast cancers in remission and with gynecologic cancers yielded prediction distributions similar to that of the control group. Using a multivariate supervised learning method and a set of 8 circulating miRNAs, we designed an accurate, minimally invasive screening tool for breast cancer.

Lipin-1 regulates cancer cell phenotype and is a potential target to potentiate rapamycin treatment

Brohee L, Demine S, Willems J, Arnould T, Colige AC, Deroanne CF. **Oncotarget**. 2015;6:11264-11280

Lipogenesis inhibition was reported to induce apoptosis and repress proliferation of cancer cells while barely affecting normal cells. Lipins exhibit dual function as enzymes catalyzing the dephosphorylation of phosphatidic acid to diacylglycerol and as co-transcriptional regulators. Thus, they are able to regulate lipid homeostasis at several nodal points. Here, we show that lipin-1 is up-regulated in several cancer cell lines and overexpressed in 50 % of high grade prostate cancers. The proliferation of prostate and breast cancer cells, but not of non-tumorigenic cells, was repressed upon lipin-1 knock-down. Lipin-1 depletion also decreased cancer cell migration through RhoA activation. Lipin-1 silencing did not significantly affect global lipid synthesis but enhanced the cellular concentration of phosphatidic acid. In parallel, autophagy was induced while AKT and ribosomal protein S6 phosphorylation were repressed. We also observed a compensatory regulation between lipin-1 and lipin-2 and demonstrated that their co-silencing aggravates the phenotype induced by lipin-1 silencing alone. Most interestingly, lipin-1 depletion or lipins inhibition with propranolol sensitized cancer cells to rapamycin. These data indicate that lipin-1 controls main cellular processes involved in cancer progression and that its targeting, alone or in combination with other treatments, could open new avenues in anticancer therapy.

The interaction of upar with vegfr2 promotes vegf-induced angiogenesis

Herkenne S, Paques C, Nivelles O, Lion M, Bajou K, Pollenus T, Fontaine M, Carmeliet P, Martial JA, Nguyen NQ, Struman I. **Science Signaling**. 2015;8:ra117

In endothelial cells, binding of vascular endothelial growth factor (VEGF) to the receptor VEGFR2 activates multiple signaling pathways that trigger processes such as proliferation, survival, and migration that are necessary for angiogenesis. VEGF-bound VEGFR2 becomes internalized, which is a key step in the proangiogenic signal. We showed that the urokinase plasminogen activator receptor (uPAR) interacted with VEGFR2 and described the mechanism by which this interaction mediated VEGF signaling and promoted angiogenesis. Knockdown of uPAR in human umbilical vein endothelial cells (HUVECs) impaired VEGFR2 signaling, and uPAR deficiency in mice prevented VEGF-induced angiogenesis. Upon exposure of HUVECs to VEGF, uPAR recruited the low-density lipoprotein receptor-related protein 1 (LRP-1) to VEGFR2, which induced VEGFR2 internalization. Thus, the uPAR-VEGFR2 interaction is crucial for VEGF signaling in endothelial cells.

Mutation of a single envelope n-linked glycosylation site enhances the pathogenicity of bovine leukemia virus

de Brogniez A, Bouzar AB, Jacques JR, Cosse JP, Gillet N, Callebaut I, Reichert M, Willems L.

Journal of Virology. 2015;89:8945-8956

Viruses have coevolved with their host to ensure efficient replication and transmission without inducing excessive pathogenicity that would indirectly impair their persistence. This is exemplified by the bovine leukemia virus (BLV) system in which lymphoproliferative disorders develop in ruminants after latency periods of several years. In principle, the equilibrium reached between the virus and its host could be disrupted by emergence of more pathogenic strains. Intriguingly but fortunately, such a hyperpathogenic BLV strain was never observed in the field or designed in vitro. In this study, we sought to understand the role of envelope N-linked glycosylation with the hypothesis that this posttranslational modification could either favor BLV infection by allowing viral entry or allow immune escape by using glycans as a shield. Using reverse genetics of an infectious molecular provirus, we identified a N-linked envelope glycosylation site (N230) that limits viral replication and pathogenicity. Indeed, mutation N230E unexpectedly leads to enhanced fusogenicity and protein stability.

Asporin is a fibroblast-derived tgf-beta1 inhibitor and a tumor suppressor associated with good prognosis in breast cancer

Maris P, Blomme A, Palacios AP, Costanza B, Bellahcene A, Bianchi E, Gofflot S, Drion P, Trombino GE, Di Valentin E, Cusumano PG, Maweja S, Jerusalem G, Delvenne P, Lifrange E, Castronovo V, Turtoi A.

PLoS Medicine. 2015;12:e1001871

Breast cancer is a leading malignancy affecting the female population worldwide. Most morbidity is caused by metastases that remain incurable to date. TGF- β 1 has been identified as a key driving force behind metastatic breast cancer, with promising therapeutic implications. Employing immunohistochemistry (IHC) analysis, we report, to our knowledge for the first time, that asporin is overexpressed in the stroma of most human breast cancers and is not expressed in normal breast tissue. In vitro, asporin is secreted by breast fibroblasts upon exposure to conditioned medium from some but not all human breast cancer cells. While hormone receptor (HR) positive cells cause strong asporin expression, triple-negative breast cancer (TNBC) cells suppress it. Further, our findings show that soluble IL-1 β , secreted by TNBC cells, is responsible for inhibiting asporin in normal and cancer-associated fibroblasts. Using recombinant protein, as well as a synthetic peptide fragment, we demonstrate the ability of asporin to inhibit TGF- β 1-mediated SMAD2 phosphorylation, epithelial to mesenchymal transition, and stemness in breast cancer cells. In two in vivo murine models of TNBC, we observed that tumors expressing asporin exhibit significantly reduced growth (2-fold; $p = 0.01$) and metastatic properties (3-fold; $p = 0.045$). A retrospective IHC study performed on human breast carcinoma ($n = 180$) demonstrates that asporin expression is lowest in TNBC and HER2+ tumors, while HR+ tumors have significantly higher asporin expression (4-fold; $p = 0.001$). Assessment of asporin expression and patient outcome ($n = 60$; 10-y follow-up) shows that low protein levels in the primary breast lesion significantly delineate patients with bad outcome regardless of the tumor HR status (area under the curve = 0.87; 95% CI 0.78-0.96; $p = 0.0001$). Survival analysis, based on gene expression ($n = 375$; 25-y follow-up), confirmed that low asporin levels are associated with a reduced likelihood of survival (hazard ratio = 0.58; 95% CI 0.37-0.91; $p = 0.017$). Although these data highlight the potential of asporin to serve as a prognostic marker, confirmation of the clinical value would require a prospective study on a much larger patient cohort. Our data show that asporin is a stroma-derived inhibitor of TGF- β 1 and a tumor suppressor in breast cancer. High asporin expression is significantly associated with less aggressive tumors, stratifying patients according to the clinical outcome. Future pre-clinical studies should consider options for increasing asporin expression in TNBC as a promising strategy for targeted therapy.

GIGA-Cardiovascular Sciences

Cardiovascular disease produces immense health and economic burdens worldwide. It is the leading cause of death in OECD countries. The prevalence and control of cardiovascular health factors and risks remain a major issue. The GIGA-Cardiovascular Sciences unit is made up of a multi-disciplinary team. Specialists in cardiology, experts in imaging, cardiovascular surgeons, biologists, chemists and engineers collaborate in the framework of a "bedside to bench" and "bench to bedside" approach with the ultimate goal of translating the developed knowledge into patient benefits. To achieve their goals, basic and clinical researchers participate in the establishment of research networks with several departments of ULg and with internationally recognized centers. The unit aims at reaching leadership and singular excellence in research and training, notably through participation of its members in European research programs. Research projects span over a broad theme of cardiovascular diseases. Correlations between clinical, imaging and biological parameters are studied in patients. Relevant and novel animal models are being developed in order to identify new pathophysiological mechanisms and potential therapeutic targets. The main ongoing studies focus on valvular heart diseases, atherosclerosis, arterial thrombosis, heart failure, vascular wall disorders, aneurysm, ventriculo-arterial coupling, heart-lung interaction. Research areas include integrative physiology, cellular and molecular biology, hemodynamic evaluation, cardiac imaging techniques, mathematical modelling, as well as polymer chemistry.



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Laboratories

- ▶ Valvular Heart Disorders
Luc Piérard, Patrizio Lancellotti, Cécile Oury
- ▶ Thrombosis Hemostasis
Cécile Oury, Patrizio Lancellotti, André Gothot
- ▶ Vascular Wall Disorders
Natzl Sakalihan, Jean-Olivier Defraigne, Joël Pincemail
- ▶ Hemodynamics
Bernard Lambermont, Philippe Kohl, Vincenzo d'Orio, Alexandre Ghuysen, Philippe Morimont, Thomas Desaive
- ▶ Experimental Surgery
Jean-Olivier Defraigne, Pierre Drion, François Jouret, Jean-Marie Krzesinski, Olivier Detry
- ▶ Bioengineering Biophysics
Pierre Dauby, Thomas Desaive

People

15 Scientists

15 Clinician researchers

12 PhD Students

6 Technicians



65%



35%

(tissue pet) vascular metabolic imaging and peripheral plasma biomarkers in the evolution of chronic aortic dissections

Sakalihan N, Nienaber CA, Hustinx R, Lovinfosse P, El Hachemi M, Cheramy-Bien JP, Seidel L, Lavigne JP, Quaniers J, Kerstenne MA, Courtois A, Ooms A, Albert A, Defraigne JO, Michel JB.

European Heart Journal - Cardiovascular Imaging 2015;16:626-633

Despite adequate medical management, dissection of the descending aorta (type B) may develop complications, including aneurysmal progression and eventually rupture. Partial false lumen thrombosis has been identified as a marker of adverse evolution in chronic dissection. The aim of this study was to test the ability of complementary information, provided by (18)F-fluorodeoxyglucose ((18)F-FDG) positron emission tomography/computed tomography (PET/CT) and peripheral biomarkers, to add pathophysiological significance and a prognostic value to morphological data. We explored serial aortic (18)F-FDG uptake by PET/CT imaging and plasma biomarkers in a series of 23 patients with type B dissection to predict complications from initial data and to investigate potential associations with aneurysmal expansion during follow-up. Complications occurred in 17 patients. Acute initial characteristics associated with complications were male gender ($P = 0.021$), arterial hypertension ($P = 0.040$), aortic dissection diameter ($P = 0.0086$), partial thrombosis of the false channel ($P = 0.0046$), and enhanced focal (18)F-FDG uptake ($P = 0.045$). During follow-up (mean 16.7 ± 8.0 months), aneurysmal expansion was associated with false lumen morphology ($P < 0.0001$), quantitative (18)F-FDG uptake, ($P = 0.0029$), elevated plasma concentrations of biomarkers of platelets (P-selectin, $P = 0.0009$) and thrombin activation (TAT complexes, $P = 0.0075$), and fibrinolysis (PAP complexes, $P < 0.0001$; D-dimers, $P = 0.0006$). Plasma markers of coagulation and fibrinolysis were related to false channel morphology, suggesting that thrombus biological dynamics may drive progressive expansion of type B dissections. Enhanced FDG uptake may be considered as a complementary imaging marker associated with secondary complications in type B dissections. During follow-up, aneurysmal progression is related to PET/CT and biomarkers of thrombus renewal and lysis.

Molding thrombus of an ECMO cannula floating in the right atrium

Morimont P, Lambermont B, Gaspard V, Defraigne JO.

Intensive Care Medicine. 2015;41:1965-1966

This article is a case report of a 23-year-old man who was referred to CHU for veno-aerterial extracorporeal membrane oxygenation (VA ECMO) support as a bridge to heart transplantation.

Multimodality imaging assessment of the deleterious role of the intraluminal thrombus on the growth of abdominal aortic aneurysm in a rat model

Nchimi A, Courtois A, El Hachemi M, Touat Z, Drion P, Withofs N, Warnock G, Bahri MA, Dogne JM, Cheramy-Bien JP, Schoysman L, Joskin J, Michel JB, Defraigne JO, Plenevaux A, Sakalihan N. *European Radiology*. 2015

To evaluate imaging changes occurring in a rat model of elastase-induced abdominal aortic aneurysm (AAA), with emphasis on the intraluminal thrombus (ILT) occurrence. The post-induction growth of the AAA diameter was characterized using ultrasound in 22 rats. ILT was reported on 13 rats that underwent 14 magnetic resonance imaging (MRI) 2-18 days post-surgery, and on 10 rats that underwent 18 fluoro-deoxyglucose (FDG) positron emission tomography (PET)/microcomputed tomography examinations 2-27 days post-surgery. Logistic regressions were used to establish the evolution with time of AAA length, diameter, ILT thickness, volume, stratification, MRI and FDG PET signalling properties, and histological assessment of inflammatory infiltrates. All of the following significantly increased with time post-induction ($p < 0.001$): AAA length, AAA diameter, ILT maximal thickness, ILT volume, ILT iron content and related MRI signalling changes, quantitative uptake on FDG PET, and the magnitude of inflammatory infiltrates on histology. However, the aneurysm growth peak followed occurrence of ILT approximately 6 days after elastase infusion. Our model emphasizes that occurrence of ILT precedes AAA peak growth. Aneurysm growth is associated with increasing levels of iron, signalling properties changes in both MRI and FDG PET, relating to its biological activities.

Activation of the calcium-sensing receptor before renal ischemia/reperfusion exacerbates kidney injury

Weekers L, de Tullio P, Boyv C, Poma L, Maree R, Bonvoisin C, Defraigne JO, Krzesinski JM, Jouret F. *American Journal of Translational Research*. 2015;7:128-138

Activation of the calcium-sensing receptor (CaSR) by ischemia/reperfusion (I/R) favours apoptosis in cardiomyocytes, hepatocytes and neurons. Its role in renal I/R is unknown. We investigated the impact of pharmacological preactivation of the CaSR on kidney structure and function in a murine model of bilateral renal 30-min ischemia and 48-hour reperfusion, and in a 6-year cohort of kidney transplant recipients (KTR). C57BL/6J mice were administered daily with CaSR agonist, R-568, or with vehicle for 48 hours. Evaluation of serum urea and creatinine levels, renal histology and urine metabolome by nuclear magnetic resonance showed that R-568 was not nephrotoxic per se. Following I/R, serum urea and creatinine levels increased higher in R-568-treated animals than in controls. Jablonski's score was significantly greater in R-568-treated kidneys, which showed a higher rate of cell proliferation and apoptosis in comparison to controls. Next, we retrospectively identified 36 patients (10.7% of our cohort) who were treated by CaSR agonist, cinacalcet, at the time of kidney transplantation (KTx). After matching these to 61 KTR upon type of donor, cold ischemic time, residual diuresis, and donor age, we observed that delayed graft function, i.e. need for dialysis in the first week after KTx, occurred in 42 and 23% of cinacalcet-treated and control groups, respectively ($p \leq 0.05$). These data suggest that pharmacological preactivation of the CaSR before renal I/R exacerbates kidney injury.

Time-varying respiratory system elastance: A physiological model for patients who are spontaneously breathing

Chiew YS, Pretty C, Docherty PD, Lambermont B, Shaw GM, Desai V, Chase JG. *PLoS One*. 2015;10:e0114847

Respiratory mechanics models can aid in optimising patient-specific mechanical ventilation (MV), but the applications are limited to fully sedated MV patients who have little or no spontaneously breathing efforts. This research presents a time-varying elastance ($E(drs)$) model that can be used in spontaneously breathing patients to determine their respiratory mechanics. A time-varying respiratory elastance model is developed with a negative elastic component ($E(demand)$), to describe the driving pressure generated during a patient initiated breathing cycle. Data from 22 patients who are partially mechanically ventilated using Pressure Support (PS) and Neurally Adjusted Ventilatory Assist (NAVA) are used to investigate the physiology relevance of the time-varying elastance model and its clinical potential. $E(drs)$ of every breathing cycle for each patient at different ventilation modes are presented for comparison. At the start of every breathing cycle initiated by patient, $E(drs)$ is < 0 . This negativity is attributed from the $E(demand)$ due to a positive lung volume intake at through negative pressure in the lung compartment. The mapping of $E(drs)$ trajectories was able to give unique information to patients' breathing variability under different ventilation modes. The area under the curve of $E(drs)$ ($AUCE(drs)$) for most patients is $> 25 \text{ cmH}_2\text{O}/l$ and thus can be used as an acute respiratory distress syndrome (ARDS) severity indicator. The $E(drs)$ model captures unique dynamic respiratory mechanics for spontaneously breathing patients with respiratory failure. The model is fully general and is applicable to both fully controlled and partially assisted MV modes.

Biological effects of cardiac magnetic resonance on human blood cells

Lancellotti P, Nchimi A, Delierneux C, Hego A, Gosset C, Gothot A, Jean-Flory Tshibanda L, Oury C.

Circulation Cardiovasc Imaging. 2015;8

Cardiac magnetic resonance (CMR) is increasingly used for the diagnosis and management of cardiac diseases. Recent studies have reported immediate post-CMR DNA double-strand breaks in T lymphocytes. We sought to evaluate CMR-induced DNA damage in lymphocytes, alterations of blood cells, and their temporal persistence. In 20 prospectively enrolled healthy men (31.4±7.9 years), blood was drawn before and after (1-2 hours, 2 days, 1 month, and 1 year) unenhanced 1.5T CMR. Blood cell counts, cell death, and activation status of lymphocytes, monocytes, neutrophils, and platelets were evaluated. The first 2-hour post-CMR were characterized by a small increase of lymphocyte B and neutrophil counts and a transient drop of total lymphocytes because of a decrease in natural killer cells. Among blood cells, only neutrophils and monocytes displayed slight and transient activation. DNA double-strand breaks in lymphocytes were quantified through flow cytometric analysis of H2AX phosphorylation (γ -H2AX). γ -H2AX intensity in T lymphocytes did not change early after CMR but increased significantly at day 2 \leq 1 month before returning to baseline levels of 1-year post-CMR. Unenhanced CMR is associated with minor but significant immediate blood cell alterations or activations figuring inflammatory response, as well as DNA damage in T lymphocytes observed from day 2 until the first month but disappearing at 1-year follow-up. Although further studies are required to definitely state whether CMR can be used safely, our findings already call for caution when it comes to repeat this examination within a month.

Dual-specificity phosphatase 3 deficiency or inhibition limits platelet activation and arterial thrombosis

Musumeci L, Kuijpers MJ, Gilio K, Hego A, Theatre E, Maurissen L, Vandereyken M, Diogo CV, Lecut C, Guilmain W, Bobkova EV, Eble JA, Dahl R, Drion P, Rascon J, Mostofi Y, Yuan H, Sergienko E, Chung TD, Thiry M, Senis Y, Moutschen M, Mustelin T, Lancellotti P, Heemskerk JW, Tautz L, Oury C*, Rahmouni S*. *these authors contributed equally to the work

Circulation. 2015;131:656-668

A limitation of current antiplatelet therapies is their inability to separate thrombotic events from bleeding occurrences. A better understanding of the molecular mechanisms leading to platelet activation is important for the development of improved therapies. Recently, protein tyrosine phosphatases have emerged as critical regulators of platelet function. This is the first report implicating the dual-specificity phosphatase 3 (DUSP3) in platelet signaling and thrombosis. This phosphatase is highly expressed in human and mouse platelets. Platelets from DUSP3-deficient mice displayed a selective impairment of aggregation and granule secretion mediated by the collagen receptor glycoprotein VI and the C-type lectin-like receptor 2. DUSP3-deficient mice were more resistant to collagen- and epinephrine-induced thromboembolism compared with wild-type mice and showed severely impaired thrombus formation on ferric chloride-induced carotid artery injury. Intriguingly, bleeding times were not altered in DUSP3-deficient mice. At the molecular level, DUSP3 deficiency impaired Syk tyrosine phosphorylation, subsequently reducing phosphorylation of phospholipase C γ 2 and calcium fluxes. To investigate DUSP3 function in human platelets, a novel small-molecule inhibitor of DUSP3 was developed. This compound specifically inhibited collagen- and C-type lectin-like receptor 2-induced human platelet aggregation, thereby phenocopying the effect of DUSP3 deficiency in murine cells. DUSP3 plays a selective and essential role in collagen- and C-type lectin-like receptor 2-mediated platelet activation and thrombus formation in vivo. Inhibition of DUSP3 may prove therapeutic for arterial thrombosis. This is the first time a protein tyrosine phosphatase, implicated in platelet signaling, has been targeted with a small-molecule drug.

Awards

Patrizio Lancellotti was awarded an ERC-Consolidator grant «Prosthetic valve bioactive surface coating to reduce the prevalence of thrombosis: PV-COAT» (European Union's Horizon 2020 Framework Programme for Research and Innovation) - see page 8.

Patrizio Lancellotti acted as co-chair of the European Society Cardiology Guidelines on the management of infective endocarditis published in the European Heart Journal. He has become Associate Editor of the European Heart Journal. He is also member of the Jury of the prestigious Belgian Galien Price 2015.

Cécile Oury was elected as Board member of the Belgian Society on Thrombosis and Haemostasis and of the ANR scientific committee CES N° 32 - « Sciences de la Vie IMCE » 2015. She participated in the jury of the Scientific Award Foundation AstraZeneca - Cardiovascular Diseases 2015.

François Jouret received an Octaaf Dupont award from the Royal Academy of Medicine of Belgium for his PhD dissertation. One of his publications was also rewarded with a prize by the Belgian Society of Nephrology.

Céline Delierneux, PhD student in Prof Lancellotti and Dr Oury's team, received a Young Investigator Award at the Congress of the International Society on Thrombosis and Haemostasis that was held in Toronto, Canada (June 20-25).

GIGA-Development, stem cells & regenerative medicine

Developmental biology studies the process by which the various tissue types and organs differentiate from the single cell zygote. Understanding developmental is not only essential from a fundamental point of view but also as the basis for the design of novel therapeutic approaches that exploit the regenerative capacity of our cells. The "Development, stems cells and regenerative medicine" unit is 25 strong including scientists, PhD students and technician. They use human and animals stem cell systems as well as the zebrafish and mouse as model organisms for their studies. They have enriched the GIGA zebrafish platform with the capacity to perform toxicological and pharmacological assays. CRISPR/CAS9 dependent mutagenesis is now an important component of their tool box. The zebrafish system is being exploited to study the development and regeneration of pancreatic cells in health and disease, bone and cartilage development and homeostasis, as well as the development of the anterior pituitary. Other groups investigate the role of neural crest stem cells present in the adult bone marrow and their potential use as autologous grafting material in various neurological diseases.



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Laboratories

- ▶ Laboratory of Zebrafish Development and disease model
Bernard Peers, Marianne Voz, Isabelle Manfroid
- ▶ Laboratory of Organogenesis and Regeneration
Marc Muller
- ▶ Laboratory of Nervous System Disorders and Therapy
Sabine Wislet, Bernard Rogister

People

9 Scientists

12 PhD Students

2 Technicians

Highlight

Bernard Peers is one of the partners of the ZENCODE - ITN programme, a Marie Curie initial training programme funded by the European Union under the H020 programme. The scientific focus of the ZENCODE-ITN consortium is to understand genome regulation through combined experimental and computational approaches in a model vertebrate.



40%



60%

Zebrafish bone and general physiology are differently affected by hormones or changes in gravity

Aceto J, Nourizadeh-Lillabadi R, Maree R, Dardenne N, Jeanray N, Wehenkel L, Alestrom P, van Loon JJ, Muller M.
PLoS One. 2015;10:e0126928

Teleost fish such as zebrafish (*Danio rerio*) are increasingly used for physiological, genetic and developmental studies. Our understanding of the physiological consequences of altered gravity in an entire organism is still incomplete. We used altered gravity and drug treatment experiments to evaluate their effects specifically on bone formation and more generally on whole genome gene expression. By combining morphometric tools with an objective scoring system for the state of development for each element in the head skeleton and specific gene expression analysis, we confirmed and characterized in detail the decrease or increase of bone formation caused by a 5 day treatment (from 5dpf to 10 dpf) of, respectively parathyroid hormone (PTH) or vitamin D3 (VitD3). Microarray transcriptome analysis after 24 hours treatment reveals a general effect on physiology upon VitD3 treatment, while PTH causes more specifically developmental effects. Hypergravity (3g from 5dpf to 9 dpf) exposure results in a significantly larger head and a significant increase in bone formation for a subset of the cranial bones. Gene expression analysis after 24 hrs at 3g revealed differential expression of genes involved in the development and function of the skeletal, muscular, nervous, endocrine and cardiovascular systems. Finally, we propose a novel type of experimental approach, the «Reduced Gravity Paradigm», by keeping the developing larvae at 3g hypergravity for the first 5 days before returning them to 1g for one additional day. 5 days exposure to 3g during these early stages also caused increased bone formation, while gene expression analysis revealed a central network of regulatory genes (*hes5*, *sox10*, *lgals3bp*, *egr1*, *edn1*, *fos*, *fosb*, *klf2*, *gadd45ba* and *socs3a*) whose expression was consistently affected by the transition from hyper- to normal gravity.

Bmp signaling regulates bone morphogenesis in zebrafish through promoting osteoblast function as assessed by their nitric oxide production

Windhausen T, Squifflet S, Renn J, Muller M.
Molecules. 2015;20:7586-7601

Bone morphogenetic proteins (BMPs) control many developmental and physiological processes, including skeleton formation and homeostasis. Previous studies in zebrafish revealed the crucial importance of proper BMP signaling before 48 h post-fertilization (hpf) for cartilage formation in the skull. Here, we focus on the involvement of the BMP pathway between 48 and 96 hpf in bone formation after 96 hpf. Using BMP inhibitors and the expression of a dominant-negative BMP receptor, we analyze whether the loss of BMP signaling affects osteoblastogenesis, osteoblast function and bone mineralization. To this end, we used the transgenic zebrafish line Tg(*osterix:mCherry*), detection of nitric oxide (NO) production, and alizarin red staining, respectively. We observed that inhibition of BMP signaling between 48 and 72 hpf led to a reduction of NO production and bone mineralization. Osteoblast maturation and chondrogenesis, on the other hand, seemed unchanged. Osteoblast function and bone formation were less affected when BMP signaling was inhibited between 72 and 96 hpf. These results suggest that for the onset of bone formation, proper BMP signaling between 48 and 72 hpf is crucial to ensure osteoblast function and ossification. Furthermore, detection of NO in developing zebrafish larvae appears as an early indicator of bone calcification activity.

Phenotype classification of zebrafish embryos by supervised learning

Jeanray N, Maree R, Pruvot B, Stern O, Geurts P, Wehenkel L, Muller M.

PLoS One. 2015;10:e0116989

Zebrafish is increasingly used to assess biological properties of chemical substances and thus is becoming a specific tool for toxicological and pharmacological studies. The effects of chemical substances on embryo survival and development are generally evaluated manually through microscopic observation by an expert and documented by several typical photographs. Here, we present a methodology to automatically classify brightfield images of wildtype zebrafish embryos according to their defects by using an image analysis approach based on supervised machine learning. We show that, compared to manual classification, automatic classification results in 90 to 100% agreement with consensus voting of biological experts in nine out of eleven considered defects in 3 days old zebrafish larvae. Automation of the analysis and classification of zebrafish embryo pictures reduces the workload and time required for the biological expert and increases the reproducibility and objectivity of this classification.

Adult bone marrow mesenchymal and neural crest stem cells are chemoattractive and accelerate motor recovery in a mouse model of spinal cord injury

Neirinckx V, Agirman G, Coste C, Marquet A, Dion V, Rogister B, Franzen R, Wislet S.

Stem Cell Research & Therapy. 2015;6:211

Stem cells from adult tissues were considered for a long time as promising tools for regenerative therapy of neurological diseases, including spinal cord injuries (SCI). Indeed, mesenchymal (MSCs) and neural crest stem cells (NCSCs) together constitute the bone marrow stromal stem cells (BMSCs) that were used as therapeutic options in various models of experimental SCI. However, as clinical approaches remained disappointing, we thought that reducing BMSC heterogeneity should be a potential way to improve treatment efficiency and reproducibility. In this study, we decided to investigate the impact of pure populations of MSCs and NCSCs isolated from adult bone marrow in a mouse model of spinal cord injury. We then analyzed the secretome of both MSCs and NCSCs, and its effect on macrophage migration in vitro. To do so, we first observed that both cell types induced motor recovery in mice, and modified the inflammatory reaction in the lesion site. We also demonstrated that NCSCs but especially MSCs were able to secrete chemokines and attract macrophages in vitro. Finally, it appears that MSC injection in the spinal cord enhance early inflammatory events in the blood and spinal cord of SCI mice. Altogether, our results suggest that both cell types have beneficial effects in experimental SCI, and that further investigation should be dedicated to the regulation of the inflammatory reaction following SCI, in the context of stem cell-based therapy but also in the early-phase clinical management of SCI patients.

Are neural crest stem cells the missing link between hematopoietic and neurogenic niches?

Coste C, Neirinckx V, Gothot A, Wislet S, Rogister B.

Frontiers in Cellular Neuroscience. 2015;9:218

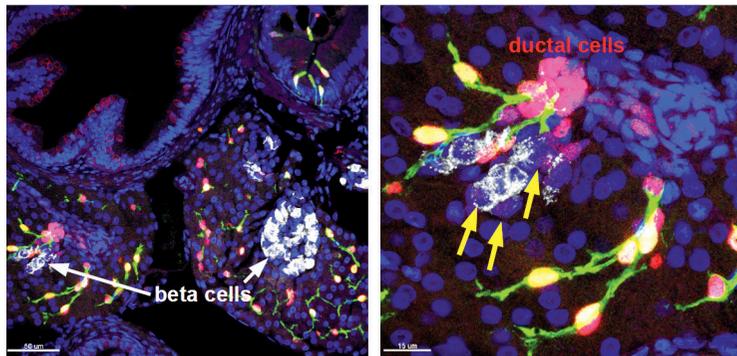
Hematopoietic niches are defined as cellular and molecular microenvironments that regulate hematopoietic stem cell (HSC) function together with stem cell autonomous mechanisms. Many different cell types have been characterized as contributors to the formation of HSC niches, such as osteoblasts, endothelial cells, Schwann cells, and mesenchymal progenitors. These mesenchymal progenitors have themselves been classified as CXC chemokine ligand (CXCL) 12-abundant reticular (CAR) cells, stem cell factor expressing cells, or nestin-positive mesenchymal stem cells (MSCs), which have been recently identified as neural crest-derived cells (NCSCs). Together, these cells are spatially associated with HSCs and believed to provide appropriate microenvironments for HSC self-renewal, differentiation, mobilization and hibernation both by cell-cell contact and soluble factors. Interestingly, it appears that regulatory pathways governing the hematopoietic niche homeostasis are operating in the neurogenic niche as well. Therefore, this review paper aims to compare both the regulation of hematopoietic and neurogenic niches, in order to highlight the role of NCSCs and nervous system components in the development and the regulation of the hematopoietic system.

Progenitor potential of nkx6.1-expressing cells throughout zebrafish life and during beta cell regeneration

Ghaye AP, Bergemann D, Tarifeno-Saldivia E, Flasse LC, Von Berg V, Peers B, Voz ML, Manfroid I.

BMC Biology. 2015;13:70

In contrast to mammals, the zebrafish has the remarkable capacity to regenerate its pancreatic beta cells very efficiently. Understanding the mechanisms of regeneration in the zebrafish and the differences with mammals will be fundamental to discovering molecules able to stimulate the regeneration process in mammals. To identify the pancreatic cells able to give rise to new beta cells in the zebrafish, we generated new transgenic lines allowing the tracing of multipotent pancreatic progenitors and endocrine precursors. Using novel bacterial artificial chromosome transgenic nkx6.1 and ascl1b reporter lines, we established that nkx6.1-positive cells give rise to all the pancreatic cell types and ascl1b-positive cells give rise to all the endocrine cell types in the zebrafish embryo. These two genes are initially co-expressed in the pancreatic primordium and their domains segregate, not as a result of mutual repression, but through the opposite effects of Notch signaling, maintaining nkx6.1 expression while repressing ascl1b in progenitors. In the adult zebrafish, nkx6.1 expression persists exclusively in the ductal tree at the tip of which its expression coincides with Notch active signaling in centroacinar/terminal end duct cells. Tracing these cells reveals that they are able to differentiate into other ductal cells and into insulin-expressing cells in normal (non-diabetic) animals. This capacity of ductal cells to generate endocrine cells is supported by the detection of ascl1b in the nkx6.1:GFP ductal cell transcriptome. This transcriptome also reveals, besides actors of the Notch and Wnt pathways, several novel markers such as id2a. Finally, we show that beta cell ablation in the adult zebrafish triggers proliferation of ductal cells and their differentiation into insulin-expressing cells. In conclusion, we have shown that, in the zebrafish embryo, nkx6.1+ cells are bona fide multipotent pancreatic progenitors, while ascl1b+ cells represent committed endocrine precursors. In contrast to the mouse, pancreatic progenitor markers nkx6.1 and pdx1 continue to be expressed in adult ductal cells, a subset of which we show are still able to proliferate and undergo ductal and endocrine differentiation, providing robust evidence of the existence of pancreatic progenitor/stem cells in the adult zebrafish. Our findings support the hypothesis that nkx6.1+ pancreatic progenitors contribute to beta cell regeneration. Further characterization of these cells will open up new perspectives for anti-diabetic therapies.



In adult zebrafish, the pancreatic ducts contain progenitors able to give rise to pancreatic beta cells. Beta cells express the Insulin marker (white). The beta cells deriving from the pancreatic ducts (highlighted by the yellow arrows) express a stable ductal marker (H2B-mCherry, red).

GIGA-Genetics

The core expertise of the Genetics thematic unit (GTU) is the forward and reverse genetic dissection of complex inherited traits in mammals. Research activities of the thematic unit can be grouped in four main topics:

1. Medical genomics - genetic dissection of inherited predisposition to inflammatory bowel disease (IBD) and cancer: the GTU is an active member of the Belgian and International IBD Genetics Consortia. We are using state-of-the-art genomic methodologies to map risk loci for IBD, to identify causative genes and variants within these loci, and to study the role of the intestinal microbiota in the pathogenesis of IBD. We study the utility of quasi-infinesimal models for IBD diagnosis and progression. We are searching for germline and somatic variants associated with cancers including familial isolated pituitary adenomas, breast cancer and glioblastoma. The GTU coordinates the Belgian Medical Genomics Initiative (BeMGI) and wants - in that capacity - to play a catalyzing role in the adoption of genomic information in the clinic.
2. Animal genomics - phenotype and genotype-driven screens for agronomically important genes and variants & genomic selection: we are using the same state-of-the-art genomics tool box to identify genes and variants underlying inherited defects, embryonic lethals and breeding values for economically important traits, including disease resistance. We are developing methods that exploit genomic information, including sequence data, for selection, i.e. «genomic selection». We work mainly in cattle and pigs, and collaborate closely with breeding organizations in Belgium, the Netherlands and New Zealand.
3. Fundamental genomics - polar overdominance, mutation and recombination in the germline, and transgenerational genetic effects: we work on the genetic dissection of polar overdominance in calipyge sheep: an unusual inheritance pattern that involves miRNA-mediated cross-talk between the paternal and maternal homologues at the CLPG locus. We are taking advantage of the unique pedigree structure of cow populations to quantify and genetically dissect inter-individual variation in de novo mutation, gene conversion and recombination rates in the bovine germline. We use a mouse model based on chromosome substitution strains to study the importance and mechanisms underlying transgenerational genetic effects.
4. BLV genomics - role and modus operandi of BLV-encoded non-coding RNAs: the team of Dr. Anne Van den Broeke continues to study the role of the cluster of miRNAs and the non-coding antisense RNAs that they discovered in the retroviral BLV genome. Genomic approaches are being applied to gain new understandings in BLV- and HTLV-dependent leukemogenesis.



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Laboratories

- ▶ Laboratory of Animal Genomics
Michel Georges
- ▶ Laboratory of Translational Gastroenterology
Edouard Louis
- ▶ Laboratory of Human Genetics
Vincent Bours

People

21 Scientists

14 PhD Students

8 Technicians



Ectopic expression of retrotransposon-derived peg11/rtl1 contributes to the callipyge muscular hypertrophy

Xu X, Ectors F, Davis EE, Pirottin D, Cheng H, Farnir F, Hadfield T, Cockett N, Charlier C, Georges M, Takeda H.

PLoS One. 2015;10:e0140594

The callipyge phenotype is an ovine muscular hypertrophy characterized by polar overdominance: only heterozygous +Mat/CLPGPat animals receiving the CLPG mutation from their father express the phenotype. +Mat/CLPGPat animals are characterized by postnatal, ectopic expression of Delta-like 1 homologue (DLK1) and Paternally expressed gene 11/Retrotransposon-like 1 (PEG11/RTL1) proteins in skeletal muscle. We showed previously in transgenic mice that ectopic expression of DLK1 alone induces a muscular hypertrophy, hence demonstrating a role for DLK1 in determining the callipyge hypertrophy. We herein describe newly generated transgenic mice that ectopically express PEG11 in skeletal muscle, and show that they also exhibit enhanced muscle mass. Our data suggest that both DLK1 and PEG11 act together in producing the muscular hypertrophy of callipyge sheep.

Evaluation of brca1-related molecular features and micrnas as prognostic factors for triple negative breast cancers

Boukerroucha M, Josse C, El Guendi S, Boujemla B, Freres P, Maree R, Wenric S, Segers K, Collignon J, Jerusalem G, Bours V.

BMC Cancer. 2015;15:755

The BRCA1 gene plays a key role in triple negative breast cancers (TNBCs), in which its expression can be lost by multiple mechanisms: germinal mutation followed by deletion of the second allele; negative regulation by promoter methylation; or miRNA-mediated silencing. This study aimed to establish a correlation among the BRCA1-related molecular parameters, tumor characteristics and clinical follow-up of patients to find new prognostic factors. BRCA1 protein and mRNA expression was quantified in situ in the TNBCs of 69 patients. BRCA1 promoter methylation status was checked, as well as cytokeratin 5/6 expression. Maintenance of expressed BRCA1 protein interaction with BARD1 was quantified, as a marker of BRCA1 functionality, and the tumor expression profiles of 27 microRNAs were determined. miR-548c-5p was emphasized as a new independent prognostic factor in TNBC. A combination of the tumoral expression of miR-548c and three other known prognostic parameters (tumor size, lymph node invasion and CK 5/6 expression status) allowed for relapse prediction by logistic regression with an area under the curve (AUC) = 0.96. BRCA1 mRNA and protein in situ expression, as well as the amount of BRCA1 ligated to BARD1 in the tumor, lacked any associations with patient outcomes, likely due to high intratumoral heterogeneity, and thus could not be used for clinical purposes. In situ BRCA1-related expression parameters could be used for clinical purposes at the time of diagnosis. In contrast, miR-548c-5p showed a promising potential as a prognostic factor in TNBC.

Reverse genetic screen for loss-of-function mutations uncovers a frameshifting deletion in the melanophilin gene accountable for a distinctive coat color in belgian blue cattle

Li W, Sartelet A, Tamma N, Coppieters W, Georges M, Charlier C.

Animal Genetics. 2016;47:110-113

In the course of a reverse genetic screen in the Belgian Blue cattle breed, we uncovered a 10-bp deletion (c.87_96del) in the first coding exon of the melanophilin gene (MLPH), which introduces a premature stop codon (p.Glu32Aspfs*1) in the same exon, truncating 94% of the protein. Recessive damaging mutations in the MLPH gene are well known to cause skin, hair, coat or plumage color dilution phenotypes in numerous species, including human, mice, dog, cat, mink, rabbit, chicken and quail. Large-scale array genotyping undertaken to identify p.Glu32Aspfs*1 homozygous mutant animals revealed a mutation frequency of 5% in the breed and allowed for the identification of 10 homozygous mutants. As expression of a colored coat requires at least one wild-type allele at the co-dominant Roan locus encoded by the KIT ligand gene (KITLG), homozygous mutants for p.Ala227Asp corresponding with the missense mutation were excluded. The six remaining colored calves displayed a distinctive dilution phenotype as anticipated. This new coat color was named 'cool gray'. It is the first damaging mutation in the MLPH gene described in cattle and extends the already long list of species with diluted color due to recessive mutations in MLPH and broadens the color palette of gray in this breed.

A stop-gain in the laminin, alpha 3 gene causes recessive junctional epidermolysis bullosa in belgian blue cattle

Sartelet A, Harland C, Tamma N, Karim L, Bayrou C, Li W, Ahariz N, Coppieters W, Georges M, Charlier C.

Animal Genetics. 2015;46:566-570

Four newborn purebred Belgian Blue calves presenting a severe form of epidermolysis bullosa were recently referred to our heredo-surveillance platform. SNP array genotyping followed by autozygosity mapping located the causative gene in a 8.3-Mb interval on bovine chromosome 24. Combining information from (i) whole-genome sequencing of an affected calf, (ii) transcriptomic data from a panel of tissues and (iii) a list of functionally ranked positional candidates pinpointed a private G to A nucleotide substitution in the LAMA3 gene that creates a premature stop codon (p.Arg2609*) in exon 60, truncating 22% of the corresponding protein. The LAMA3 gene encodes the alpha 3 subunit of the heterotrimeric laminin-332, a key constituent of the lamina lucida that is part of the skin basement membrane connecting epidermis and dermis layers. Homozygous loss-of-function mutations in this gene are known to cause severe junctional epidermolysis bullosa in human, mice, horse, sheep and dog. Overall, our data strongly support the causality of the identified gene and mutation.

On the use of the transmission disequilibrium test to detect pseudo-autosomal variants affecting traits with sex-limited expression

Elansary M, Stinckens A, Ahariz N, Cambisano N, Coppieters W, Grindflek E, van Son M, Buys N, Georges M.

Animal Genetics. 2015;46:395-402

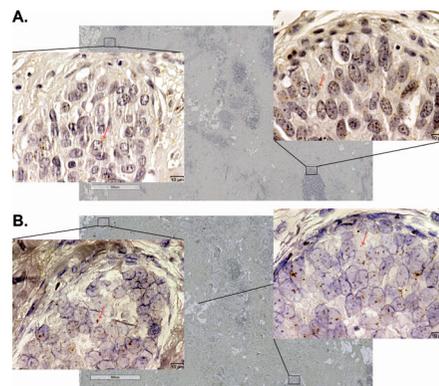
We herein describe the realization of a genome-wide association study for scrotal hernia and cryptorchidism in Norwegian and Belgian commercial pig populations. We have used the transmission disequilibrium test to avoid spurious associations due to population stratification. By doing so, we obtained genome-wide significant signals for both diseases with SNPs located in the pseudo-autosomal region in the vicinity of the pseudo-autosomal boundary. By further analyzing these signals, we demonstrate that the observed transmission disequilibria are artifactual. We determine that transmission bias at pseudo-autosomal markers will occur (i) when analyzing traits with sex-limited expression and (ii) when the allelic frequencies at the marker locus differ between X and Y chromosomes. We show that the bias is due to the fact that (i) sires will preferentially transmit the allele enriched on the Y (respectively X) chromosome to affected sons (respectively daughters) and (ii) dams will appear to preferentially transmit the allele enriched on the Y (respectively X) to affected sons (respectively daughters), as offspring inheriting the other allele are more likely to be non-informative. We define the conditions to mitigate these issues, namely by (i) extracting information from maternal meiosis only and (ii) ignoring trios for which sire and dam have the same heterozygous genotype. We show that by applying these rules to scrotal hernia and cryptorchidism, the pseudo-autosomal signals disappear, confirming their spurious nature.

Brca1 germline mutation and glioblastoma development: Report of cases

Boukerroucha M, Josse C, Segers K, El-Guendi S, Freres P, Jerusalem G, Bours V.

BMC Cancer. 2015;15:181

Germline mutations in breast cancer susceptibility gene 1 (BRCA1) increase the risk of breast and ovarian cancers. However, no association between BRCA1 germline mutation and glioblastoma malignancy has ever been highlighted. Here we report two cases of BRCA1 mutated patients who developed a glioblastoma multiform (GBM). Two patients diagnosed with triple negative breast cancer (TNBC) were screened for BRCA1 germline mutation. They both carried a pathogenic mutation introducing a premature STOP codon in the exon 11 of the BRCA1 gene. Few years later, both patients developed a glioblastoma and a second breast cancer. In an attempt to clarify the role played by a mutated BRCA1 allele in the GBM development, we investigated the BRCA1 mRNA and protein expression in breast and glioblastoma tumours for both patients. The promoter methylation status of this gene was also tested by methylation specific PCR as BRCA1 expression is also known to be lost by this mechanism in some sporadic breast cancers. Our data show that BRCA1 expression is maintained in glioblastoma at the protein and the mRNA levels, suggesting that loss of heterozygosity (LOH) did not occur in these cases. The protein expression is tenfold higher in the glioblastoma of patient 1 than in her first breast carcinoma, and twice higher in patient 2. In agreement with the high protein expression level in the GBM, BRCA1 promoter methylation was not observed in these tumours. In these two cases, despite of a BRCA1 pathogenic germline mutation, the tumour-suppressor protein expression is maintained in GBM, suggesting that the BRCA1 mutation is not instrumental for the GBM development.



C.

	N	N relapse	Cox (PFS)					
			pval	B	pval (B)	Exp(B)	95% CI (B)	
mRNA. BRCA	61	19	.525	.002	.526	1.002	.996	1.007
prot. BRCA	61	20	.496	.002	.496	1.002	.995	1.009
% BARD1-BRCA1	55	18	.270	.005	.267	1.005	.996	1.014

	Spearman correlations					
	prot. BRCA			BARD1-BRCA1		
	Cor.	pval	N	Cor.	pval	N
mRNA. BRCA	.294	.022	60	.154	.265	54
prot. BRCA				.506	9.34E-05	54

In situ BRCA1 expression in TNBC tumors. A. Proximity ligation assay showing a representative BRCA1 protein expression across the tumor. Two different subzones were magnified to illustrate high and faint expression. B. In situ hybridization assay showing BRCA1 mRNA expression across the same tumor and subzones used for protein detection. In both cases, high heterogeneity of the localization of expression is observed. C. Cox univariate regression and correlation analyses of BRCA1 expression relative to patient clinicopathological features shows that no relationship of BRCA1 expression with patient outcome was observed.

GIGA-Inflammation, Infection & Immunity

The GIGA-Inflammation, Infection & Immunity (GIGA-I3) research unit is composed of 7 laboratories that study various but complementary aspects of immunity. Independently of each other, they carry research in varied fields of immunology. Nevertheless, 4 research themes are particularly explored and give rise to numerous collaborations within the GIGA-I3. These research themes are inflammation, hematology, virology and immunoendocrinology. During the year 2015, members of the GIGA-I3 produced or contributed to 76 significant scientific publications. The cellular and molecular mechanisms implicated in inflammation, and particularly in chronic inflammation, are extensively studied in GIGA-I3. The GIGA-I3 laboratories mainly focus their research on the most common inflammatory lung diseases, namely asthma and chronic obstructive pulmonary disease (COPD), on gut inflammatory diseases such as Inflammatory Bowel Diseases (IBDs) and on persistent inflammatory joint diseases. GIGA-I3 is also involved in clinical studies and translational research in the field of cell therapy (mesenchymal stem cells and Tregs) and hematopoietic stem cell transplantation (HSCT). We investigate new methods for preventing and treating graft-versus-host disease and the consequences of HSCT on the immune system, as well as the impact of multiple myeloma on immune function and bone disease, and of cancer in general on erythropoiesis. The GIGA-I3 unit pays particular attention to the study of viral diseases. GIGA-I3 indeed investigates the role and the regulation of Varicella-Zoster Virus (VZV) proteins, develops humanized murine models for rapid and large scale screening of anti-HIV responses to new immunostimulatory approaches, and takes advantage of a research model, the uterine cervical cancer associated with infection by the human papillomavirus (HPV), to study the role of natural immunity (NK cells and TCR $\gamma\delta$) in anti-tumor and anti-viral responses. Finally, GIGA-I3 is particularly involved in research aimed at identifying the relationships between the immune and endocrine systems. In this context, GIGA-I3 studies thymic IGF-2 in programming central self-tolerance to pancreatic islet β cells, the role of the GH/IGF-1 axis on thymic function and T-cell development and implantation/tolerance of the embryo.



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Vincent Geenen
- ▶ Laboratory of Immunology & Infectious Diseases
Michel Moutschen
- ▶ Laboratory of Pneumology
Renaud Louis
- ▶ Laboratory of Rheumatology
Michel Malaise
- ▶ Laboratory of Virology and Immunology
Jacques Piette, Catherine Sadzot

People

44 Scientists

33 PhD Students

19 Technicians



38%



62%

Immune recovery after allogeneic hematopoietic stem cell transplantation following flu-tbi versus tli-atg conditioning

Hannon M, Beguin Y, Ehx G, Servais S, Seidel L, Graux C, Maertens J, Kerre T, Daulne C, de Bock M, Fillet M, Ory A, Willems E, Gothot A, Humblet-Baron S, Baron F.

Clinical Cancer Research. 2015;21:3131-3139

A conditioning regimen for allogeneic hematopoietic cell transplantation (HCT) combining total lymphoid irradiation (TLI) plus anti-thymocyte globulin (ATG) has been developed to induce graft-versus-tumor effects without graft-versus-host disease (GVHD). We compared immune recovery in 53 patients included in a phase II randomized study comparing nonmyeloablative HCT following either fludarabine plus 2 Gy total body irradiation (TBI arm, n = 28) or 8 Gy TLI plus ATG (TLI arm, n = 25). In comparison with TBI patients, TLI patients had a similarly low 6-month incidence of grade II-IV acute GVHD, a lower incidence of moderate/severe chronic GVHD (P = 0.02), a higher incidence of CMV reactivation (P < 0.001), and a higher incidence of relapse (P = 0.01). While recovery of total CD8(+) T cells was similar in the two groups, with median CD8(+) T-cell counts reaching the normal values 40 to 60 days after allo-HCT, TLI patients had lower percentages of naïve CD8 T cells. Median CD4(+) T-cell counts did not reach the lower limit of normal values the first year after allo-HCT in the two groups. Furthermore, CD4(+) T-cell counts were significantly lower in TLI than in TBI patients the first 6 months after transplantation. Interestingly, while median absolute regulatory T-cell (Treg) counts were comparable in TBI and TLI patients, Treg/naïve CD4(+) T-cell ratios were significantly higher in TLI than in TBI patients the 2 first years after transplantation. Immune recovery differs substantially between these two conditioning regimens, possibly explaining the different clinical outcomes observed (NCT00603954).

Validation of a multicolor staining to monitor phosphostat5 levels in regulatory t-cell subsets

Ehx G, Hannon M, Beguin Y, Humblet-Baron S, Baron F.

Oncotarget. 2015;6:43255-43266

Regulatory T cells (Tregs) are key players in immune tolerance. They express the transcription factor FOXP3 and are dependent of the STAT5 signaling for their homeostasis. So far, the study of phosphorylated epitopes by flow cytometry required treating the cells with methanol, which is harmful for several epitopes. Here we assessed whether the PerFix EXPOSE reagent kit (PFE)(Beckman Coulter) allowed monitoring the phosphorylation level of STAT5 in Treg subpopulations together with complex immunophenotyping. Results observed with the PFE kit were compared to those observed without cell permeabilization for surface markers, with paraformaldehyde permeabilization for non-phosphorylated intracellular epitopes, and with methanol-based permeabilization for phosphoSTAT5 staining. In human PBMCs, the PFE kit allowed the detection of surface antigens, FOXP3, KI67 and phosphoSTAT5 in similar proportions to what was observed without permeabilization (for surface antigens), or with PFA or methanol permeabilizations for FOXP3/KI67 and phosphoSTAT5, respectively. Comparable observations were made with murine splenocytes. Further, the PFE kit allowed determining the response of different human and murine Treg subsets to IL-2. It also allowed demonstrating that human Treg subsets with the highest levels of phosphoSTAT5 had also the highest suppressive activity in vitro, and that anti-thymocyte globulin (ATG) induced Treg independently of the STAT5 pathway, both in vitro and in vivo. We have validated a multicolor staining method that allows monitoring phosphoSTAT5 levels in Treg subsets. This staining could be useful to monitor responses of various Treg subsets to IL-2 therapy.

Circadian and circannual variations in cord blood hematopoietic cell composition

Servais S, Baudoux E, Brichard B, Bron D, Debruyen C, De Hemptinne D, Deneys V, Paulus JM, Schaaps JP, Van Cauwenberge JR, Seidel L, Delforge A, Beguin Y.

Haematologica. 2015;100:e32-34

Several previous studies have demonstrated that cord blood unit composition is an important factor that may predict outcomes after cord blood transplantation, with higher doses of transplanted nucleated cells and hematopoietic stem and progenitor cells being associated with faster engraftment and better overall survival. In the setting of this study involving 3 University centers, we analyzed factors potentially influencing cord blood cell composition. In accordance with the results of several previous publications, we observed that gestational age, birth weight and baby's gender impacted concentrations of nucleated and hematopoietic progenitor cells in cord blood. We also showed that uses of epidural anesthesia and of oxytocin were associated with higher concentrations of hematopoietic progenitor cells. Interestingly, we observed that nucleated cell and progenitor cell concentrations were also determined by time of day and month of delivery. Recent studies have suggested chronological rhythmic egress of hematopoietic stem and progenitor cells from the bone marrow to the peripheral blood in adult individuals. Our findings suggest that such physiological rhythm may not be restricted to post-natal life. We think our study may have practical implications for cord blood banking strategies and also raises questions about chronological rhythm in hematopoietic cell trafficking during fetal life.

Selective glucocorticoid receptor modulator compound a, in contrast to prednisolone, does not induce leptin or the leptin receptor in human osteoarthritis synovial fibroblasts

Malaise O, Relic B, Quesada-Calvo F, Charlier E, Zeddou M, Neuville S, Gillet P, Louis E, de Seny D, Malaise MG.

Rheumatology (Oxford). 2015;54:1087-1092

Glucocorticoids are powerful anti-inflammatory compounds that also induce the expression of leptin and leptin receptor (Ob-R) in synovial fibroblasts through TGF- β signalling and Smad1/5 phosphorylation. Compound A (CpdA), a selective glucocorticoid receptor agonist, reduces inflammation in murine arthritis models and does not induce diabetes or osteoporosis, thus offering an improved risk:benefit ratio in comparison with glucocorticoids. Due to the detrimental role of leptin in OA pathogenesis, we sought to determine whether CpdA also induced leptin and Ob-R protein expression as observed with prednisolone. Human synovial fibroblasts and chondrocytes were isolated from the synovium and cartilage of OA patients after joint surgery. The cells were treated with prednisolone, TGF- β 1, TNF- α and/or CpdA. Levels of leptin, IL-6, IL-8, MMP-1 and MMP-3 were measured by ELISA and expression levels of Ob-R phospho-Smad1/5, phospho-Smad2, α -tubulin and glyceraldehyde 3-phosphate dehydrogenase were analysed by western blotting. CpdA, unlike prednisolone, did not induce leptin secretion or Ob-R protein expression in OA synovial fibroblasts. Moreover, CpdA decreased endogenous Ob-R expression and down-regulated prednisolone-induced leptin secretion and Ob-R expression. Mechanistically, CpdA, unlike prednisolone, did not induce Smad1/5 phosphorylation. CpdA, similarly to prednisolone, down-regulated endogenous and TNF- α -induced IL-6, IL-8, MMP-1 and MMP-3 protein secretion. The dissociative effect of CpdA was confirmed using chondrocytes with no induction of leptin secretion, but with a significant decrease in IL-6, IL-8, MMP-1 and MMP-3 protein secretion. CpdA, unlike prednisolone, did not induce leptin or Ob-R in human OA synovial fibroblasts, thereby demonstrating an improved risk:benefit ratio.

Deletion of the orf9p acidic cluster impairs the nuclear egress of varicella-zoster virus capsids

Riva L, Thiry M, Lebrun M, L'Homme L, Piette J, Sadzot-Delvaux C.

Journal of Virology. 2015;89:2436-2441

The protein encoded by ORF9 is essential for varicella-zoster virus (VZV) replication. Previous studies documented its presence in the trans-Golgi network and its involvement in secondary envelopment. In this work, we deleted the ORF9p acidic cluster, destroying its interaction with ORF47p, and this resulted in a nuclear accumulation of both proteins. This phenotype results in an accumulation of primary enveloped capsids in the perinuclear space, reflecting a capsid de-envelopment defect.

Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: the promesse study

Frippiat F, Musuamba FT, Seidel L, Albert A, Denooz R, Charlier C, Van Bambeke F, Wallemacq P, Descy J, Lambermont B, Layios N, Damas P, Moutschen M.

Journal of Antimicrobial Chemotherapy. 2015;70:207-216

The objective of this study was to propose an optimal treatment regimen of meropenem in critically ill patients with severe nosocomial pneumonia. Among 55 patients in intensive care treated with 1 g of meropenem every 8 h for severe nosocomial pneumonia, 30 were assigned to intermittent infusion (II; over 0.5 h) and 25 to extended infusion (EI; over 3 h) groups. Based on plasma and epithelial lining fluid (ELF) concentrations determined at steady-state, pharmacokinetic modelling and Monte Carlo simulations were undertaken to assess the probability of attaining drug concentrations above the MIC for 40%-100% of the time between doses (%T > 1-fold and 4-fold MIC), for 1 or 2 g administered by either method. Penetration ratio, measured by the ELF/plasma ratio of AUCs, was statistically higher in the EI group than in the II group (mean \pm SEM: 0.29 ± 0.030 versus 0.20 ± 0.033 , $P = 0.047$). Considering a maximum susceptibility breakpoint of 2 mg/L, all dosages and modes of infusions achieved 40%-100% T > 1-fold MIC in plasma, but none did so in ELF, and only the 2 g dose over EI achieved 40%-100% T > 4-fold MIC in plasma. The optimum regimen to treat severe nosocomial pneumonia was 2 g of meropenem infused over 3 h every 8 h. This regimen achieved the highest pharmacodynamic targets both in plasma and in ELF.

Awards

Thomas Marichal, principal investigator in the laboratory of Cellular and Molecular Immunology has been awarded the 2015 Acteria Early Career Research Prize in Allergology. Thanks to a partnership established in 2012 between the Fondation ACTERIA – ACTing on European Research in Immunology and Allergology - and EFIS – European Federation of Immunological Societies - this prize is awarded for the best early career research work of investigators with up to 10 years postdoctoral experience in the fields of immunology and allergology. The ACTERIA Early Career Research Prize carry cash awards of €30,000 each, plus the possibility of financing of €50,000/year for three-year research projects to be performed in European institutions.

Christophe Desmet received a WELBIO Starter Grant for the projet «Translational regulation of T cells» - see page 89.

GIGA-Neurosciences

The Neurosciences thematic unit currently includes 6 research units that focus on neuroscience at the cellular and molecular level. Research at the GIGA-Neurosciences spans an impressively diverse array of questions and techniques. Since its creation in 2009, research at the GIGA-Neurosciences focuses on the cellular and molecular underpinnings of normal central and peripheral nervous systems development and function. In addition, researchers at the GIGA-Neurosciences investigate the causes related to the failure of those functions, particularly in the case of epilepsy, Parkinson's and Alzheimer's diseases, autism spectrum disorders, depression, deafness and sexual orientation and gender identity disorders. GIGA neuroscientists accomplish their research goals using a wide range of methods to identify and manipulate the molecular components of cells. These approaches involve extensive interdisciplinary skills including expertise in molecular biology, biochemistry, cell biology, anatomy, behaviour, cellular imaging and electrophysiological recordings and the testing of transgenic animals. One area in which GIGA-Neurosciences researchers make important scientific contribution is in the neuroendocrine and neurochemical mechanisms that mediate the activation and sexual differentiation of reproductive behaviour. The study of cellular and molecular facets of post-lesional neuroplasticity following spinal cord or peripheral nerve injury is another powerful research area at GIGA-neurosciences. Neurophysiology constitutes a particular strength of the GIGA-Neurosciences. Particularly, researchers evaluate the role of various ionic channels in the control of the excitability of monoaminergic neurons. Another specific area of focus is on understanding the interplay between neuronal bioenergetics, excitability and cell survival. Endocrine disrupting chemicals constitute an important public health issue that is specifically addressed at the GIGA-Neurosciences with special emphasis on the pathogenic interaction between endocrine disrupters and insufficient prenatal nutrition. More recently, a new program is developing translational research into the biology and behaviour of glioma. Finally, an important area of research in cellular and molecular neuroscience at the GIGA-Neurosciences is focused on the identification of new cellular and molecular mechanisms involved in key developmental processes such as the production of neurons, inner ear hair cells and glial cells, their differentiation and their migration in the central and peripheral nervous system in health and disease. Robust interactions among GIGA neuroscientists are enhanced by weekly meetings and technical support is provided by a number of core facilities. Neuroscientists further benefit from collaborations with colleagues in other GIGA thematic research units, particularly those who excel at understanding cell and molecular pathways in normal development and diseases.



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Vincent Seutin
- ▶ Laboratory of Nervous System Disorders and Therapy
Bernard Rogister
- ▶ Laboratory of Cellular and Tissular Biology
Marc Thiry
- ▶ Laboratory of Pathological Aging and Epilepsies
Lucien Bettendorff

People

32 Scientists

38 PhD Students

11 Technicians



Hypervulnerability to sound exposure through impaired adaptive proliferation of peroxisomes

Delmaghani S, Defourny J, Aghaie A, Beurg M, Dulon D, Thelen N, Perfettini I, Zelles T, Aller M, Meyer A, Emptoz A, Giraudet F, Leibovici M, Dartevielle S, Soubigou G, Thiry M, Vizi ES, Safieddine S, Hardelin JP, Avan P, Petit C.

Cell. 2015;163:894-906

A deficiency in pejvakin, a protein of unknown function, causes a strikingly heterogeneous form of human deafness. Pejvakin-deficient (Pjvk^{-/-}) mice also exhibit variable auditory phenotypes. Correlation between their hearing thresholds and the number of pups per cage suggest a possible harmful effect of pup vocalizations. Direct sound or electrical stimulation show that the cochlear sensory hair cells and auditory pathway neurons of Pjvk^{-/-} mice and patients are exceptionally vulnerable to sound. Subcellular analysis revealed that pejvakin is associated with peroxisomes and required for their oxidative-stress-induced proliferation. Pjvk^{-/-} cochleas display features of marked oxidative stress and impaired antioxidant defenses, and peroxisomes in Pjvk^{-/-} hair cells show structural abnormalities after the onset of hearing. Noise exposure rapidly upregulates Pjvk cochlear transcription in wild-type mice and triggers peroxisome proliferation in hair cells and primary auditory neurons. Our results reveal that the antioxidant activity of peroxisomes protects the auditory system against noise-induced damage.

A dynamic unfolded protein response contributes to the control of cortical neurogenesis

Laguesse S, Creppe C, Nedialkova DD, Prevot PP, Borgs L, Huysseune S, Franco B, Duysens G, Krusy N, Lee G, Thelen N, Thiry M, Close P, Chariot A, Malgrange B, Leidel SA, Godin JD, Nguyen L.

Developmental Cell. 2015;35:553-567

The cerebral cortex contains layers of neurons sequentially generated by distinct lineage-related progenitors. At the onset of corticogenesis, the first-born progenitors are apical progenitors (APs), whose asymmetric division gives birth directly to neurons. Later, they switch to indirect neurogenesis by generating intermediate progenitors (IPs), which give rise to projection neurons of all cortical layers. While a direct lineage relationship between APs and IPs has been established, the molecular mechanism that controls their transition remains elusive. Here we show that interfering with codon translation speed triggers ER stress and the unfolded protein response (UPR), further impairing the generation of IPs and leading to microcephaly. Moreover, we demonstrate that a progressive downregulation of UPR in cortical progenitors acts as a physiological signal to amplify IPs and promotes indirect neurogenesis. Thus, our findings reveal a contribution of UPR to cell fate acquisition during mammalian brain development.

Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J.

Psychoneuroendocrinology. 2015;55:59-71

The sexual differentiation of the brain is primarily driven by gonadal hormones during fetal development. Leading theories on the etiology of gender dysphoria (GD) involve deviations herein. To examine whether there are signs of a sex-atypical brain development in GD, we quantified regional neural gray matter (GM) volumes in 55 female-to-male and 38 male-to-female adolescents, 44 boys and 52 girls without GD and applied both univariate and multivariate analyses. In girls, more GM volume was observed in the left superior medial frontal cortex, while boys had more volume in the bilateral superior posterior hemispheres of the cerebellum and the hypothalamus. Regarding the GD groups, at whole-brain level they differed only from individuals sharing their gender identity but not from their natal sex. Accordingly, using multivariate pattern recognition analyses, the GD groups could more accurately be automatically discriminated from individuals sharing their gender identity than those sharing their natal sex based on spatially distributed GM patterns. However, region of interest analyses indicated less GM volume in the right cerebellum and more volume in the medial frontal cortex in female-to-males in comparison to girls without GD, while male-to-females had less volume in the bilateral cerebellum and hypothalamus than natal boys. Deviations from the natal sex within sexually dimorphic structures were also observed in the untreated subsamples. Our findings thus indicate that GM distribution and regional volumes in GD adolescents are largely in accordance with their respective natal sex. However, there are subtle deviations from the natal sex in sexually dimorphic structures, which can represent signs of a partial sex-atypical differentiation of the brain.

High dendritic expression of Ih in the proximity of the axon origin controls the integrative properties of nigral dopamine neurons

Engel D, Seutin V.

Journal of Physiology. 2015;593:4905-4922

Dendrites of most neurons express voltage-gated ion channels in their membrane. In combination with passive properties, active currents confer to dendrites a high computational potential. The hyperpolarization-activated cation current Ih present in the dendrites of some pyramidal neurons affects their membrane and integration properties, synaptic plasticity and higher functions such as memory. A gradient of increasing h-channel density towards distal dendrites has been found to be responsible for the location independence of excitatory postsynaptic potential (EPSP) waveform and temporal summation in cortical and hippocampal pyramidal cells. However, reports on other cell types revealed that smoother gradients or even linear distributions of Ih can achieve homogeneous temporal summation. Although the existence of a robust, slowly activating Ih current has been repeatedly demonstrated in nigral dopamine neurons, its subcellular distribution and precise role in synaptic integration are unknown. Using cell-attached patch-clamp recordings, we find a higher Ih current density in the axon-bearing dendrite than in the soma or in dendrites without axon in nigral dopamine neurons. Ih is mainly concentrated in the dendritic membrane area surrounding the axon origin and decreases with increasing distances from this site. Single EPSPs and temporal summation are similarly affected by blockade of Ih in axon- and non-axon-bearing dendrites. The presence of Ih close to the axon is pivotal to control the integrative functions and the output signal of dopamine neurons and may consequently influence the downstream coding of movement.

Microrna-124 regulates cell specification in the cochlea through modulation of sfrp4/5

Huyghe A, Van den Ackerveken P, Sacheli R, Prevot PP, Thelen N, Renauld J, Thiry M, Delacroix L, Nguyen L, Malgrange B.

Cell Reports. 2015;13:31-42

The organ of Corti, the auditory organ of the mammalian inner ear, contains sensory hair cells and supporting cells that arise from a common sensory progenitor. The molecular bases allowing the specification of these progenitors remain elusive. In the present study, by combining microarray analyses with conditional deletion of Dicer in the developing inner ear, we identified that miR-124 controls cell fate in the developing organ of Corti. By targeting secreted frizzled-related protein 4 (Sfrp4) and Sfrp5, two inhibitors of the Wnt pathway, we showed that miR-124 controls the β -catenin-dependent and also the PCP-related non-canonical Wnt pathways that contribute to HC differentiation and polarization in the organ of Corti. Thus, our work emphasizes the importance of miR-124 as an epigenetic safeguard that fine-tunes the expression of genes critical for cell patterning during cochlear differentiation.

Adult mouse subventricular zones stimulate glioblastoma stem cells specific invasion through cxcl12/cxcr4 signaling

Goffart N, Kroonen J, Di Valentin E, Dedobbeleer M, Denne A, Martinive P, Rogister B.

Neuro Oncology. 2015;17:81-94

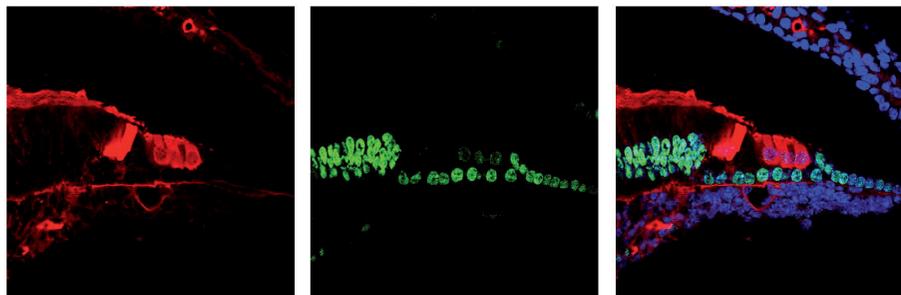
Patients with glioblastoma multiforme (GBM) have an overall median survival of 15 months. This catastrophic survival rate is the consequence of systematic relapses that could arise from remaining glioblastoma stem cells (GSCs) left behind after surgery. We previously demonstrated that GSCs are able to escape the tumor mass and specifically colonize the adult subventricular zones (SVZs) after transplantation. This specific localization, away from the initial injection site, therefore represents a high-quality model of a clinical obstacle to therapy and relapses because GSCs notably retain the ability to form secondary tumors. In this work, we questioned the role of the CXCL12/CXCR4 signaling in the GSC-specific invasion of the SVZs. We demonstrated that both receptor and ligand are respectively expressed by different GBM cell populations and by the SVZ itself. In vitro migration bio-assays highlighted that human U87MG GSCs isolated from the SVZs (U87MG-SVZ) display stronger migratory abilities in response to recombinant CXCL12 and/or SVZ-conditioned medium (SVZ-CM) compared with cancer cells isolated from the tumor mass (U87MG-TM). Moreover, in vitro inhibition of the CXCR4 signaling significantly decreased the U87MG-SVZ cell migration in response to the SVZ-CM. Very interestingly, treating U87MG-xenografted mice with daily doses of AMD3100, a specific CXCR4 antagonist, prevented the specific invasion of the SVZ. Another in vivo experiment, using CXCR4-invalidated GBM cells, displayed similar results. Taken together, these data demonstrate the significant role of the CXCL12/CXCR4 signaling in this original model of brain cancer invasion.

Cochlear supporting cell transdifferentiation and integration into hair cell layers by inhibition of ephrin-b2 signalling

Defourny J, Mateo Sanchez S, Schoonaert L, Robberecht W, Davy A, Nguyen L, Malgrange B.

Nature Communications. 2015;6:7017

In mammals, cochlear sensory hair cells that are responsible for hearing are postmitotic and are not replaced after loss. One of the most promising strategies to regenerate hair cells is to identify and inhibit the factors preventing the conversion of adjacent non-sensory supporting cells into hair cells. Here we demonstrate that mammalian hair cells can be directly generated from supporting cells by inhibition of ephrin-B2 signalling. Using either ephrin-B2 conditional knockout mice, shRNA-mediated gene silencing or soluble inhibitors, we found that downregulation of ephrin-B2 signalling at embryonic stages results in supporting cell translocation into hair cell layers and subsequent switch in cell identity from supporting cell to hair cell fate. As transdifferentiation is here a result of displacement across boundary, this original finding presents the interest that newly generated hair cells directly integrate either hair cell layer, then would be likely more rapidly able to fit into functional circuitry.



Parvalbumin

EPhrin B2

merge

Ephrin B2 is specifically expressed in supporting cells and greater epithelial ridge, at the border of hair cells.

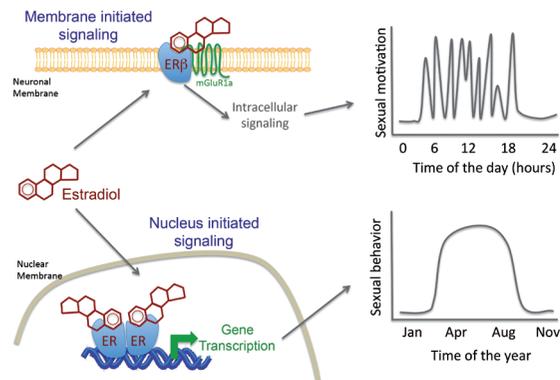


Estrogen receptor beta activation rapidly modulates male sexual motivation through the transactivation of metabotropic glutamate receptor 1a

Seredynski AL, Balthazart J, Ball GF, Cornil CA.

Journal of Neuroscience. 2015;35:13110-13123

In addition to the transcriptional activity of their liganded nuclear receptors, estrogens, such as estradiol (E2), modulate cell functions, and consequently physiology and behavior, within minutes through membrane-initiated events. The membrane-associated receptors (mERs) underlying the acute effects of estrogens on behavior have mostly been documented in females where active estrogens are thought to be of ovarian origin. We determined here, by acute intracerebroventricular injections of specific agonists and antagonists, the type(s) of mERs that modulate rapid effects of brain-derived estrogens on sexual motivation in male Japanese quail. Brain aromatase blockade acutely inhibited sexual motivation. Diarylpropionitrile (DPN), an estrogen receptor β (ER β)-specific agonist, and to a lesser extent 17 α -estradiol, possibly acting through ER-X, prevented this effect. In contrast, drugs targeting ER α (PPT and MPP), GPR30 (G1 and G15), and the Gq-mER (STX) did not affect sexual motivation. The mGluR1a antagonist LY367385 significantly inhibited sexual motivation but mGluR2/3 and mGluR5 antagonists were ineffective. LY367385 also blocked the behavioral restoration induced by E2 or DPN, providing functional evidence that ER β interacts with metabotropic glutamate receptor 1a (mGluR1a) signaling to acutely regulate male sexual motivation. Together these results show that ER β plays a key role in sexual behavior regulation and the recently uncovered cooperation between mERs and mGluRs is functional in males where it mediates the acute effects of estrogens produced centrally in response to social stimuli. The presence of an ER-mGluR interaction in birds suggests that this mechanism emerged relatively early in vertebrate history and is well conserved. Significance statement: The membrane-associated receptors underlying the acute effects of estrogens on behavior have mostly been documented in females, where active estrogens are thought to be of ovarian origin. Using acute intracerebroventricular injections of specific agonists and antagonists following blockade of brain aromatase, we show here that brain-derived estrogens acutely facilitate male sexual motivation through the activation of estrogen receptor β interacting with the metabotropic glutamate receptor 1a. This behavioral effect occurring within minutes provides a mechanistic explanation of how an estrogen receptor not intrinsically coupled to intracellular effectors can signal from the membrane to govern behavior in a very rapid fashion. It suggests that different subtypes of estrogen receptors could regulate the motivation versus performance aspects of behavior.



Along with the long term regulation of reproductive behavior by the transcriptional activity of estrogen receptors, membrane-initiated actions of neuroestrogens provide a mechanism of acute, moment-to-moment, regulation of sexual motivation through the transactivation of metabotropic glutamate receptors by the liganded estrogen receptor beta. Therefore, the nuclear estrogen receptors can after translocation to the membrane associate with a classical neurotransmitter receptor to signal in a neurotransmitter-like fashion.

Awards

Laurent Nguyen won the 3rd triennial prize of the Pierre and Simone Clerdent Foundation

The prize (400 000 €) was given on September 21 by Princess Astrid of Belgium. Laurent Nguyen and his team study the mechanisms of the cortical development. Their research includes the study of genes whose mutation is closely linked to the appearance of cortical malformations in humans, such as lissencephaly, microcephaly and polymicrogyria.

Rachelle Franzen won a prize of 36 000 € for 2 years of the Charcot foundation (Multiple sclerosis) for her project «Multiple sclerosis : insights into the molecular aspects of central nervous system demyelination and remyelination. The role of Elongator complex».

Jacques Balthazart became fellow of the AAAS (America, Association for the Advancement of Science).

Jean-Pierre Bourguignon won the Endocrine Society Outstanding Public Service Award.

Thomas Lombard won the Lejeune-Lechien foundation award for the project «Characterization of the impact of neural crest or mesenchymal stem cell graft in mouse model for medication-related osteonecrosis of the jaw (10 000 €).

Julie Fudvoye won the Belgian Society for Paediatrics Research Award.

GIGA-Signal Transduction

Understanding body and organ function in health and disease requires a thorough knowledge of the molecular events that take place at the level of individual cells. These cellular processes are carried out by thousands of different molecules, from single proteins to sophisticated megadalton-sized protein complexes. How these molecules work (individually or as part of signaling pathways) to control cellular activities and how are these molecular machineries dysregulated in various pathological states are the fundamental questions tackled by the teams in the thematic unit "Signal Transduction". With the ultimate goal of translating molecular advances into novel therapeutic approaches we bring together a multifaceted and multidisciplinary group of researchers. The Signal Transduction thematic unit establishes an interactive environment in which 8 laboratories with complementary expertise synergistically interact.



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Laboratories

- ▶ Laboratory of Protein Signaling and Interactions
Franck Dequiedt, Jean-Claude Twizere ,
Denis Mottet
- ▶ Laboratory of Molecular Immunology and
Signal Transduction
Emmanuel Dejardin
- ▶ Laboratory of Medical Chemistry
Alain Chariot
- ▶ Laboratory of Cancer Signaling
Pierre Close
- ▶ Laboratory of Immunology and Infectious
Diseases
Souad Rahmouni
- ▶ Laboratory of Molecular Pharmacology
Julien Hanson
- ▶ Laboratory of Virology and Immunology
Jacques Piette, Yvette Habraken,
Sylvie Legrand-Poels
- ▶ Laboratory of Functional Genetics
Stephane Schurmans

People

32 Scientists

28 PhD Students

6 Technicians



48%



52%

Elp3 drives wnt-dependent tumor initiation and regeneration in the intestine

Ladang A, Rapino F, Heukamp LC, Tharun L, Shostak K, Hermand D, Delaunay S, Klevernic I, Jiang Z, Jacques N, Jamart D, Migeot V, Florin A, Goktuna S, Malgrange B, Sansom OJ, Nguyen L, Buttner R, Close P, Chariot A.

Journal of Experimental Medicine. 2015;212:2057-2075

Tumor initiation in the intestine can rapidly occur from Lgr5(+) crypt columnar stem cells. Dclk1 is a marker of differentiated Tuft cells and, when coexpressed with Lgr5, also marks intestinal cancer stem cells. Here, we show that Elp3, the catalytic subunit of the Elongator complex, is required for Wnt-driven intestinal tumor initiation and radiation-induced regeneration by maintaining a subpool of Lgr5(+)/Dclk1(+)/Sox9(+) cells. Elp3 deficiency dramatically delayed tumor appearance in Apc-mutated intestinal epithelia and greatly prolonged mice survival without affecting the normal epithelium. Specific ablation of Elp3 in Lgr5(+) cells resulted in marked reduction of polyp formation upon Apc inactivation, in part due to a decreased number of Lgr5(+)/Dclk1(+)/Sox9(+) cells. Mechanistically, Elp3 is induced by Wnt signaling and promotes Sox9 translation, which is needed to maintain the subpool of Lgr5(+)/Dclk1(+) cancer stem cells. Consequently, Elp3 or Sox9 depletion led to similar defects in Dclk1(+) cancer stem cells in ex vivo organoids. Finally, Elp3 deficiency strongly impaired radiation-induced intestinal regeneration, in part because of decreased Sox9 protein levels. Together, our data demonstrate the crucial role of Elp3 in maintaining a subpopulation of Lgr5-derived and Sox9-expressing cells needed to trigger Wnt-driven tumor initiation in the intestine.

Nik promotes tissue destruction independently of the alternative nf-kappab pathway through tnfr1/rip1-induced apoptosis

Boutaffala L, Bertrand MJ, Remouchamps C, Seleznik G, Reisinger F, Janas M, Benezech C, Fernandes MT, Marchetti S, Mair F, Ganef C, Hupalowska A, Ricci JE, Becher B, Piette J, Knolle P, Caamano J, Vandennebeele P, Heikenwalder M, Dejardin E.

Cell Death & Differentiation. 2015;22:2020-2033

NF- κ B-inducing kinase (NIK) is well-known for its role in promoting p100/NF- κ B2 processing into p52, a process defined as the alternative, or non-canonical, NF- κ B pathway. Here we reveal an unexpected new role of NIK in TNFR1-mediated RIP1-dependent apoptosis, a consequence of TNFR1 activation observed in c-IAP1/2-depleted conditions. We show that NIK stabilization, obtained by activation of the non-death TNFRs Fn14 or LT β R, is required for TNF α -mediated apoptosis. These apoptotic stimuli trigger the depletion of c-IAP1/2, the phosphorylation of RIP1 and the RIP1 kinase-dependent assembly of the RIP1/FADD/caspase-8 complex. In the absence of NIK, the phosphorylation of RIP1 and the formation of RIP1/FADD/caspase-8 complex are compromised while c-IAP1/2 depletion is unaffected. In vitro kinase assays revealed that recombinant RIP1 is a bona fide substrate of NIK. In vivo, we demonstrated the requirement of NIK pro-death function, but not the processing of its substrate p100 into p52, in a mouse model of TNFR1/LT β R-induced thymus involution. In addition, we also highlight a role for NIK in hepatocyte apoptosis in a mouse model of virus-induced TNFR1/RIP1-dependent liver damage. We conclude that NIK not only contributes to lymphoid organogenesis, inflammation and cell survival but also to TNFR1/RIP1-dependent cell death independently of the alternative NF- κ B pathway.

Forskolin-free camp assay for gi-coupled receptors

Gilissen J, Geubelle P, Dupuis N, Laschet C, Pirotte B, Hanson J.

Biochemical Pharmacology. 2015;98:381-391

G protein-coupled receptors (GPCRs) represent the most successful receptor family for treating human diseases. Many are poorly characterized with few ligands reported or remain completely orphans. Therefore, there is a growing need for screening-compatible and sensitive assays. Measurement of intracellular cyclic AMP (cAMP) levels is a validated strategy for measuring GPCRs activation. However, agonist ligands for Gi-coupled receptors are difficult to track because inducers such as forskolin (FSK) must be used and are sources of variations and errors. We developed a method based on the GloSensor system, a kinetic assay that consists in a luciferase fused with cAMP binding domain. As a proof of concept, we selected the succinate receptor 1 (SUCNR1 or GPR91) which could be an attractive drug target. It has never been validated as such because very few ligands have been described. Following analyses of SUCNR1 signaling pathways, we show that the GloSensor system allows real time, FSK-free detection of an agonist effect. This FSK-free agonist signal was confirmed on other Gi-coupled receptors such as CXCR4. In a test screening on SUCNR1, we compared the results obtained with a FSK vs FSK-free protocol and were able to identify agonists with both methods but with fewer false positives when measuring the basal levels. In this report, we validate a cAMP-inducer free method for the detection of Gi-coupled receptors agonists compatible with high-throughput screening. This method will facilitate the study and screening of Gi-coupled receptors for active ligands.

A role for appl1 in tlr3/4-dependent tbk1 and ikkε activation in macrophages

Chau TL, Göktuna SI, Rammal A, Casanova T, Duong HQ, Gatot JS, Close P, Dejardin E, Desmecht D, Shostak K, Chariot A.

Journal of Immunology. 2015;194:3970-3983

Endosomes have important roles in intracellular signal transduction as a sorting platform. Signaling cascades from TLR engagement to IRF3-dependent gene transcription rely on endosomes, yet the proteins that specifically recruit IRF3-activating molecules to them are poorly defined. We show that adaptor protein containing a pleckstrin-homology domain, a phosphotyrosine-binding domain, and a leucine zipper motif (APPL)1, an early endosomal protein, is required for both TRIF- and retinoic acid-inducible gene 1-dependent signaling cascades to induce IRF3 activation. APPL1, but not early endosome Ag 1, deficiency impairs IRF3 target gene expression upon engagement of both TLR3 and TLR4 pathways, as well as in H1N1-infected macrophages. The IRF3-phosphorylating kinases TBK1 and IKKε are recruited to APPL1 endosomes in LPS-stimulated macrophages. Interestingly, APPL1 undergoes proteasome-mediated degradation through ERK1/2 to turn off signaling. APPL1 degradation is blocked when signaling through the endosome is inhibited by chloroquine or dynasore. Therefore, APPL1 endosomes are critical for IRF3-dependent gene expression in response to some viral and bacterial infections in macrophages. Those signaling pathways involve the signal-induced degradation of APPL1 to prevent aberrant IRF3-dependent gene expression linked to immune diseases.

Dusp3 genetic deletion confers m2-like macrophage-dependent tolerance to septic shock

Singh P, Dejager L, Amand M, Theatre E, Vandereyken M, Zurashvili T, Singh M, Mack M, Timmermans S, Musumeci L, Dejardin E, Mustelin T, Van Ginderachter JA, Moutschen M, Oury C, Libert C, Rahmouni S.

Journal of Immunology. 2015;194:4951-4962

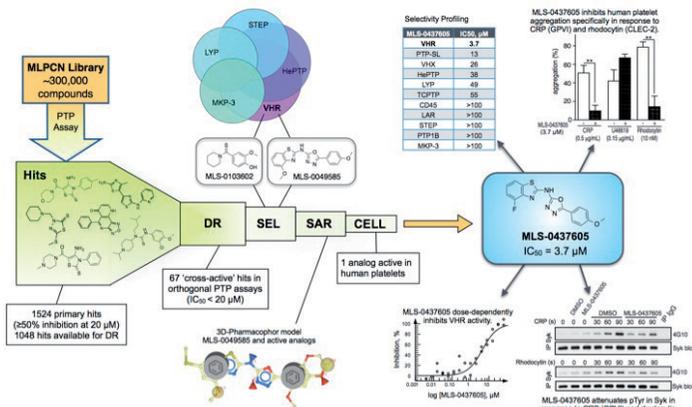
DUSP3 is a small dual-specificity protein phosphatase with an unknown physiological function. We report that DUSP3 is strongly expressed in human and mouse monocytes and macrophages, and that its deficiency in mice promotes tolerance to LPS-induced endotoxin shock and to polymicrobial septic shock after cecal ligation and puncture. By using adoptive transfer experiments, we demonstrate that resistance to endotoxin is macrophage dependent and transferable, and that this protection is associated with a striking increase of M2-like macrophages in DUSP3(-/-) mice in both the LPS and cecal ligation and puncture models. We show that the altered response of DUSP3(-/-) mice to sepsis is reflected in decreased TNF production and impaired ERK1/2 activation. Our results demonstrate that DUSP3 plays a key and nonredundant role as a regulator of innate immune responses by mechanisms involving the control of ERK1/2 activation, TNF secretion, and macrophage polarization.

Dual-specificity phosphatase 3 deficiency or inhibition limits platelet activation and arterial thrombosis

Musumeci L, Kuijpers MJ, Gilio K, Hego A, Theatre E, Maurissen L, Vandereyken M, Diogo CV, Lecut C, Guilmain W, Bobkova EV, Eble JA, Dahl R, Drion P, Rascon J, Mostofi Y, Yuan H, Sergienko E, Chung TD, Thiry M, Senis Y, Moutschen M, Mustelin T, Lancellotti P, Heemskerck JW, Tautz L*, Oury C*, Rahmouni S*. *these authors contributed equally to the work

Circulation. 2015;131:656-668

A limitation of current antiplatelet therapies is their inability to separate thrombotic events from bleeding occurrences. A better understanding of the molecular mechanisms leading to platelet activation is important for the development of improved therapies. Recently, protein tyrosine phosphatases have emerged as critical regulators of platelet function. This is the first report implicating the dual-specificity phosphatase 3 (DUSP3) in platelet signaling and thrombosis. This phosphatase is highly expressed in human and mouse platelets. Platelets from DUSP3-deficient mice displayed a selective impairment of aggregation and granule secretion mediated by the collagen receptor glycoprotein VI and the C-type lectin-like receptor 2. DUSP3-deficient mice were more resistant to collagen- and epinephrine-induced thromboembolism compared with wild-type mice and showed severely impaired thrombus formation on ferric chloride-induced carotid artery injury. Intriguingly, bleeding times were not altered in DUSP3-deficient mice. At the molecular level, DUSP3 deficiency impaired Syk tyrosine phosphorylation, subsequently reducing phosphorylation of phospholipase Cy2 and calcium fluxes. To investigate DUSP3 function in human platelets, a novel small-molecule inhibitor of DUSP3 was developed. This compound specifically inhibited collagen- and C-type lectin-like receptor 2-induced human platelet aggregation, thereby phenocopying the effect of DUSP3 deficiency in murine cells. DUSP3 plays a selective and essential role in collagen- and C-type lectin-like receptor 2-mediated platelet activation and thrombus formation in vivo. Inhibition of DUSP3 may prove therapeutic for arterial thrombosis. This is the first time a protein tyrosine phosphatase, implicated in platelet signaling, has been targeted with a small-molecule drug.



Development of a VHR/DUSP3-specific inhibitor. High-throughput screening steps followed by dose-response hit confirmation assays and selectivity profiling experiments (SEL) against additional PTPs (HePTP, STEP, LYP, and MKP-3) led to the identification of MLS-0437605 compound as a highly specific DUSP3 inhibitor. MLS-0437605 inhibited specifically human platelets activation and subsequent signalling in response to GPVI and CLEC-2, but not to G-coupled receptors, agonist stimulation, thereby phenocopying the effect of DUSP3 deficiency on mouse platelets. Selectivity to DUSP3 was evaluated against a total of 10 recombinant PTPs and on DUSP3-deficient platelets (not shown).

Awards

Alain Chariot, whose previous project was also selected in the first call of WELBIO, gets a «Grant Senior» from the FRFS (Fonds de la Recherche Fondamentale Stratégique) in the framework of the FRFS-WELBIO-2015 call for the project «Dissecting oncogenic pathways» - see page 89.

GIGA-Systems Biology & Chemical Biology

The Systems Biology and Chemical Biology thematic research unit at GIGA aims to make advances in the fields of Systems Biology and Chemical Biology and to foster synergies between both. On one hand, the unit is heavily involved in developing improved data acquisition techniques and experimental work (e.g., in proteomics). On the other hand, it has a strong component in data analysis and complex data modeling (e.g., in genomics). In particular, the machine learning and bioimage informatics group's general research interest is the design and analysis of machine learning, optimization, and simulation techniques and their applications in various domains including life sciences, computer vision, electrical energy systems, and computer networks. The group's methodological effort focuses in particular on the development of scalable and interpretable methods for analyzing large volumes of heterogeneous and structured data. Applications in computational and systems biology include biomarker discovery, data integration for biological network inference, in-silico prediction of functional and structural properties of proteins, and bioimage informatics, i.e., the development and application of computational methods for the exploration and quantification of high-throughput imaging data. As part of this research effort, the group also delivers user-friendly, mostly open-source, software solutions implementing the developed methods. The BIO3 group leverages a systems approach to exploit the recent explosion of information in medicine. Its goal is to create a cohesive group bringing together diverse life science scientists. The theoretic component of BIO3's mission is to make significant methodological contributions to statistical genetics and systems genetics. The applied component of BIO3's mission is to help biomedical researchers carrying out their investigations and contributing to their data analysis. Its current interests lie in computational/statistical approaches to unravel the genotype–phenotype map on a genome-wide scale and in developing novel methods in statistical genetics for improved interactome analyses, stratified omics for precision medicine, and multi-omics meta-analyses, hereby addressing adequate handling of different sources of “noise” and “heterogeneity”.



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- ▶ BIO3 – Systems Genetics at the intersection of Biostatistics, Biomedicine and Bioinformatics
Kristel Van Steen
- ▶ Laboratory of Mass Spectrometry
Edwin De Pauw
- ▶ Laboratory of Mammalian Cell Culture
Marie-Claire Gillet-De Pauw
- ▶ Laboratory of Systems and Modeling - Machine learning and bioimage informatics
Louis Wehenkel, Pierre Geurts
Raphael Marée
- ▶ Laboratory of Molecular Biomimetic and Protein Engineering
Cécile Van de Weerd

People

20 Scientists

10 PhD Students

4 Technicians



53%



47%

Integration analysis of three omics data using penalized regression methods: an application to bladder cancer

Pineda S, Real FX, Kogevinas M, Carrato A, Chanock SJ, Malats N, Van Steen K.

PLoS Genetics. 2015;11:e1005689

Omics data integration is becoming necessary to investigate the genomic mechanisms involved in complex diseases. During the integration process, many challenges arise such as data heterogeneity, the smaller number of individuals in comparison to the number of parameters, multicollinearity, and interpretation and validation of results due to their complexity and lack of knowledge about biological processes. To overcome some of these issues, innovative statistical approaches are being developed. In this work, we propose a permutation-based method to concomitantly assess significance and correct by multiple testing with the MaxT algorithm. This was applied with penalized regression methods (LASSO and ENET) when exploring relationships between common genetic variants, DNA methylation and gene expression measured in bladder tumor samples. The overall analysis flow consisted of three steps: (1) SNPs/CpGs were selected per each gene probe within 1Mb window upstream and downstream the gene; (2) LASSO and ENET were applied to assess the association between each expression probe and the selected SNPs/CpGs in three multivariable models (SNP, CPG, and Global models, the latter integrating SNPs and CPGs); and (3) the significance of each model was assessed using the permutation-based MaxT method. We identified 48 genes whose expression levels were significantly associated with both SNPs and CPGs. Importantly, 36 (75%) of them were replicated in an independent data set (TCGA) and the performance of the proposed method was checked with a simulation study. We further support our results with a biological interpretation based on an enrichment analysis. The approach we propose allows reducing computational time and is flexible and easy to implement when analyzing several types of omics data. Our results highlight the importance of integrating omics data by applying appropriate statistical strategies to discover new insights into the complex genetic mechanisms involved in disease conditions.

Classifying pairs with trees for supervised biological network inference

Schrynemackers M, Wehenkel L, Babu MM, Geurts P.

Molecular Biosystems. 2015;1(8): 2116–2125

Networks are ubiquitous in biology, and computational approaches have been largely investigated for their inference. In particular, supervised machine learning methods can be used to complete a partially known network by integrating various measurements. Two main supervised frameworks have been proposed: the local approach, which trains a separate model for each network node, and the global approach, which trains a single model over pairs of nodes. Here, we systematically investigate, theoretically and empirically, the exploitation of tree-based ensemble methods in the context of these two approaches for biological network inference. We first formalize the problem of network inference as a classification of pairs, unifying in the process homogeneous and bipartite graphs and discussing two main sampling schemes. We then present the global and the local approaches, extending the latter for the prediction of interactions between two unseen network nodes, and discuss their specializations to tree-based ensemble methods, highlighting their interpretability and drawing links with clustering techniques. Extensive computational experiments are carried out with these methods on various biological networks that clearly highlight that these methods are competitive with existing methods.

Combined use of ion mobility and collision-induced dissociation to investigate the opening of disulfide bridges by electron-transfer dissociation in peptides bearing two disulfide bonds

Massonnet P, Upert G, Smargiasso N, Gilles N, Quinton L, De Pauw E.

Analytical Chemistry. 2015;87:5240-5246

Disulfide bonds are post-translational modifications (PTMs) often found in peptides and proteins. They increase their stability toward enzymatic degradations and provide the structure and (consequently) the activity of such folded proteins. The characterization of disulfide patterns, i.e., the cysteine connectivity, is crucial to achieve a global picture of the active conformation of the protein of interest. Electron-transfer dissociation (ETD) constitutes a valuable tool to cleave the disulfide bonds in the gas phase, avoiding chemical reduction/alkylation in solution. To characterize the cysteine pairing, the present work proposes (i) to reduce by ETD one of the two disulfide bridges of model peptides, resulting in the opening of the cyclic structures, (ii) to separate the generated species by ion mobility, and (iii) to characterize the species using collision-induced dissociation (CID). Results of this strategy applied to several peptides show different behaviors depending on the connectivity. The loss of SH[•] radical species, observed for all the peptides, confirms the cleavage of the disulfides during the ETD process.

Evaluation of a class of polyurethane materials for intraocular lens manufacturing Inc.

Bozukova D, Bertrand V, Pagnouille C, De Pauw-Gillet M-C.

Journal of Biomedical Materials Research Part B: Applied Biomaterials. 103B: 1274-1286, 2015.

Ophthalmic lenses are medical devices with considerable requirements in terms of optical, biomechanical and biological performance. There is limited number of materials used for their manufacturing, comprising mainly silicones and poly(meth)acrylates. This series of publications aims at investigating the applicability of thermoplastic polyurethane elastomers (TPU) for the manufacturing of ophthalmic lenses and examining the properties of the respective devices. This study is related to the synthesis of TPUs with chemical compositions that comprise chemically grafted filters for the hazardous-light. GC-MS, attenuated total reflectance Fourier transform infrared spectroscopy, and UV-vis spectroscopies confirmed the reaction completion and the beneficial effect of the filters on the light transmittance, respectively. Relatively high refractive index of the material was measured and allows for the manufacturing of thinner lenses. The contrast sensitivity determined for a model intraocular lens (IOL) was satisfactory. Few optical defects were, however, present on the model lens prepared by thermoplastic injection molding. The elasticity of the materials was evaluated in view to their potential applicability as foldable IOLs by determining their glass transition temperature and their Young modulus and measuring their shore A. The TPU materials demonstrated more bioadhesive character compared with a benchmark hydrophilic acrylic reference material, which is already used for IOL manufacturing.

Letter to the Editor: On the term 'interaction' and related phrases in the literature on Random Forests

Boulesteix AL, Janitza S, Hapfelmeier A, Van Steen K, Strobl C.

Briefings in Bioinformatics. 2015;16(2): 338-345.

In an interesting and quite exhaustive review on Random Forests (RF) methodology in bioinformatics Touw et al. address --among other topics-- the problem of the detection of interactions between variables based on RF methodology. We feel that some important statistical concepts, such as 'interaction', 'conditional dependence' or 'correlation', are sometimes employed inconsistently in the bioinformatics literature in general and in the literature on RF in particular. In this letter to the Editor, we aim to clarify some of the central statistical concepts and point out some confusing interpretations concerning RF given by Touw et al. and other authors.

GIGA-Coma Science Group

The Coma Science Group assesses the recovery of neurological disability and of neuronal plasticity in severely brain damaged patients with altered states of consciousness by means of multimodal functional neuroimaging. It aims at characterizing the brain structure and the residual cerebral function in patients who survive a severe brain injury: patients in coma, vegetative state, minimally conscious state and locked-in syndrome. The importance of this project is twofold. First, these patients represent a problem in terms of diagnosis, prognosis, treatment and daily management. Second, these patients offer the opportunity to explore human consciousness, which is presently one major conundrum neurosciences have to solve. Indeed, these patients present a complete, nearly graded, range of conscious states from unconsciousness (coma) to full awareness (locked-in syndrome). Our research confronts clinical expertise and bedside behavioral evaluation of altered states of consciousness with state-of-the-art multimodal imaging combining the information from positron emission tomography (PET), functional magnetic resonance imaging (fMRI), structural MRI, electroencephalography (EEG) and event related potential (ERP) data.



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People

9 Clinicians

10 Neuropsychologists

2 Physiotherapists

1 Biologist

3 Engineers

2 Physicians

1 Nurse



41%



59%

Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients

Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los Angeles C, Bahri MA, Di Perri C, Vanhaudenhuyse A, Charland-Verville V, Kronbichler M, Trinka E, Phillips C, Gomez F, Tshibanda L, Soddu A, Schiff ND, Whitfield-Gabrieli S, Laureys S. **Brain.** 2015;138:2619-2631

Despite advances in resting state functional magnetic resonance imaging investigations, clinicians remain with the challenge of how to implement this paradigm on an individualized basis. Here, we assessed the clinical relevance of resting state functional magnetic resonance imaging acquisitions in patients with disorders of consciousness by means of a systems-level approach. Three clinical centres collected data from 73 patients in minimally conscious state, vegetative state/unresponsive wakefulness syndrome and coma. The main analysis was performed on the data set coming from one centre (Liège) including 51 patients (26 minimally conscious state, 19 vegetative state/unresponsive wakefulness syndrome, six coma; 15 females; mean age 49 ± 18 years, range 11-87; 16 traumatic, 32 non-traumatic of which 13 anoxic, three mixed; 35 patients assessed >1 month post-insult) for whom the clinical diagnosis with the Coma Recovery Scale-Revised was congruent with positron emission tomography scanning. Group-level functional connectivity was investigated for the default mode, frontoparietal, salience, auditory, sensorimotor and visual networks using a multiple-seed correlation approach. Between-group inferential statistics and machine learning were used to identify each network's capacity to discriminate between patients in minimally conscious state and vegetative state/unresponsive wakefulness syndrome. Data collected from 22 patients scanned in two other centres (Salzburg: 10 minimally conscious state, five vegetative state/unresponsive wakefulness syndrome; New York: five minimally conscious state, one vegetative state/unresponsive wakefulness syndrome, one emerged from minimally conscious state) were used to validate the classification with the selected features. Coma Recovery Scale-Revised total scores correlated with key regions of each network reflecting their involvement in consciousness-related processes. All networks had a high discriminative capacity (>80%) for separating patients in a minimally conscious state and vegetative state/unresponsive wakefulness syndrome. Among them, the auditory network was ranked the most highly. The regions of the auditory network which were more functionally connected in patients in minimally conscious state compared to vegetative state/unresponsive wakefulness syndrome encompassed bilateral auditory and visual cortices. Connectivity values in these three regions discriminated congruently 20 of 22 independently assessed patients. Our findings point to the significance of preserved abilities for multisensory integration and top-down processing in minimal consciousness seemingly supported by auditory-visual crossmodal connectivity, and promote the clinical utility of the resting paradigm for single-patient diagnostics.

Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine

Sarasso S, Boly M, Napolitani M, Gosseries O, Charland-Verville V, Casarotto S, Rosanova M, Casali AG, Bricchant JF, Boveroux P, Rex S, Tononi G, Laureys S, Massimini M. **Current Biology.** 2015;25:3099-3105

A common endpoint of general anesthetics is behavioral unresponsiveness [1], which is commonly associated with loss of consciousness. However, subjects can become disconnected from the environment while still having conscious experiences, as demonstrated by sleep states associated with dreaming [2]. Among anesthetics, ketamine is remarkable [3] in that it induces profound unresponsiveness, but subjects often report «ketamine dreams» upon emergence from anesthesia [4-9]. Here, we aimed at assessing consciousness during anesthesia with propofol, xenon, and ketamine, independent of behavioral responsiveness. To do so, in 18 healthy volunteers, we measured the complexity of the cortical response to transcranial magnetic stimulation (TMS)—an approach that has proven helpful in assessing objectively the level of consciousness irrespective of sensory processing and motor responses [10]. In addition, upon emergence from anesthesia, we collected reports about conscious experiences during unresponsiveness. Both frontal and parietal TMS elicited a low-amplitude electroencephalographic (EEG) slow wave corresponding to a local pattern of cortical activation with low complexity during propofol anesthesia, a high-amplitude EEG slow wave corresponding to a global, stereotypical pattern of cortical activation with low complexity during xenon anesthesia, and a wakefulness-like, complex spatiotemporal activation pattern during ketamine anesthesia. Crucially, participants reported no conscious experience after emergence from propofol and xenon anesthesia, whereas after ketamine they reported long, vivid dreams unrelated to the external environment. These results are relevant because they suggest that brain complexity may be sensitive to the presence of disconnected consciousness in subjects who are considered unconscious based on behavioral responses.

GIGA-Platforms



GIGA-Platforms

Access to unique technological equipment for research and innovation is challenging, given to their cost and growing expertise they require. Considering the rapid evolution of technologies and the necessary expertise to meet increasingly sophisticated requests, it is essential to gather in a single structure all equipment and optimize their use. This model has already been successfully applied in major international research centers. As a pioneer in the Walloon Region, GIGA has been part of this dynamic since 2007, using structural funds (ERDF : European Regional Development Fund) to prime the pump. High quality equipment and expertise have been integrated into so called GIGA-Technology Platforms ensuring optimal use and accessibility for scientists coming either from academy or industry. The ERDF 2007-2014 program which ended in December 2015, has substantially improved the technology offer, leading to a great dynamic between all actors of the biomedical sector. These interactions will be further amplified thanks to the next ERDF program (2015-2020) that will strongly support the platforms, ensuring acquisitions of state-of-the art technologies and reinforcing the platforms teams.

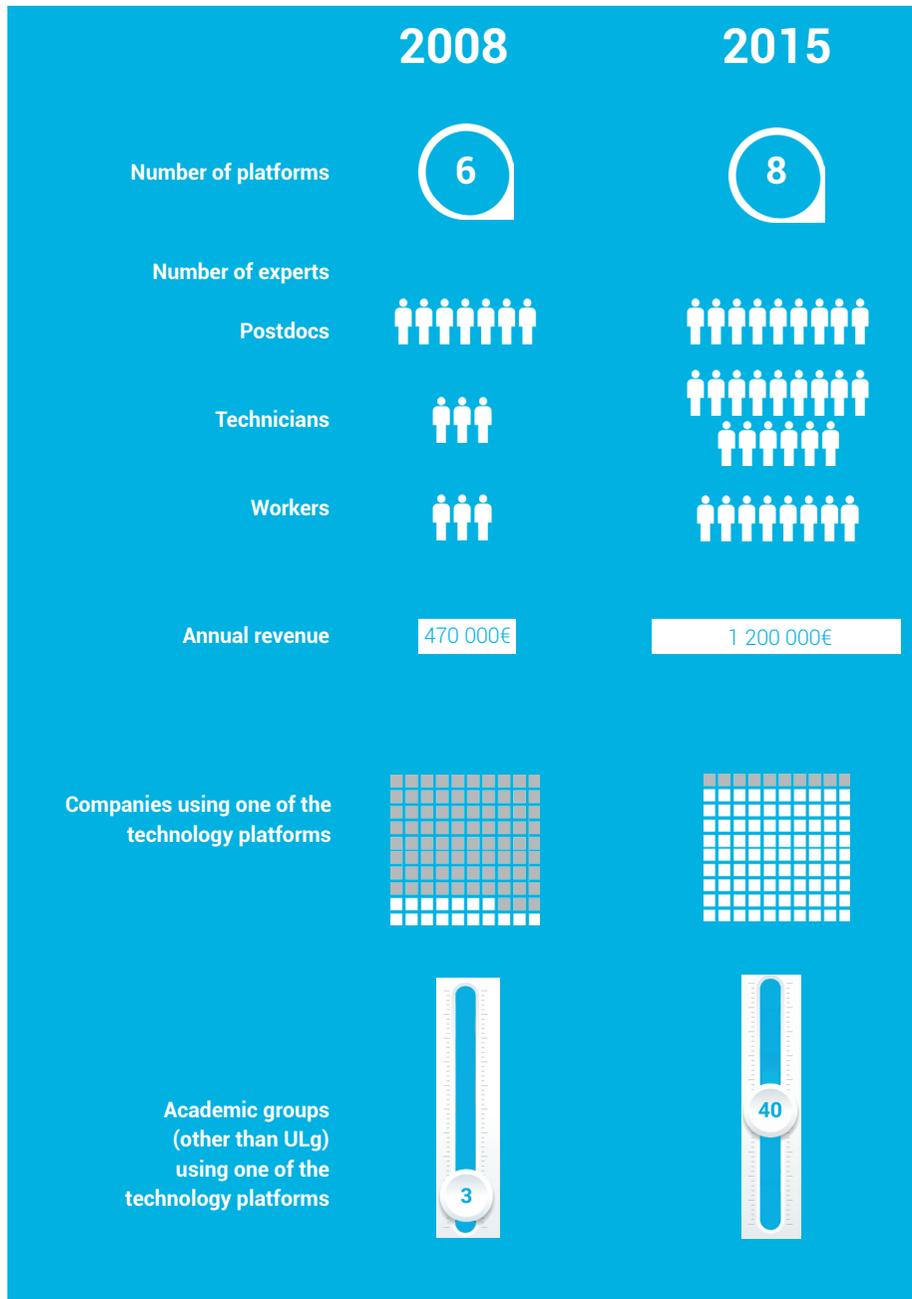


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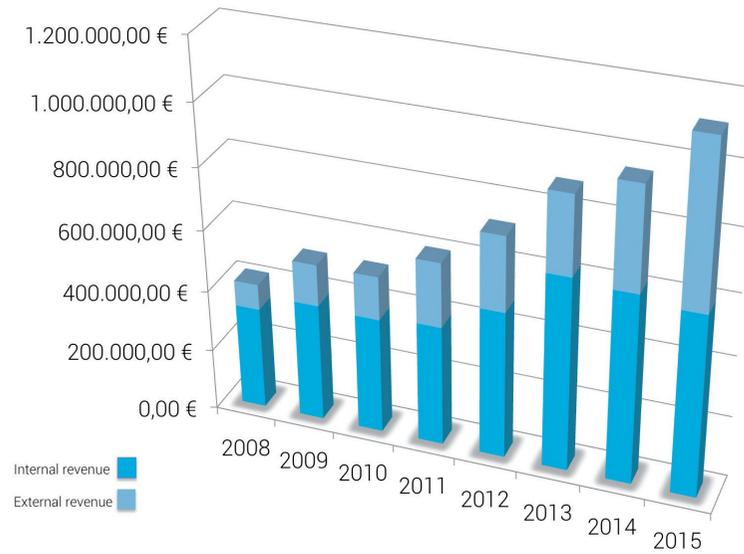
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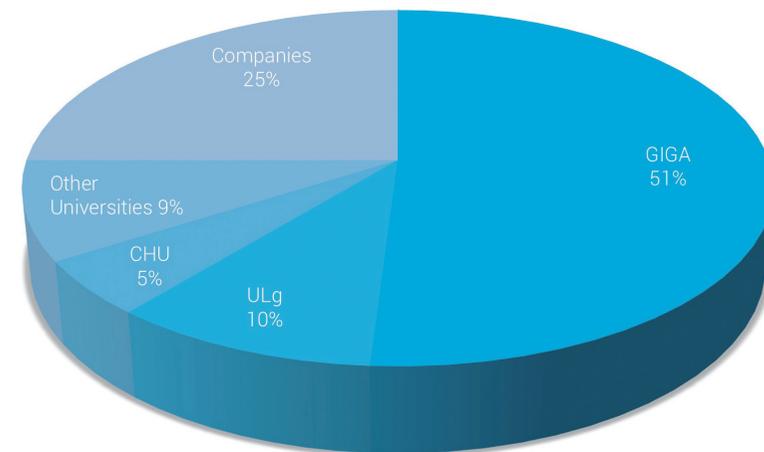
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Total revenue 2008-2015 (Mice Facility excepted)



Revenue since 2012 (Mice Facility excepted)



GIGA-Genomics

End of 2014, the genomics platform acquired a new high throughput DNA sequencer. This Illumina NextSeq500 is capable of generating up to 120 gigabases in 29 hours. The number of DNA fragments sequenced in only one run is 400 million, making it very well suited for RNA sequencing. As a result, RNA sequencing has become our method of choice to perform transcriptome profiling. Using RNA-seq adds an extra layer of information in the exploration of the transcriptome. For instance, RNA isoforms profiling, promotor usage, detection of novel transcripts, all at a high dynamic range become possible. In 2015, this new equipment was fully deployed. A total 67 flow cells were run on the new sequencer, generating exome and whole genome data, also methylation profile and RNA-seq data. In 2015, the 16S bacterial genomics has been expanding rapidly on the Illumina MiSeq with more than one run a week, adding up to a total of more than 6000 samples analyzed. Sample types can be very diverse and range from food samples to environmental and ecological samples. In addition to this new equipment, the genomics team has also been growing steadily. A total of 10 persons (12 in 2016) are now providing services from sanger sequencing to high throughput sequencing. Although high throughput sequencing is gaining more and more importance in generation of genomic data, an important part of the activity of the genomics platform is still using high density DNA arrays to generate big data at very low cost and high throughput.



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Publications

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FACTS

10 432 NGS Sequencing

15 986 Sanger Sequencing

55 434 Genotyping

960 Methylation

GIGA-Proteomics

Since 2013, the proteomics platform provides routine analysis on a quadrupole-orbitrap instrument from Thermo Scientific bought thanks to FEDER funds: the Q Exactive. The main advantages of Q Exactive instrument are the high mass resolution and high mass accuracy obtained in a time-scale compatible with UPLC separations. At the beginning, only multi-enzymatic digestion analyses for maximum protein sequence coverage were run in routine on this instrument. Its performances enable not only to obtain better results on sequence homology database searches but also in combination with multi-enzymatic digestion performing de novo sequencing: a hot topic in the mass spectrometry field and necessary for validation of protein production batches. Since 2014, the Proteomics platform has switched the label-free differential proteomics analyses from the Synapt G2 HDMS (data independent analysis - DIA) to the Q Exactive (data dependent analysis - DDA). Indeed, a comparative study done on serum showed that we obtained a 30% increase in the number of identified proteins with Q Exactive (Poster presented at ASMS Conference 2013). Based on these results and the fact that for data dependent analysis, Open Source softwares can deal with the processing of data, we advised our customers to perform their new differential studies on Q Exactive. In 2014, we did 51 differential analyses on Synapt G2 and 58 on Q Exactive. In 2015, waiting times of about 2 months between receipt of the samples and time slot on the instrument for samples injection were problematic! So in order to decrease these delays for researchers and companies and to allow more people to have access to this technology but also to provide some instrument time slots for future developments, the Mass Spectrometry Laboratory invested in a second Q Exactive and granted a privileged access to the Proteomics Facility. In June 2015, the Q Exactive Plus, back-up instrument for Q Exactive, was installed. Since the waiting time is around 15 days for routine identification analyses and around one month for differential label-free proteomics analysis which requires longer time slot.

Having these 2 orbitrap instruments allowed in 2015:

- 180 label-free differential analyses (2D-LC separation – 10 hours per run)
- 250 1D-LC-MS/MS runs for identification of proteins in less complex mixtures
- Development of differential label-free proteomics on micro-dissected tissue pieces as small as 3000 cells! Around 1000 proteins can be identified with 3000 cells (more information in the paper of Longuespée et al. in Methods 2016, In Press). This analysis is already used in specific research programs with GIGA-R collaborating teams and will be proposed as a service by the platform by mid-2016!
- Development of coupling a Capillary Electrophoresis separation instrument to the Q Exactive for Top Down Proteomics. This type of analysis is of interest for biopharmaceutical companies.



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Publications

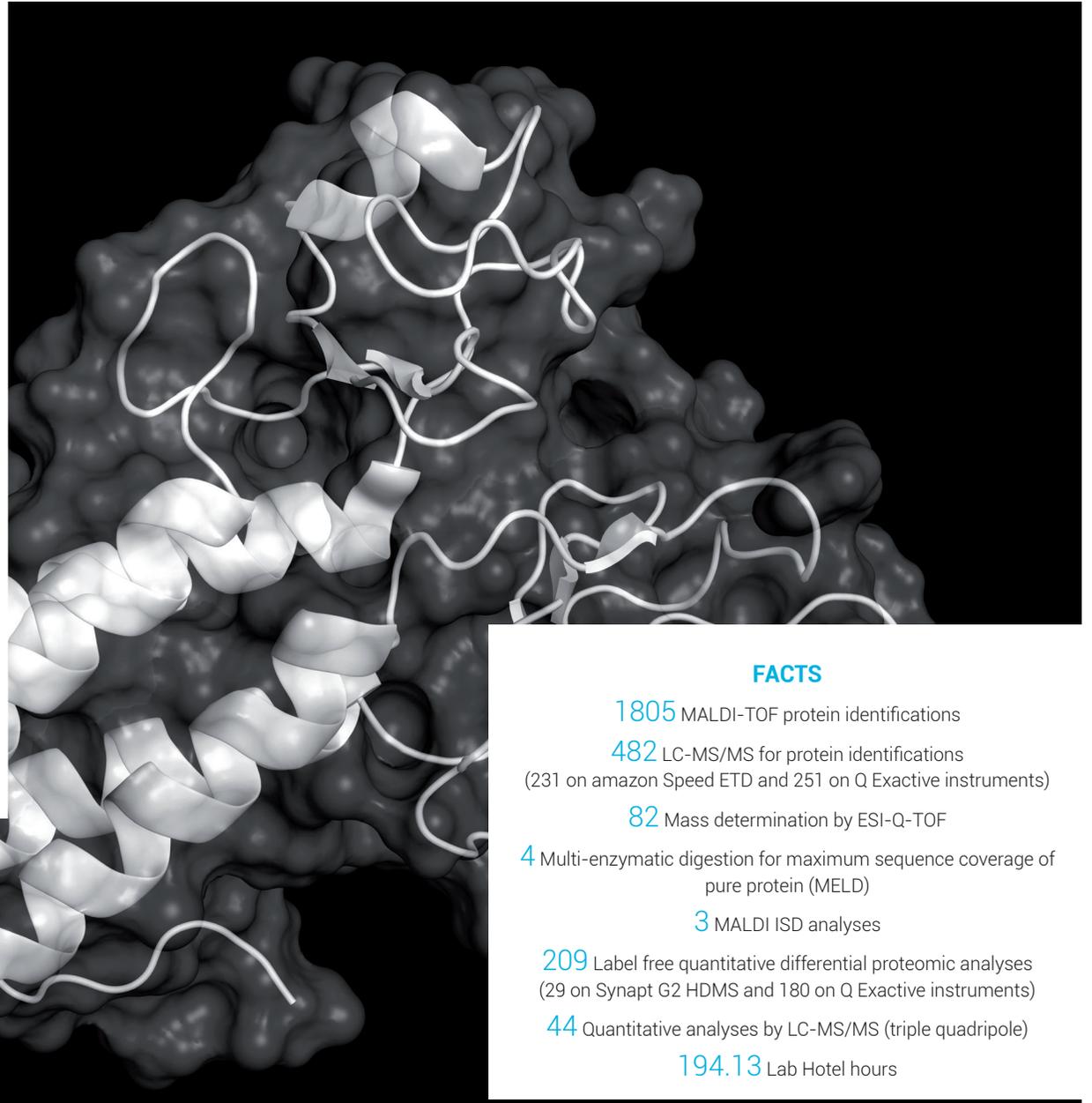
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FACTS

1805 MALDI-TOF protein identifications

482 LC-MS/MS for protein identifications
(231 on amazon Speed ETD and 251 on Q Exactive instruments)

82 Mass determination by ESI-Q-TOF

4 Multi-enzymatic digestion for maximum sequence coverage of pure protein (MELD)

3 MALDI ISD analyses

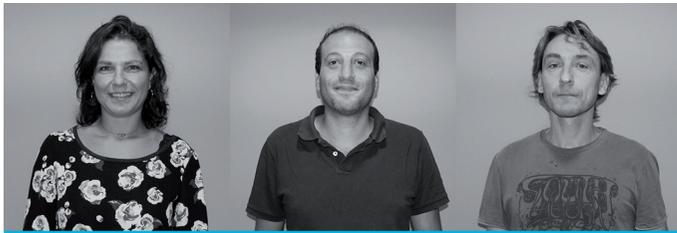
209 Label free quantitative differential proteomic analyses
(29 on Synapt G2 HDMS and 180 on Q Exactive instruments)

44 Quantitative analyses by LC-MS/MS (triple quadripole)

194.13 Lab Hotel hours

GIGA-Cell Imaging & Flow Cytometry

Over the last decade, Confocal imaging and flow cytometry have become essential for most biomedical research programs. Quite complex technologies, they allow for the fast and accurate study of molecules at the cellular level. Through detection using fluorochrome-coupled molecules emitting at different wavelengths, confocal microscopy can simultaneously highlight a large number of fluorochromes and can extremely precisely determine intracellular localization. Thanks to thermostated chambers built on the microscopes, the cells can be maintained alive in optimal conditions, which allows to record sequential images and track over time the subcellular localization of a protein of interest or the behavior of cells in response to a stimulus over time. Flow cytometry allows qualitative and quantitative analysis of particles, for example monodispersed cells that have been marked with fluorescent probes targeting very diverse molecules such as membrane antigens, cytokines, nucleic acids, viral receptors, calcium ions.... The technique, which allows the analysis of blood cells, cells isolated from tissue or from a cell line or any particles larger than one micron (platelets, bacteria, yeast...), is an essential tool, not only for the simultaneous detection of several molecules of interest, but also for the study of cell cycle, cell ploidy, cell proliferation, DNA damage or cell viability. Recent developments using microbeads specifically recognizing soluble molecules allow to detect and quantify from biological fluids or culture media, molecules such as immunoglobulins or cytokines involved in the inflammatory response and signaling pathways, in biological fluids or culture media. Sorter flow cytometers can also clone cells or sort up to 4 cell populations simultaneously, under sterile conditions. Technologies such as high throughput imaging or laser microdissection are also available in the Cell Imaging and Flow Cytometry platform.



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New equipment and upgrades in 2015

In September 2015, the GIGA Cell Imaging core facility acquired a new super resolution confocal microscope : the LSM 880 AiryScan Elyra S.1 (Zeiss). This microscope pushes the sensitivity beyond the limits of all conventional confocal microscopes that belong to our core facility. Indeed, with the Airyscan technology, Zeiss introduces a new concept : instead of throwing light away at the pinhole, a 32 channel area detector collects all light of an Airy pattern simultaneously. Each detector element functions as a single, very small pinhole. This enables a very light-sensitive imaging since all of the photons that the objective collected can now be used. Moreover, with the LSM 880, the researcher can achieve up to 13 frames per second at 512 x 512 pixels. With the option called «Elyra S.1» that has been set on the LSM 880 microscope, this microscope is also able to do super resolution structured illumination (SR-SIM) : therefore it is now possible to image fine structural details while remaining free to label the samples with conventional dyes. Indeed, «Elyra S.1» images any fluorophore – with up to twice the resolution of a conventional light microscope.

At the end of the year 2015, the Nikon A1R confocal microscope belonging to the Cell Imaging core facility has been upgraded with a new 16.25 megapixel monochrome camera that perfectly captures low light fluorescence and large fields of view (36 mm X 23,9 mm). This camera features high pixel density, high sensitivity and ultra-low noise, making it an excellent choice for applications in quantitative fluorescence imaging. With a linearity error of $\pm 1\%$, this new camera is a superb tool for measuring intensities in fluorescence samples. Moreover, it enables high-speed live imaging and image capture at up to 45 fps (1636x1088 pixels) and allows fluorescent time-lapse imaging through integration with the NIS-Elements software.

During the year 2015, the decision to purchase a new high performance multi-color flow cytometer was taken. This new FACS analyser will be installed and operational by the half of 2016.



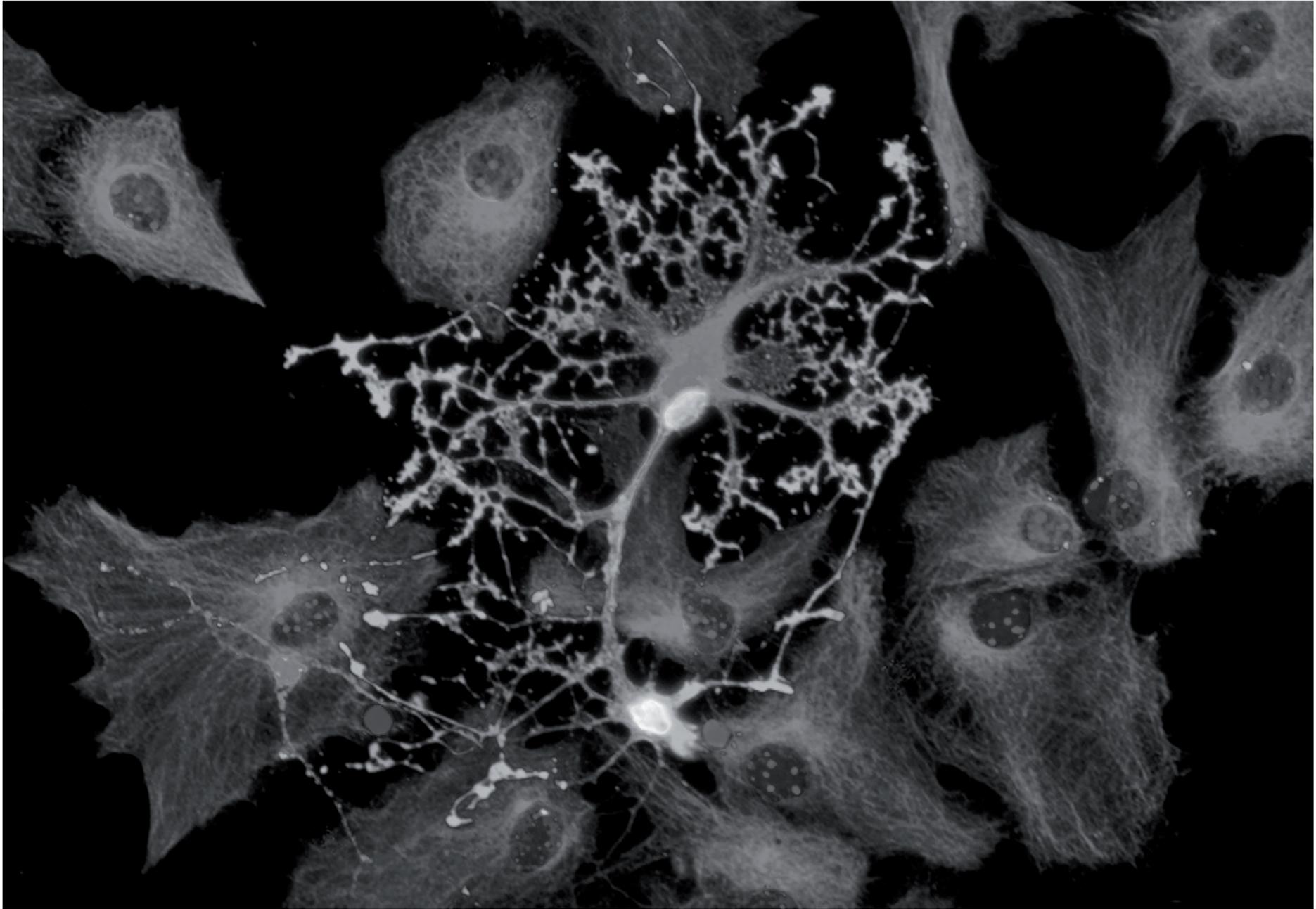
Users' opinions

"Over the last two decades, science has been spectacularly evolving in many ways. One of its most impressive evolutions is without a doubt the expansion of high-tech techniques which are powerful tools for the scientists. Professional use of these tools requires access to up-to-date platforms and to the know-how required to use them properly. At the University of Liège, we are very lucky to have access to the PF of Cell Imaging of the GIGA. The equipment and the know-how provided have been a great help in the development of many of our research projects. Thanks!"

Pr Alain Vanderplasschen, FARAHA, Faculty of Veterinary Medicine, University of Liège

"For our young biotech startup - AmplyCell - to benefit from the latest high-tech innovations represents a major advantage for our development. The "GIGA Cell Imaging and Flow Cytometry platform" has allowed us to dramatically increase the number of processed samples thanks to the high-throughput cell sorting capacity of the flow cytometry technology. The dedication and expert knowledge of the platform managers were really helpful to perform our experiments allowing us to save valuable time during our bioprocess. We have now established a trusty relationship that should continue throughout our future projects".

Maximilien Fléron, Chief – Boosting – Science Officer, AmplyCell S.A.



Publications

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FACTS

- 1616 Confocal analyses
- 19 Confocal time-lapse acquisitions
- 551 Epifluorescence analyses
- 1946 Flow cytometry analyses
- 491 Cell sorting
- 8 High content screening analyses
- 42 Multiplex Immunoassays
- 19 Laser microdissections
- 255 Users
- 73 Research groups

GIGA-Viral Vectors

Created in 2012, the Viral Vector platform produces customized viral vectors whose production requires to work in Biosafety 2 or 3 labs (BSL2 or BSL3). This platform also trains ULg scientists who need to work in the BSL2 or BSL3 (A3) laboratories of the GIGA. This allows scientists to work into a safe environment with different virus or viral vectors in accordance with biosafety rules.

The different services proposed in this GIGA Viral vectors platform are:

1. Viral plasmid design: Our staff can help you for the design and the cloning into viral vector plasmids or we can also advise you in choosing the best plasmid manufacturer.
2. Maxiprep service: Once the viral plasmid is designed, the platform offers a service for plasmid amplification and purification (+ storage >2 years). Our plasmids are produced using Promega purification kit that guarantee Endotoxin –free plasmids. Plasmids are then filtered through 0.1 μ M filter in order to avoid mycoplasma contamination.
3. Viral vector production: These plasmids are used for production of overexpression vectors (universal, specific or inducible promoters, multicistronic constructs , tagged vectors, ...), imaging Vectors (eGFP, Luciferase, RFP, mCherry, BFP), RNA interference vectors (shRNA RNAi-vectors polIII-dependent promoters or inducible promoters) and CRISPR/cas9 for stable knock-down. These viral vectors are produced within two weeks.
 - Lentiviral vectors: Co-transfection with minimum 3 different plasmids is used to produce non-replication competent retroviral particles (non-RCR), this technique narrows the chance of recombination between the plasmids and prevents the production of hypothetical wild type viruses. A titration is performed by RTqPCR and a titer of a minimum $1E+08$ transduction units per milliliters (TU/mL) in a volume of 300 μ L is obtained. The platform has also developed lentiviral vectors combined to Cas9/CRISPR technology and we are members of SIGMA core partnership. This technology is specifically designed to generate a knockdown or a point mutation in on both alleles through an homologous recombination. Your lentiviral CRISPR vectors can be also non-integrative. This allows a short time expression of Cas9 and guide RNA without random genome integration.
 - recombinant Adeno Associated Virus (rAAV) vectors: AAV are not currently known to cause human disease and consequently AAV lead to a very mild immune response. rAAV can transduce both dividing and non-dividing cells. Those rAAV vectors are specifically designed to allow an overexpression (or inhibition) of the gene of interest without DNA integration into host genome. A titration is performed by RT-qPCR (100 μ L, $>1E+12$ GC/mL) or by FACS analysis.
4. Cells transduction: The platform also transduce your specific cells with these viral vectors. After selection and an amplification of the transduced cells, supernatants are checked for absence of recombinant viral vectors (which allows using cells into BSL1) and mycoplasma. The entire process takes approximately 4 weeks. All the produced vectors and cells can be used in vitro and in vivo (in animals).



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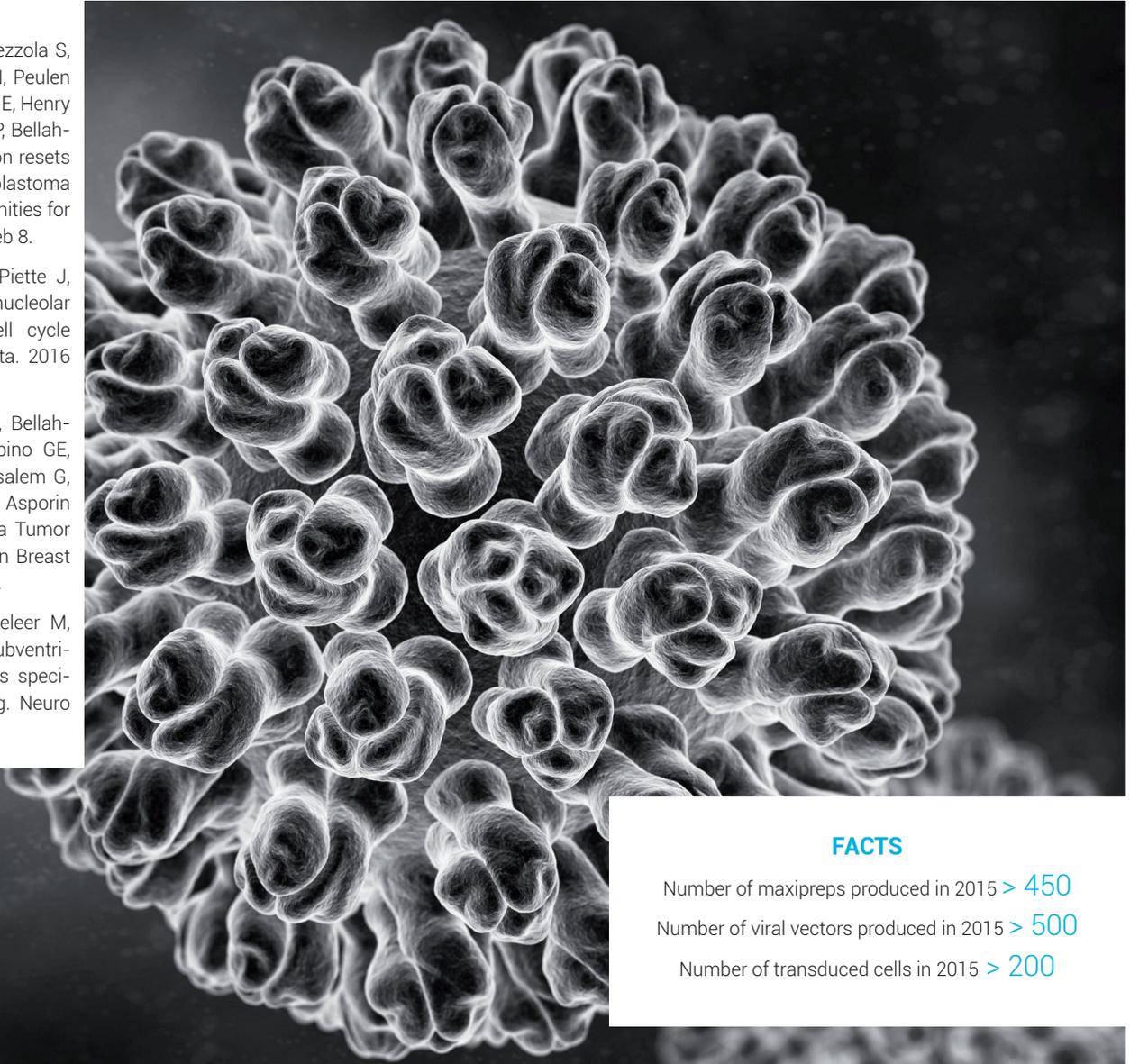
Publications

Peixoto P, Blomme A, Costanza B, Ronca R, Rezzola S, Palacios AP, Schoysman L, Boutry S, Goffart N, Peulen O, Maris P, Di Valentin E, Hennequière V, Bianchi E, Henry A, Meunier P, Rogister B, Muller RN, Delvenne P, Bellahcène A, Castronovo V, Turtoi A. HDAC7 inhibition resets STAT3 tumorigenic activity in human glioblastoma independently of EGFR and PTEN: new opportunities for selected targeted therapies. *Oncogene*. 2016 Feb 8.

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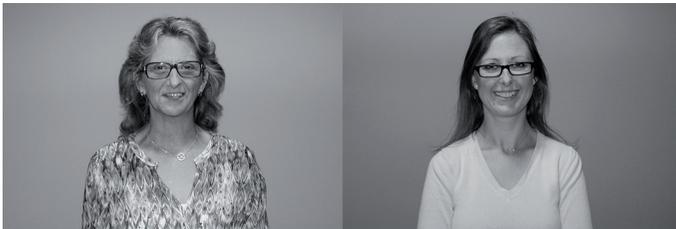


FACTS

- Number of maxipreps produced in 2015 > 450
- Number of viral vectors produced in 2015 > 500
- Number of transduced cells in 2015 > 200

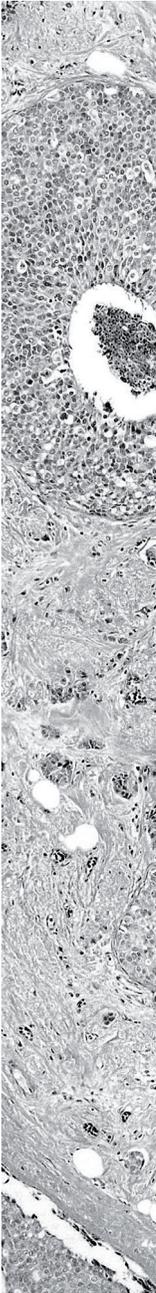
GIGA-Immunohistology

Processing tissue to get high quality sections, optimizing the histology of tissues, immunohistochemical detection of antigens that could be weakly expressed can be a long and sometimes difficult process. Since its creation, the immunohistology platform helps the researchers (of the GIGA, of the ULG but also some companies) in that task either by giving access and advice to use the equipment or by processing samples from embedding to histochemistry and immunostaining. The platform has optimized many protocols for human, mouse or rabbit antigens detection for manual staining or for the Discovery XT system that allows automation of the immunostaining process, ensuring reproducibility. The platform has also developed expertise in the treatment of "solid tissues" (ex: bone): decalcification, embedding, realization of good sections, histochemistry and immunostaining. The GIGA-Immunohistology relies on a technician to realize all the steps: Alice Marquet began to work in the platform at the beginning of 2015 and she has great experience (more than 10 years) in histology and the different techniques of immunostaining. The platform works in close collaboration with the Biobank and the slides can also be imaged on an automated scanner for storage and computer analysis.



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Publications

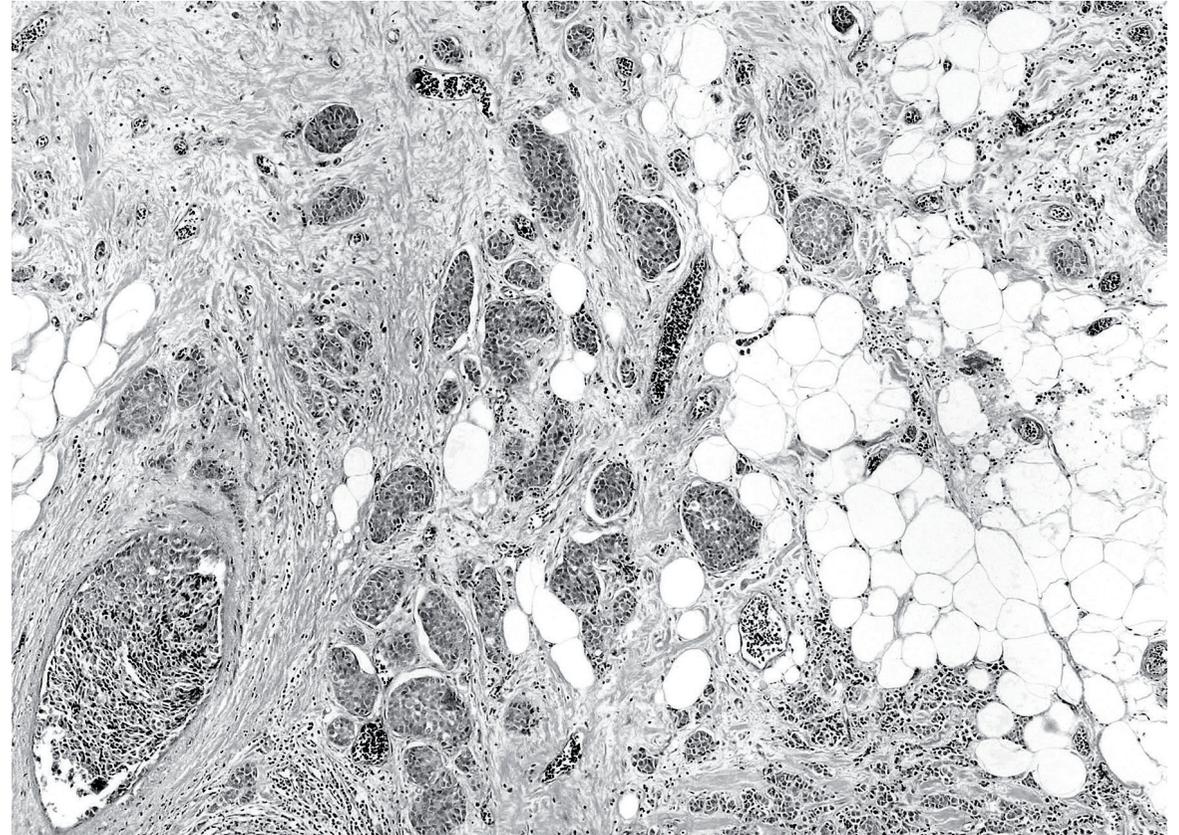
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FACTS

3486 Paraffin embedding

18655 Paraffin sections

4161 Staining

(HE, PAS, Trichrome Masson, Fast Green Safranin, Toluidine Bleue, Von Kossa)

1683 Immunohistochemistry

GIGA-Zebrafish Facility & Transgenics

The past year has been mostly devoted to improving the organization of the zebrafish facility. New staff has been trained to help researchers in managing their strains and to provide the best possible care for the fish. Particular emphasis has also been placed on stronger health surveillance, on implementing specific diets and on improved training of all users. The good reputation of the facility has continued to attract internal researchers as well as collaborators from other universities and companies. A great asset of the facility is to provide consultancy services for new users who would like to develop a zebrafish project. Morpholino knockdowns projects have been undertaken as well as various original projects meant to decipher the molecular basis of melanoma, diabetes, galactosemia, thrombosis...



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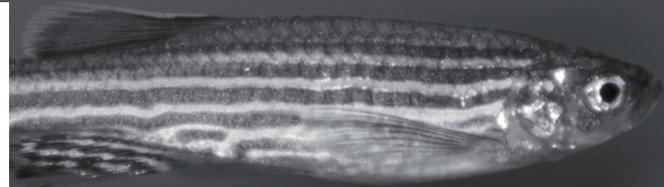
FACTS

About **13000** fish are currently housed into the facility.

258 different lines are housed: precious transgenic and CRISP/CAS mutant fish

Thousands of fertilized eggs are provided to the researchers on a weekly basis

450 adult fish have been sent to other organizations in 2015



Publications

Ghaye AP, Bergemann D, Tarifeno-Saldivia E, Flasse LC, Von Berg V, Peers B, Voz ML, Manfroid I. Progenitor potential of nkx6.1-expressing cells throughout zebrafish life and during beta cell regeneration. BMC Biol. 2015;13:70

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Windhausen T, Squifflet S, Renn J, Muller M. Bmp signaling regulates bone morphogenesis in zebrafish through promoting osteoblast function as assessed by their nitric oxide production. Molecules. 2015;20:7586-7601

GIGA-Mouse Facility & Transgenics

Animal experimental models are of great importance for both fundamental and applied research. GIGA SPF Mouse Facility & Transgenic works mainly on the creation, management of reproduction and housing of transgenic lines in order to provide the necessary tools for researchers. In 2015, over 200 lines were housed within the SPF area. The GIGA Mouse Facility also offers services for the (cryo) storage of genetically modified strains. The GIGA Mouse Transgenic Platform is located inside our SPF mouse facility (A1 biosafety level). We perform gene targeting in different types of murine embryonic stem cells (mESCs). After positive and negative selection, the targeted mESCs are injected into the blastocoel of 3.5 days recipient embryos and implant the injected blastocysts implanted into foster mothers to obtain chimeric mice. This is a crucial step in the production of mice carrying a targeted mutation. We have been very successful at producing chimeric mice giving high rates of germline transmission of targeted mESCs carrying the desired mutation. Since several years, the GIGA Mouse Facility performs embryo cryopreservation by the aseptic vitrification procedure. This approach is recommended for complex and/or homozygous strains and for the preservation of the genetic background. Since 2015, the GIGA Mouse Facility has also developed sperm cryopreservation according to the method of N. Nakagata (Mammalian Genome 11, 572-576). The cryopreservation of sperm followed by IVF is an easier and cheaper method than embryo cryopreservation for the storage and transport of mouse lines. It could also be used to rescue some strain with very low effectiveness. This approach is also a good way to reduce the number of mice used to cryopreserve a strain (principle of the 3R's). The GIGA SPF Mouse Facility provides other (internal and external) services such as in vivo imaging, surgery, experimental behavior recording, while monitoring carefully the sanitary status of the housed animals. If needed, experiments can be performed in biosafety level 2 or 3. Prior to any experiment, the experimental protocol has to be approved by the Institutional Animal Care and Use Committee.

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Publications

Musumeci L, Kuijpers MJ, Gilio K, Hego A, Theatre E, Maurissen L, Vandereyken M, Diogo CV, Lecut C, Guilmain W, Bobkova EV, Eble JA, Dahl R, Drion P, Rascon J, Mostofi Y, Yuan H, Sergienko E, Chung TD, Thiry M, Senis Y, Moutschen M, Mustelin T, Lancellotti P, Heemskerk JW, Tautz L, Oury C, Rahmouni S. Dual-specificity phosphatase 3 deficiency or inhibition limits platelet activation and arterial thrombosis. *Circulation*. 2015;131:656-668

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Xu X, Ectors F, Davis EE, Pirottin D, Cheng H, Farnir F, Hadfield T, Cockett N, Charlier C, Georges M, Takeda H. Ectopic expression of retrotransposon-derived *peg11/rtl1* contributes to the callipyge muscular hypertrophy. *PLoS One*. 2015;10:e0140594



FACTS

398 Mouse embryo assays

220 Colonies Housed

9 Electroporations/selection + mESCs Injections

4 Lines cryopreservations/Revitalisation or sanitisations

GIGA-Biobank

The "Biothèque Universitaire de Liège" (BUL) is a biobank which is in charge of the daily collection of human biological samples (pathological or normal) in the respect of ethical, legal and quality requirements. These samples are flash frozen at -80°C and the corresponding paraffin embedded tissue is available in the archive of the pathology department. The biobank selects samples in the database that meet researcher's specific criteria. Tissue sections are then prepared for immunohistochemistry, immunofluorescence, mass spectrometry analysis, protein and nucleic acid extraction. Samples are only provided for research projects that have been approved by a committee.

Stéphanie Gofflot

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FACTS

- 30 GIGA researchers requested the biobank material in 2015
- 313 Frozen samples and 1376 paraffin samples provided in the context of experimental studies in 2015
- 787 Frozen samples collected and characterized (371 tumoral and 416 non tumoral)



Publications

Maris P, Blomme A, Palacios AP, Costanza B, Bellahcène A, Bianchi E, Gofflot S, Drion P, Trombino GE, Di Valentin E, Cusumano PG, Maweja S, Jerusalem G, Delvenne P, Lifränge E, Castronovo V, Turtoi A. Asporin Is a Fibroblast-Derived TGF- β 1 Inhibitor and a Tumor Suppressor Associated with Good Prognosis in Breast Cancer. *PLoS Med.* 2015 Sep 1;12(9):e1001871.

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Bianchi E, Roncarati P, Hougrand O, Guéin-El Khourouj V, Boreux R, Kroonen J, Martin D, Robe P, Rogister B, Delvenne P, Deprez M. Human cytomegalovirus and primary intracranial tumours: frequency of tumour infection and lack of correlation with systemic immune anti-viral responses. *Neuropathol Appl Neurobiol.* 2015 Feb;41(2):e29-40.

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GIGA-Business



GIGA-Business

GIGA comprises 3 Business Facilities offering a place where biotech companies (spin-offs, start-ups or subsidiaries of established companies) can develop their activities. Just like the previous one, 2015 has been a great year for biotechs at GIGA. Two new companies have joined us: Belma Technologies and EyeD Pharma. Both offer implantable devices for administering hormones to animal models and for human intraocular drug delivery systems, respectively. Moreover, Imcyse, a company already established in GIGA since 2013, has made a capital increase of 7.5M€ and extended its team.



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GIGA-Companies

GIGA 1

Amplycell
Biosourcing
Estetra
EyeD Pharma
Fabro
Hyloris Pharma
Mithra RDP
Sponcken Orthopedics

GIGA 2

Artialis
Astrea
Belma Technologies
Labage
LaCAR MDx Technologies
Physiol
Scinnamic
Symbiose
WBC Incubator
Xpress Biologics

GIGA 3

Sonicbio

Labhotel

Imcyse
Symbiose



New company - Belma Technologies

Belma Technologies came out of the meeting of two researchers in the vanguard of animal models and pharmaceutical technology. Given the proven lack of quality and reliability of the products already on the market and having determined the real needs of all the research teams who must administer hormones as part of their work, they decided to create in 2015 Belma Technologies to provide the research community with a solution for administering hormones to animal models. With the close proximity of the animal facility and centers of excellence in pharmaceutical technology and life sciences, the establishment of Belma Technologies on the Giga's business facilities center was a natural choice. In the context of ever increasing legal requirements for the welfare and protection of animals used for scientific purposes, the judicious choice of a reliable and accurate drug release system in the experimental models is fully in the spirit of respecting the 3R's rule. Belma Technologies adheres to this policy, as advocated by organizations such as FELASA and AAALAC. The users of Belma products boost their compliance with the AWA, PHS Policy, and EU 2010/63 directives. The use of Belma products has been proven to have a huge impact on Refining experimental designs and Reducing the number of animals used. Today, with its more than fifty years of cumulative experience and after three years of specific development, Belma proposes reliable products of irreproachable quality that respect the "three Rs" of animal welfare in research. Belma Technologies use the most modern, innovative, and environmentally friendly technologies to produce implants. They are the guarantees of total reliability, backed up by strict quality control. Belma implants will give researchers all the accuracy required to Refine experimental designs and Reduce the number of animals used in experiments. With the support of a grant from the Walloon region, Belma is in the process of developing other solutions for the management of laboratory animals. The valorization of our expertise in the field of pets will be the next step.

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New company - EyeD Pharma

EyeD Pharma was founded in 2012 by Professor JM Rakic, head of ophthalmology at University Hospital of Liege, and by Professor JM Foidart, co-founder of Mithra Pharmaceuticals, and is dedicated to the development of innovative intraocular drug delivery systems. The first system patented by EyeD Pharma is a core-shell polymeric intraocular implant releasing a fixed amount of drug per day for a period of 12 months minimum. In a first step, EyeD Pharma has decided to focus on glaucoma treatment. By replacing the drug in the implant EyeD will be able to increase its pipeline with several implants against pathologies like Age Related Macular Degeneration, Uveitis,... Glaucoma is a pathology most often appearing in patients older than 55 years old and is associated with an increased intraocular pressure leading to optical nerve degeneration and vision loss. Glaucoma affects 5.6 million people in US and 5.3 million people in EU with a turnover of 2.16 billion \$ in US and 309 million \$ in EU. The most prescribed drugs in this pathology require a daily administration of eye drops but the compliance is very poor in elderly people (mainly due to tremor) leading to vision loss in most cases. With EyeD implant, locally releasing a fixed amount of drug, the compliance will be significantly higher and the side effects significantly decreased. Phase I/IIa clinical trial for the glaucoma implant will begin current 2017. In the next few months, EyeD Pharma will also implement its pipeline with other new intraocular delivery products. With an initial 600 K€ capital, the company has built many collaborations with other companies, research centers and academic laboratories particularly in the Walloon Region. A capital increase of 2.8 M€ will be ended by April 2016.

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Focus on ImCyse, a company hosted in the labhotel

ImCyse is a biomedical company, spin-off of the University of Leuven, Belgium, with a cutting-edge biotechnology platform to develop novel, disease specific, active immunotherapies. Imcyse technology involves peptide vaccines that specifically block the immune responses causing the diseases. There is potential for cure of severe chronic diseases, and subsequently to induce regeneration of damaged cells and organs. Imcyse most advanced products in development are vaccines to treat multiple sclerosis and type 1 diabetes. However Imcyse technology platform is applicable to numerous indications: auto immune and inflammatory diseases, infectious diseases, allergies, solid tumors, prevention of graft rejection, prevention of immune response to treatment and to viral vectors. Since its creation in 2010, Imcyse is based in Leuven and in 2013 established part of its activities in the lab hotel of GIGA tower of the Sart Tilman, Liège. In 2015, the management has been strengthened to improve the development skills of what was primarily a research group. In total 6 employees and 3 consultants have been recruited. Imcyse will also move soon to new, proper labs and offices on the third floor of the GIGA. Projects have been prioritized with two of them entering in clinics early 2017. A capital increase of 7.5M€ has been completed in November. The challenges for 2016 are to complete the integration of the development activities and the preparation of the clinical trials, while consolidating the financing for the next 2-3 years.

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GIGA-Training



Forem-GIGA **Biotechnology Training Center**

The Forem-GIGA Biotechnology Training Center was created in 2005 by the Walloon Office for Employment and Training of Liège (Le FOREM) in partnership with the Interdisciplinary Cluster in Applied Genoproteomics (GIGA) of the University of Liège, supported by the European Regional Development Fund (ERDF) and the Walloon Region. Our aims are to develop and organize biotechnology training programs for job-hunters and company staff, in response to market needs and to complement the training offered by technical colleges in terms of techniques and specific expertise. Current topics addressed are: molecular biology, molecular diagnostics, immunology, protein production and purification, gas and liquid chromatography, cell culture, quality control, quality assurance, validation, biosafety, GxP's, bioinformatics, regulatory affairs, and project management. Besides these subjects, training sessions can be tailored to customer needs. To achieve our goals, the Biotechnology Training Centre works in close collaboration with both the academic and industrial biotechnology worlds, and most of the company-staff training programmes are validated by BioWin, the Health Cluster of Wallonia.

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Highlights 2015

Thanks to the ERDF program, we have set up a brand new laboratory dedicated to protein production and purification and acquired 2 new bioreactors.

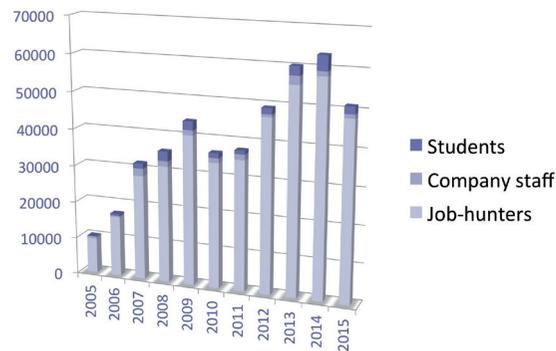
Besides our «standard» training sessions, our highly successful Quality Assurance (QA) training program is also worth highlighted. It was developed as a «University certificate» in close collaboration with the «Réseau des Laboratoires» and the Faculty of Medicine of the ULg. At the end of the training session, many trainees have found a job in this field.

We also organised for the second year the new long-term training program focused on the Regulatory Affairs in close collaboration with Culture in vivo ASBL. Work is in progress to create, on its basis, an «Interuniversity Certificate» (Universities of Liège and Namur).

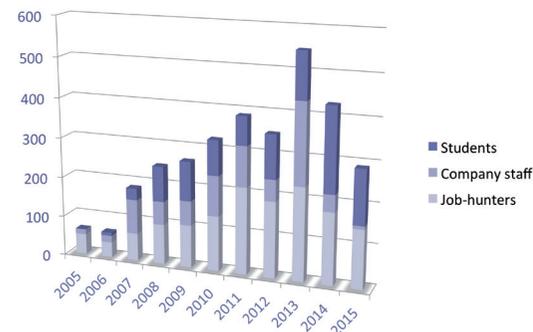
In summary, in 2015, we have delivered approximately 51 000 hours of training for job-hunters, students of technical colleges and workers from biotech companies.

We also prepared the future since, in close collaboration with other training centers (Cefochim ASBL, Culture in vivo ASBL and Biopark Formation), we have submitted an important training program focused on cell culture and therapy to the support of BioWin - 16th call).

Hours of training



Numbers of trainees



Despite a steady progression during the previous years, there is unfortunately a slight drop in numbers this year, mostly because of a lessening in the fundings of the center. This should also be the case in 2016. The activity rate will rise again as soon as the team will grow. However, the occupational integration rate of the trainees at the end of the training still demonstrates their quality.

Key numbers

Overall numbers

51 000 hours of training

289 trainees

74% occupational integration rate

Job-hunters

7 long-term training programs

5 shorter transverse training sessions

Students

9 short-term modules

Company staff

2 modules

- Quality assurances

- Bioinformatics

Results of 2015

Job-hunters

In 2015, seven long-term training programs and five shorter transverse training sessions were organized for 146 people from the entire Walloon Region. Each long-term session included training in transversal skills (biosafety, GxP's, QA, QC, validation, regulatory affairs, scientific English, good communication, and team work) in addition to core technical training related to:

- Antibody production and analysis
- Protein production and characterization (2 sessions)
- Analytical techniques: HPLC-GC-CE
- Bioinformatics
- Biostatistics
- Project and team management in biotechnology (2 sessions)
- Quality Assurance
- Regulatory Affairs

Most of the trainees topped off their training and boosted their chances on the job market with a 2(3)-months internship in a biotech company. According to the final measurement for 2014, the percentage of occupational integration was 74 %.

Company staff

The following modules were organized for a total of 8 people:

- Quality Assurance
- Bioinformatics

Higher education - technical college students

Nine short-term modules specifically designed for 136 students and their teachers were organized in 2015. The aim was to complement their academic courses and give them access to state-of-the art technology that is unaffordable for technical colleges, promoting interactions with researchers and experts in the field.

The modules focused on:

- PCR, advanced
- Practical introduction to HPLC
- GLP, GMP, Validation
- Introduction to project management





GIGA-Grants/Publications



Research **Funding**



3 WELBIO grants to GIGA members

This year (3rd WELBIO call for projects), 3 GIGA projects were selected. Alain Chariot, whose previous project was also selected in the first call, gets a «Grant Senior» and Kristel Van Steen and Christophe Desmet both get a «Starting Grant» from the FRFS (Fonds de la Recherche Fondamentale Stratégique) in the framework of this FRFS-WELBIO-2015 call. The projects will be funded for a two-year period.

Alain Chariot

Dissecting oncogenic pathways

Cancer is a highly heterogeneous disease characterized by thousands of mutations. These genetic alterations ultimately impact on a dozen of oncogenic pathways that sustain cell proliferation, survival, dedifferentiation and invasion. Therefore, understanding why those oncogenic pathways are constitutively activated in cancer is of paramount importance to define new therapeutic targets and to circumvent resistance to targeted therapies. We have been interested in characterizing signaling proteins acting in these oncogenic pathways by focusing our work on candidates that transmit signals from EGFR as well as on proteins expressed through NF- κ B, a family of transcription factors aberrantly activated in cancer. We are also exploring the role of the acetylase ELP3 in tumor initiation and progression to better understand how tRNA modifications control cancer development. Our project will be dedicated to the characterization of all oncogenic pathways in which KIAA1199, a candidate that links NF- κ B-dependent transcription to EGFR signaling as well as ELP3, are acting. We will also explore whether and how these oncogenic proteins promote resistance to targeted therapies.



Christophe Desmet

Translational regulation of T cells

Hematopoietic progenitors ensure the production of blood cells throughout life, whereas classical T cells are essential cells of the adaptive immune system that contribute to protection against pathogens and cancer development. Both cell systems represent some of the best-characterized models of physiologic cell differentiation. Cell differentiation is driven by changes in the cell gene expression program, which restrict the expression of pluripotency- or self-renewal-associated genes, while promoting the expression of lineage commitment-associated genes. Changes in the gene expression program that drive cell differentiation are generally assessed at the level of gene transcription, which is technically the most amenable. Yet, burgeoning evidence suggests that translational control of gene expression is as prominent as transcription in determining the composition of the cell proteome. In this project, we aim to assess the consequences of impairing specific enzymatic modules of translational control on the differentiation of hematopoietic cells and classical T cells. This project should identify radically novel mechanisms regulating cell differentiation and open wide perspectives of basic and clinical development in immunology/hematology.



Kristel Van Steen

DESTINCT: DEtecting STatistical INteractions in Complex Traits

Large-scale epistasis studies can give new clues to systems-level genetic mechanisms and a better understanding of the underlying biology of human complex disease traits. Many novel methods have been proposed to carry out such studies. So far only a few of them have demonstrated replicable results with genetic markers, despite attempts to reconcile statistical with biological epistasis. We claim that this is in part caused by unresolved problems, including those arising from shared genetic ancestry, and problems related to model-dependent meta-analyses. Apart from tackling these issues, in this project, we aim to develop an integrated gene-centric approach to epistasis analysis. The latter is believed to increase interpretability and replicability of results. Only when epistasis detection becomes routine practice, we will truly be able to show the impact of it on personalized medicine, disease risk prediction, and evolutionary genetics.



New FNRS Mandates

Five researchers from GIGA were given new FRS-FNRS mandates.

Alain Chariot (GIGA-Signal Transduction) becomes Research Director, Cécile Oury (GIGA-Cardiovascular Sciences) is now Senior Research Associate, Sophie Servais (GIGA-I3), Post-doctoral Researcher, Stella Dederen (GIGA-Cancer) and Aude Delferrière (GIGA-I3) are Research Fellows.



FNRS Research projects

Projets de recherche – PDR Research projects

Midbrain dopaminergic systems : from mechanisms of single neuron firing to network activity in behaviorally relevant physiological conditions
Seutin Vincent (01/01/2013 – 30/06/2017)

Fonctionnalités de la kisspeptine et des neurones exprimant le récepteur à la GnRH au sein du circuit neural contrôlant le comportement de lordose
Bakker Julie (01/07/2013 – 30/06/2017)

Role of Myoferlin, a Member of Ferlin Family, in Cancer Progression and Angiogenesis
Castronovo Vincent (01/07/2013 – 30/06/2017)

Regulation of the activity of ADAMTS2, 3 et 14 and analysis of their specific functions during physiological and pathological processes
Colige Alain (01/07/2013 – 30/06/2017)

Contribution to the study of the physiopathological basis of juvenile myoclonic epilepsy
Lakaye Bernard (01/07/2013 – 30/06/2017)

Mechanism and inhibition of VHR-mediated platelet activation in thrombosis
Rahmouni Souad (01/07/2013 – 30/06/2017)

Robust Machine Learning Forests in Network Construction for Integrative Omic Analyses
Van Steen Kristel (01/07/2013 – 30/06/2017)

Mesenchymal stromal cell therapy in the context of hematopoietic stem cell transplantation
Beguin Yves (01/07/2014 – 30/06/2018)

Insights into the oncogenic potential of PINB in colon cancer
Chariot Alain (01/07/2014 – 30/06/2018)

Early extranigral and nigral MRI biomarkers in Parkinson's disease
Garraux Gaëtan (01/07/2014 – 30/06/2018)

Implication of Epithelial-to-Mesenchymal Transitions (EMTs) on coagulant properties of Circulating Tumor Cells (CTCs): impacts for the metastatic progression
Gilles Christine (01/07/2014 – 30/06/2018)

New Insights into the Development and Progression of Aortic valve Stenosis (The NID-PAS Study)
Lancellotti Patrizio (01/07/2014 – 30/06/2018)

Deciphering the role of protein acetylation in kinocilium genesis and inner ear development
Malgrange Brigitte (01/07/2014 – 30/06/2018)

Post transcriptional gene regulatory networks in endothelial cells
Struman Ingrid (01/07/2014 – 30/06/2018)

Role of bovine leukemia virus microRNAs in viral infectivity, replication and pathogenesis
Willems Luc (01/07/2014 – 30/06/2018)

Regulatory T cells and graft-versus-host disease
Baron Frédéric (01/10/2015 – 30/09/2019)

Role of membrane estrogen receptor alpha on the control of hypothalamic-pituitary-gonadal axis
Cornil Charlotte (01/10/2015 -30/09/2019)

RNA-seq reveals cancer drive genomic changes in delta-retrovirus-induced leukemia : novel mechanisms of transcriptome rewiring by chimeric long noncoding RNAs
Georges Michel (01/10/2015 – 30/09/2019)

Caractérisation in vitro et validation par LC-MS microfluidique d'un fragment de la sous-unité V65 de la vitronectine, du complément C3f and du CTAPIII comme marqueurs de sévérité de l'arthrose

Malaise Michel (01/10/2015 – 30/09/2019)

Rôle de la modification post-traductionnelle des protéines dans la migration neuronale

Nguyen Laurent (01/10/2015 – 30/09/2019)

Exploration of EGFR/MT4-MMP axis for improving anti-EGFR targeted therapy

Noël Agnès (01/10/2015 – 30/09/2019)

Study of the role of the CXCR4 in specific invasion of glioblastoma initiating cells (GIC) in subventricular zones and the mechanisms of their radioresistance induced by this neurogenic niche

Rogister Bernard (01/10/2015- 30/09/2019)

In vitro and in vivo functional analysis of Rasa3, a Ras and Rap1GTPase activating protein, in angiogenesis

Schurmans Stéphane (01/10/2015- 30/09/2019)

Crédits de recherche - CDR Research credits

Study of the role of lung-resident eosinophils

Bureau Fabrice (01/01/2015 – 31/12/2015)

Insights into the role of IKKepsilon in a Wnt-driven model of intestinal cancer

Chariot Alain (01/01/2015 – 31/12/2015)

Members of Ets family of transcription factors are involved in mRNA degradation processes

Dequiedt Franck (01/01/2015 – 31/12/2015)

Deciphering the mechanisms underlying the adjuvant activity of alum

Desmet Christophe (01/01/2015 – 31/12/2015)

Characterization of the role of Cdk activating kinase (CAK) in neuronal survival and adult neurogenesis in mammals

Malgrange Brigitte (01/01/2015 – 31/12/2015)

Influence of metabolism on both adaptive and resistant response of cancer cells to HDAC inhibitors treatment

Mottet Denis (01/01/2015 – 31/12/2015)

Alterations of puberty after neonatal exposure to Bisphenol : characterization of hypothalamic gene networks targeted by endocrine disruption

Parent Anne-Simone (01/01/2015 – 31/12/2015)

Receptor crosstalk and interaction in angiogenesis and Hereditary Hemorrhagic Telangiectasia

Struman Ingrid (01/01/2015 – 31/12/2015)

Mandats d'Impulsion Scientifique - MIS Incentive grants for scientific research

Implication of protein acetylation in cancer development and progression

Close Pierre (01/01/2013 – 31/12/2015)

Pharmacology and physiological roles of SREB family GPCRs

Hanson Julien (01/01/2014 – 31/12/2016)

Crédits d'équipement - EQP Equipment grants

Request for an ultracentrifuge to isolate and purify exomes and lipid-rafts

Struman Ingrid (01/01/2015 – 31/12/2016)



2015 TELEVIE funded projects

Homeostasis of regulatory T cells in chronic graft-versus-host disease (GVHD)

Frédéric BARON, Yves BEGUIN

Role of osteopontin in human glioblastoma radioresistance

Akeila BELLAHCÈNE, Vincent CASTRONOVO

Methylglyoxal-mediated carbonyl stress in breast cancer

Akeila BELLAHCÈNE

The involvement of galectin-1 in multiple myeloma-induced osteoclast and endothelial cell recruitment

Jo CAERS, Yves BEGUIN, Roy HEUSSCHEN

Unveiling the Phenotypic Heterogeneity of Liver Metastases to Overcome Resistance to Therapies

Vincent CASTRONOVO

Discovery of Soluble Markers Predictive of Therapy Resistance in Patients with Colorectal Cancer Liver Metastases

Vincent CASTRONOVO, Guy JERUSALEM, Olivier DETRY, Andrei TURTOI

Role of Myoferlin in Regulating Cellular Metabolism in Triple Negative Breast Cancer

Vincent CASTRONOVO

Role of estrogens in carcinogenesis and cancer progression in bronchial carcinoma

Didier CATALDO, Christel PEQUEUX

Insights into mechanisms underlying the degradation of the IKK-related kinase IKKepsilon in breast cancer

Alain CHARIOT

3 ligases and Diffuse Large B cell lymphomas: Insights into mechanisms underlying BCL-3 degradation in lymphomas

Alain CHARIOT

Expression and functional characterization of the CXCR3-CXCR7 heterodimer in glioblastoma

Andy CHEVIGNÉ, Julien HANSON

Processing of « pro-VEGF-C » into active VEGF-C by ADAMTS3: impact on tumor lymphangiogenesis and metastasis dissemination

Alain COLIGE

Squamocolumnar junctions: histologic, cellular, molecular and clinical considerations

Philippe DELVENNE

New and unexpected functions for oncogenic Ets factors in mRNA processing : contribution mRNA decay and alternative splicing

Franck DEQUIEDT

Roles of lipins in cancer progression and analysis of their potential as targets for cancer therapy

Christophe DEROANNE

Antisense RNA-dependent cis-perturbation of host genes determines clonal expansion in Deltaretrovirus induced leukemia

Michel GEORGES, Dominique BRON, Anne VAN DEN BROEKE

Implication of Epithelial-to-Mesenchymal Transitions (EMTs) on coagulant properties of Circulating Tumor Cells (CTCs): impacts for the metastatic progression

Christine GILLES, Cécile OURY, Guy JERUSALEM

Functionality of «Melanoma Antigen D2» a protein frequently overexpressed in many tumors

Yvette HABRAKEN

Development of a therapeutic approach aiming to inhibit tumor promotion of squamous cell carcinomas by using HMGB1 inhibitors

Pascale HUBERT

Implication of defensin superfamily in tumor microenvironment

Pascale HUBERT, Philippe DELVENNE

Colorectal Dysplasia Diagnosis Proteomic Biomarkers

Edouard LOUIS, Philippe DELVENNE, Edwin DE PAUW

Glioblastoma : correlation of tumor aggressiveness with clinical and biological factors, and recurrence reoperation

Didier MARTIN, Felix SCHOLTES

Implication of the membrane receptor uPARAP/Endo 180 in tumoral lymphangiogenesis

Agnès NOËL

Search for substrates and partners of the pro-metastatic MT4-MMP

Agnès NOËL, Alain COLIGE

Tumor adaptation to anti-angiogenic drugs

Agnès NOËL, Edwin DE PAUW

Study of the mechanisms underlying the antitumoral effect of the antiplatelet drug clopidogrel in a mouse model of colitis-associated cancer

Cécile OURY, André GOTHOT

Understanding the role of the dual-specificity protein phosphatase DUSP3 in obesity-induced hepatocellular carcinoma

Souad RAHMOUNI, Cécile OURY

The GP VAC project: identification and exosomal biomarkers of the MHCII-restricted immunogenic peptidome for the peptide vaccination against GBM and GBM tumor-initiating cells

Pierre ROBE, Vincent BOURS

The ToP-NAG project: Targeting of Phosphatase-dependent NF-kappaB network Activation in Glioblastoma

Pierre ROBE, Vincent BOURS

NADEGE : Novel Apigenin formulations : Development and Evaluation for Glioma Eradication

Pierre ROBE, Vincent BOURS, Géraldine PIEL

Energetic resources in tumor microenvironment

Nor Eddine SOUNNI

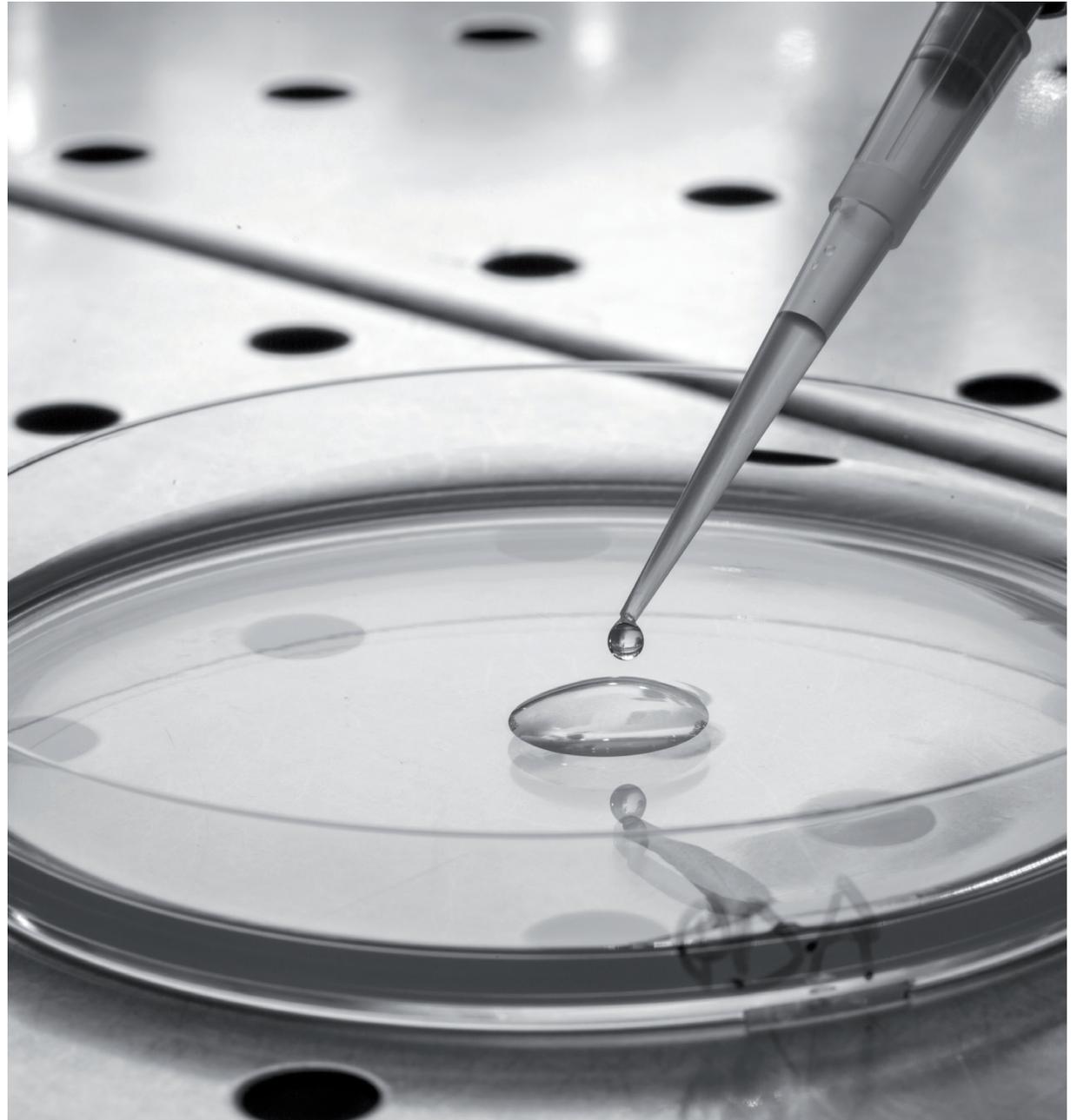
Impact of endothelial-derived microRNA transfer on tumor growth
Ingrid STRUMAN

The Yeast Reference Interactome as a resource to identify novel cancer orthologous
Jean-Claude TWIZERE

PDAC-xome: Exome Sequencing in Pancreatic Ductal Adeno-Carcinoma
Kristel VAN STEEN

Genesis of a virus-induced APOBEC3 mutational signature in lung cancer: mechanisms and therapeutic applications
Lucas WILLEMS

BLV microRNAs
Lucas WILLEMS



Fonds Léon Frédéricq

PhD grants (9 months)

Anne GALLEZ
Sébastien VERTENEUIL

PhD grants (6 months)

Susana MATEO SANCHEZ
Stéphanie RAULIER
Céline DELIERNEUX
Thomas WINDHAUSEN
Alexandre CARPENTIER
Pierre-Yves BAREZ
David STERN
Alice TRUONG

Traveling grants

Adeline JACQUINET
Florence DURIEUX
Céline GERARD
Gilles DUFOUR
Meggy SUAREZ-CARMONA
Charlotte ERPICUM

Grants for equipment

PhD students
Mathias DEBOBBELEER
Valérie DION
Antoine FRERE
Julie FUDVOYE
Marco GIANFRANCESCO
Vincent HELLIER
Post-doc
Catherine CREPPE
Stephen FREEMAN
Carla GOMES DA SILVA

Specific awards and awards of Foundations linked to the Fonds Léon Frédéricq

Prix du Département des Sciences Biomédicales et Pré-cliniques
Laure NOEL

Bourse de la Ligue Belge de la Sclérose en Plaques
Renaud VANDENBOSCH
Bourse Mr et Madame Fabri
Alexandra BRIQUET
Prix AstraZeneca
Natacha ROCKS
Prix Nicolas JACQUET
Arnaud LOMBARD
Prix Frédéric VAN DEN BRULE
Sophie SERVAIS
Prix Josée et Jean schmets
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Kim DONATI
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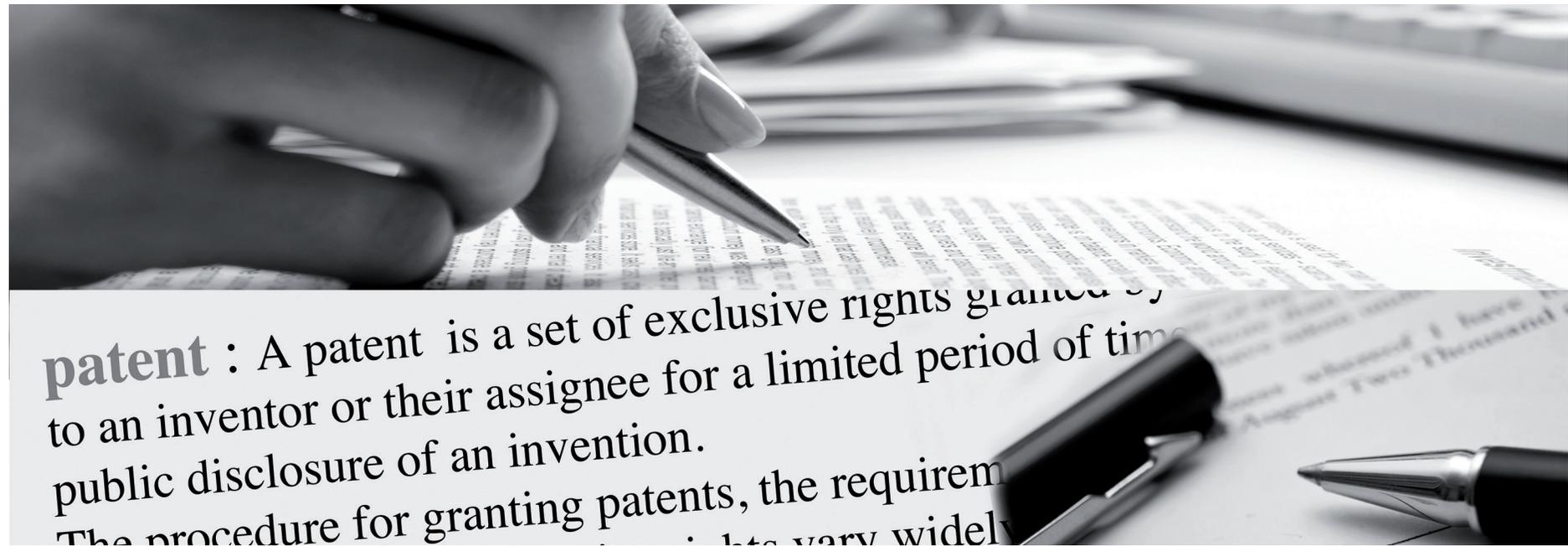
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GIGA Patents



patent : A patent is a set of exclusive rights granted by to an inventor or their assignee for a limited period of time public disclosure of an invention.
The procedure for granting patents, the requirements vary widely

In 2015

* GIGA-R researchers have been involved in 2 priority patent applications;

* 9 patent families issued from GIGA-R led to publications;

* 3 patents have been granted.

Patents granted

Use of cyclodextrin for treatment and prevention of bronchial inflammation diseases

Didier Cataldo, Brigitte Evrard, Agnes Noel, Jean-Michel Foidart

US 9,034,846 B2

Double-muscling in mammals

Luc Grobet, Michel Georges, Dominique Poncelet

EP 2 045 322 B1 (designated contracting states: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE)

Markers for impaired bone fracture healing

Valérie Gangji, Jean-Philippe Hauzeur, Dominique de Seny, Myrielle Mathieu, Aude Ingels, Sabrina Rigutto, Delphine Spruyt, Enrico Bastianelli, Valentina Albarani, Xavier Pesesse, Michel Malaise

EP 2 718 714 B1 (designated contracting states: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR)

Patents published

Estrogenic components for use in the treatment of neurological disorders

Jean-Michel Foidart, Ekaterine Tskitishvili
CN104379148

Method for increasing the bioavailability of inhaled compounds

Rita Vanbever, Salomé Koussoroplis, Didier Cataldo, Jacques Van Snick
WO2015/107176

Combination treatment of cancer

Agnès Noel, Nor Eddine Sounni, Alexandra Paye
US2015/0232572

Detecting a brachyspina mutation

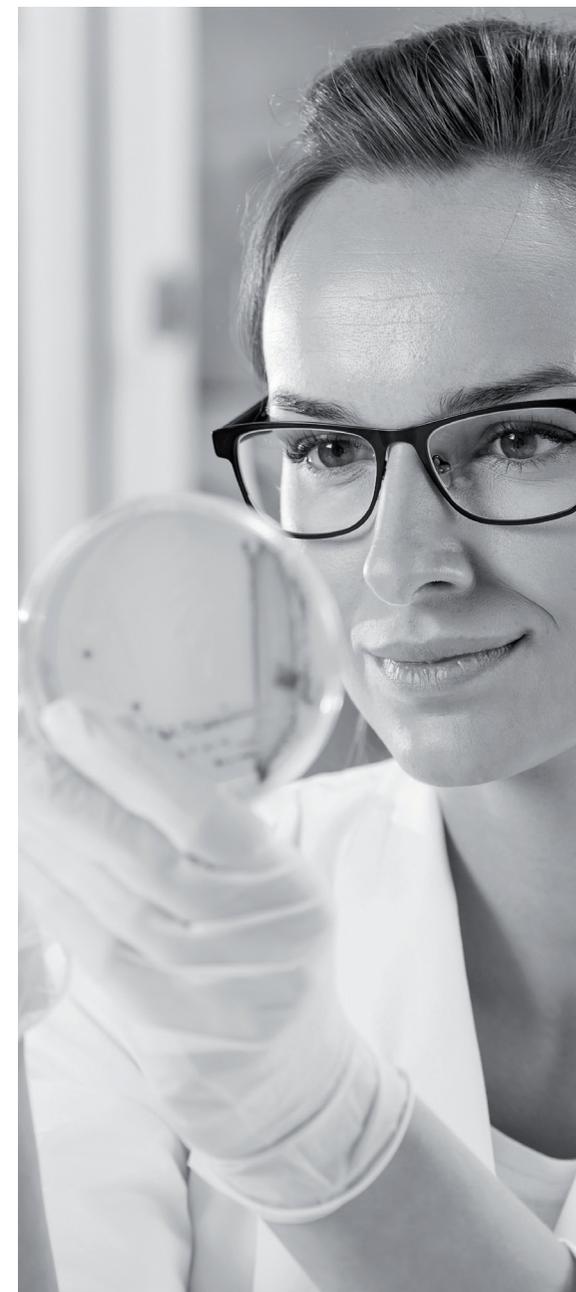
Michel Georges, Wouter Coppieters, Carole Charlier, Steen Agerholm, Merete Fredholm, Karlskov Mortensen
US2015/0247195

Peptide antagonists of the vasopressin-2 receptor

Nicolas Gilles, Denis Servent, Loïc Quinton, Helen Reinfrank, Ralph Witzgall, Bernard Mouillac, Christiane Mendre
US2015/0252086

Cyclodextrin and budesonide derivative compositions and methods

Didier Cataldo, Brigitte Evrard, Gilles Dufour, Pascal De Tullio
WO2015/144938



GIGA **Publications**



Publications with a GIGA member as first or last author

Aceto J, Nourizadeh-Lillabadi R, Maree R, Dardenne N, Jeanray N, Wehenkel L, Alestrom P, van Loon JJ, Muller M. Zebrafish bone and general physiology are differently affected by hormones or changes in gravity. *PLoS One*. 2015;10:e0126928

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2015

323 publications

26 with IF > 10

73 with IF 5-10

126 with IF 3-5

98 with IF < 3

24 PhD thesis

36 Seminars/Conferences

PhD Theses

Hormones, Simulated Microgravity and Hypergravity affect Bone and other Physiological Systems in Zebrafish Larvae
Aceto Jessica, Laboratory of Organogenesis and Regeneration, GIGA-Development

Role of RASA3 in endothelial cells biology and angiogenesis
Bovy Nicolas, Laboratory of Molecular Angiogenesis, GIGA-Cancer

Role of metabolic Reprogramming in Tumor Adaptation to Anti-angiogenic Therapy
Cimino Jonathan, Laboratory of Mass spectrometry, GIGA-Systems Biology

Contrôle neurochimique et fonction de l'aromatase cérébrale chez la caille japonaise
De Burnonville Catherine, Laboratory of Neuroendocrinology, GIGA-Neurosciences

Identification et caractérisation des progéniteurs pancréatiques et des précurseurs endocrines durant l'embryogenèse chez le poisson zèbre
Ghaye Aurélie, Laboratory of Organogenesis and regeneration, GIGA-Development

Role of Subventricular Zone-Released CXCL12 in Glioblastoma Invasion and Radioresistance
Goffart Nicolas, Laboratory of Developmental Neurobiology, GIGA-Neurosciences

L'implantation embryonnaire : étude des récepteurs endométriaux à l'HCG/LH blastocytaire et intérêt de la mesure du G-CSF folliculaire
Gridelet Virginie, Laboratory of Immunoendocrinology, GIGA-I3

Utilisation des cellules souches humaines à pluripotence induite normales et mutantes pour l'étude et le traitement des surdités génétiques
Grobarczyk Benjamin, Laboratory of Developmental Neurobiology, GIGA-Neurosciences

Etude de la reconstitution immunitaire après greffe de cellules souches hématopoïétiques : focus sur la fonction thymique et les lymphocytes T régulateurs
Hannon Muriel, Laboratory of Hematology, GIGA-I3

Erythropoiesis and iron metabolism after stem cell transplantation
Jaspers Aurélie, Laboratory of Hematology, GIGA-I3

Metabolic significance of inorganic triphosphate, thiamine triphosphate and their hydrolyzing enzymes
Kohn Grégory, Laboratory of Pathological aging and epilepsies, GIGA-Neurosciences

Effects of free fatty acids on innate immunity in human macrophage : implication in obesity-associated inflammation
L'homme Laurent, Laboratory of Virology and immunology, GIGA-I3

Effects of adenosine on lymphangiogenesis
Lenoir Bénédicte, Laboratory of Biology of Tumor and development, GIGA-Cancer

Implication des cellules souches mésenchymateuses dans la progression tumorale et la lymphangiogenèse
Maertens Ludovic, Laboratory of Molecular Angiogenesis, GIGA-Cancer

Rôle d'HDAC5 dans la biologie des cellules cancéreuses
Mathéus Nicolas, Laboratory of Proteins signaling and interactions, GIGA-Signal Transduction

Etude des sous-populations de cellules souches stromales de la moelle osseuse adulte, et de leur utilisation dans des protocoles de thérapie pour les maladies du système nerveux central.
Neirinckx Virginie, Laboratory of Developmental Neurobiology, GIGA-Neurosciences

Effets de la mithramycine dans la biologie du myélome multiple
Otjacques Eléonore, Laboratory of Biology of Tumor and development, GIGA-Cancer

Caractérisation et étude des cellules endocrines du tractus gastro-intestinal chez le zebrafish (Danio rerio)
Pirson Justine, Laboratory of Zebrafish Development and Disease Model, GIGA-Development

Supervised inference of biological networks with trees: Application to genetic interactions in yeast
Schrynemackers Marie, Laboratory of Systems Biology, GIGA-Systems Biology

Transcriptomic analysis of pancreatic cells in zebrafish
Tarifeno Estefania, Laboratory of Zebrafish Development and Disease Model, GIGA-Development

Therapeutic challenges in disorders of consciousness
Thibaut Aurore, Coma Science Group

A genetic etiology-study of Intellectual Disability in Rwandan patients
Uwineza Annette, Laboratory of Human Genetic, GIGA-Genetics

Identification des microARNs qui contribuent au développement de la portion auditive de l'oreille interne
Van den Ackerveken Priscilla, Laboratory of Developmental Neurobiology, GIGA-Neurosciences

Imagerie de l'intégrine $\alpha v \beta 3$ par tomographie à émission de positons au ^{18}F -FPRGD2 combinée à une tomodensitométrie
Withofs Nadia, Laboratory of Pneumology, GIGA-I3

Seminars/Conferences

Amunts Katrin - Institute of Neuroscience and Medicine of Jülich, Germany
The human brain atlas challenges and perspectives

Ardeshirdavani Amin – KUL, Belgium
NGS-Logistics: Federated analysis of NGS sequence variants across multiple locations

Bagni Claudia – VIB, Belgium
From molecules to behaviour : disentangling FXS and ASD

Bayens Nicolas - Yale Medical School, New Haven, USA
Role of shear stress in vascular remodeling and development of arterio-venous malformations

Bentires-Alj Mohamed - Friedrich Miescher Institute for Biomedical Research (FMI), Switzerland
Tumor heterogeneity: act locally, think globally

Bouvier Michel - University of Montreal, Canada
Molecular and structural determinants of GPCR functional selectivity

Bovy Nicolas – GIGA, Ulg, Belgium
Analyse des propriétés anti-tumorales des exosomes endothéliaux dans le cancer du sein suite au transfert du microARN miR-503

Brockman Michael - NimbleGen R&D, USA
Targeted Enrichment for Next Generation Sequencing Applications

Calegari Federico - CRTD Dresden, Germany
Conditional expansion of neural stem cells in the mammalian brain

Charloteaux Benoît - Dana-Farber Cancer Institute, Boston, USA
Alternative views of the human interactome

Diederich Marc - Hôpital Kirchberg, Luxembourg
Pharmacological regulation of epigenetic and cell death mechanisms

Duvillie Bertrand - INSERM Paris, France
Hypoxia and its consequences on pancreas development

Ferrer Jorge - Imperial College London, UK
Epigenetics of diabetes

Flint Jonathan - University of Oxford, UK
The role of genes in psychiatric disorders

Gradwohl Gérard - Igbmc Strasbourg, France
Transcriptional regulation of endocrine cell development and function in the pancreas and intestine

Hippenmeyer Simon – Institute of Science and Technology, Vienna, Austria
Genetic Dissection of Cerebral Cortex Development

Johnston Sebastian - Imperial College, London, UK
Mechanisms of Asthma exacerbation

Khaliq Zayd - NINDS, NIH, Washington, USA
Excitability and integration in dendrites of midbrain dopamine neurons

Koopman Werner - Radboud University Medical Center, Nijmegen, The Netherlands
Mitochondrial dynamics and redox metabolism in mitochondrial (dys)function

Ladewig Julia - Institute of Reconstructive Neurobiology, Bonn, Germany
Human neurons: generation and application

Marrion Neil - Bristol University, UK
A novel heteromeric SK channel contributing to action potential repolarization in atrial myocytes

Martin Maud - Utrecht University, The Netherlands
Microtubule functions during sprouting angiogenesis

Montcouquiol Mireille - Université de Bordeaux, France
Molecular differences between tissue and translational polarity in mammalian inner ear epithelia

Sahai Erik - London Research Institute, UK
Undersatnding of metastasis progression

Schwamborn Jens - Université du Luxembourg, Luxembourg
Utilization of stem cells for Parkinson's disease modelling and treatment

Seeger Michael - Universidad Técnica Federico Santa María, Chile
Revealing metabolic pathways and bioproducts in bacteria using functional genomics

Steineifer Ulrich - University Hospital Aachen, Germany
Cardiovascular Engineering for better patient outcomes

Trudeau Louis-Eric - Université de Montréal, Canada
Axonal arborization and energetic metabolism of nigral dopamine neurons: a window into selective vulnerability in Parkinson's disease

Stern David - Loudoun County, Virginia, USA
The genetics and neurobiology of rapidly evolving sexual behaviors

Van Steen Kristel – GIGA, ULg, Belgium
Integromics : integrating multiple omics datasets

Vanhaesebroeck Bart - University College London, UK
Isoforms of PI 3-kinase: from the bench to the clinic

Van Niel Guillaume - Institut Curie, Paris, France
Exosomes: biogenesis and function(s) of intercellular nano-shuttles

Verdin Eric - Gladstone Institute, California, USA
The emerging biology of protein acylation: from HDACs to protein malonylation

Viatour Patrick - Université de Pennsylvania, USA
E2F, cancer and stem cells: beyond the cell cycle

Webster Matthew - Uppsala University, Sweden
Honeybee evolution revealed by genome sequencing

Wery Jean-Pierre - President of Crown Bioscience, Inc - Silicon Valley, USA
Applications of surrogate mouse clinical trial (MCT) to improve preclinical predictions and translational decisions in cancer drug development



New look for the GIGA website

www.giga.ulg.ac.be

Since September 2015, the GIGA website is in responsive design to be adaptive on tablets and smartphones.
It's clearer, more complete and more modern.

What is responsive design ?

A responsive design simply means a website that has been constructed so that all of the content, images and structure of the site remains the same on any device.

Also follow the GIGA on



www.facebook.com/GIGAresearch



www.twitter.com/GIGA_ULg



Access

The GIGA centre is located on the Sart Tilman campus, University of Liege (Belgium).

The GIGA tower is situated in the CHU (University hospital). Most research units are located in the GIGA tower (B34) and some are located in B23 and B36 (also within the CHU).

The entrance of the hospital is at 50.573262 N, 5.567521 E.

Parking

There is a parking at 50.574570 N, 5.569431 E. If that one is full, you can go to 50.578801 N, 5.550366 E and take a shuttle to the Hospital (CHU).

Entry

Entry to GIGA tower (elevators) is in the main hall of the hospital (main entry next to the bakery) in front of the hairdresser.

Directions for getting to Liège and the Sart Tilman

By car

Follow the signs ring E25, exit at Embourg and follow the signs Ulg then CHU

By train or bus

From Liège Guillemins station, take bus 58 operated by TEC (+/- 25 minutes)

From the city center (Opera), take bus 48 operated by TEC (+/- 35 minutes)

By plane

Brussels Airport (Zaventem) + taxi (+/- 1 hour 15 minutes) or train + bus (+/- 1 hour 30 minutes)

Liege Airport + taxi (+/- 30 minutes)

Brussels South Charleroi Airport (Ryanair) + taxi (+/- 1 hour 15 minutes)

Address

GIGA
Quartier Hôpital
Avenue de l'Hôpital 11
4000 Liège
Belgium

GPS coordinates : 50.573262 N, 5.567521 E



The GIGA is supported by



www.giga.ulg.ac.be



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