GIGA
Université de Liège

ANNUAL REPORT 2014

2014

GIGA

Annual Report

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

Wallonie

SPW
Service public de Wallonie

Université de Liège

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«*University of Liège is presently establishing a large strategic initiative in order to define the institution's targeted research priorities through the consolidation of its research units towards an enhanced research and creative program. For so doing, the university research program will be embedded in a formal structure driven by the academic actors through a new organizational model for research teams which strengthen the Faculties research profiles and the coherence of research.*

Building on a long history of outstanding contributions to health research thanks to the establishment of a research program that facilitates and generates collaboration between Faculties and the Hospital within the University campus, GIGA is internationally recognized and well positioned in our model to provide more and more distinctive contributions to research.

One of the GIGA goals is to improve health care through invention and implementation of new medical technologies which are sustained by high level basic research. In such a way, GIGA appears as a world leader in translating discoveries from basic research into clinical outcomes !

It is thus crucial that we optimize the university funding research and administrative systems to deliver outstanding supports that help researchers to compete and succeed all over the world.

We have to invest and to enable in research advances that maintain and strengthen our competitiveness and excellence even in the face of a restricted funding climate. Scientific excellence and innovation must be the watchword of our mission !»

Rudy Cloots, Associate Vice-Rector for Research, University of Liège

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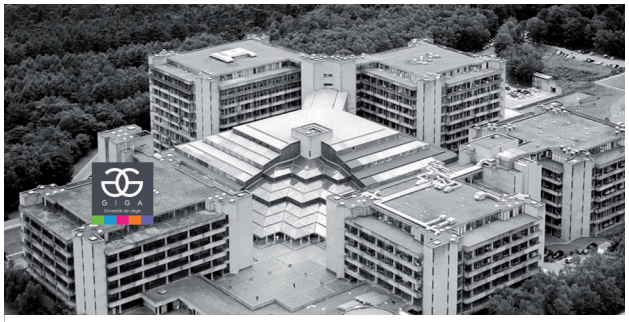

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Structure

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Research

Highlights

27/01/2014
GIGA-Day
The technology platforms and their impact for the research
More than 250 people assist to this GIGA Day where the links between research and technology platforms were presented.

24/04/2014
BeMGI Annual Meeting 2014
Genomic Advances in Disease Biology and Diagnostics
Conference organized by the Belgian Medical Genomics Initiative (Belspo-Interuniversity Attraction Poles project) with Cisca Wijmenga from the University Medical Center Groningen

19/05/2014
GIGA-Cancer Day
«The lymphatic system : the bed and bench point of views»

23-26/05/2014
The 8th International Conference on Thiamine
Thiamine biochemistry - «From Catalysis to Pathology» took place at the GIGA this year.

09/07/2014
Photos exhibition - Microscopy of the living
A photo exhibition on the microscopy of the living was inaugurated at the lobby of the GIGA. The infinitely small seen in big... An opportunity to show what is undertaken in Imaging in our center.

25/11/2014
Start of the «GIGA-Conferences» cycle
In 2014, GIGA has initiated a cycle of international conferences. Each thematic research unit (TRU) has invited a world-renowned speaker to present his work. The GIGA-I3 thematic research unit was honored to invite the first speaker of the 2014-2015 cycle of conferences. The Professor Eric Vivier will give his talk on November 25 on his latest discoveries regarding Natural killer cells (NK) and innate immunity. These recent findings show that the suppression of one of the major activation systems of the mice NK cells, increases the anti-tumoral properties of NK cells and the capacity of the animals to resist to virus.

04/12/2014
Scientific day
Cancer, Alzheimer's disease, cardiovascular diseases, hearing loss... 6 significant research from GIGA at 2014 were presented.
Each year, the 600 GIGA researchers are behind 200 publications at an international level.

16-19/12/2014
Thematic week in Virology
The GIGA is organizing a thematic week in virology with several lectures each day.

Prizes

Edouard Louis, prize of the clinical research of the Inbev-Baillet Latour Founds

The InBev-Baillet Latour Prizes for Clinical Research, intended for outstanding researchers under the age of 50, aim at rewarding clinical research carried out by medical doctors who are affiliated with an academic institution, in both the Dutch and the French speaking communities. For Wallonia, this year's Prizes were awarded to Professors Denis Franchimont (ULB) & Edouard Louis for the their study «Pathogeny and natural history of inflammatory bowel disease : optimizing treatment strategies and searching for new pharmaceutical targets».

Brigitte Malgrange and Laurent Nguyen - Fondation Médicale Reine Elisabeth grant and Solvay prize

They received the Fondation Médicale Reine Elisabeth grant for the project "deciphering the role of protein acetylation in primary ciliogenesis" and the Solvay prize for the project "Unravelling the roles of lysine acetylation in neural development".

Stéphanie Hody (GIGA-Neurosciences), winner of the Coërs Prize 2013-2014

This prize was awarded by the Royal Academy of Medicine on September 6 at the «Palais des Académies», for her work entitled «Study of the neural determinism of the changes in muscle fiber typology following eccentric muscular contraction training»

Michel Georges, officer of the Walloon Merit

Michel Georges (GIGA-Genetics) received this award from the Minister-President Paul Magnette on September 18. The Walloon Merit is awarded to «any person or entity, whose talent or merit honors Wallonia in an exceptional extent and contributes significantly to its influence».

Virginie Neirinckx (GIGA-Development), winner of the Rotary Award «Hope in Head» for a project entitled «Exploiting bone marrow stromal cell secretomes for treating spinal cord injuries» .

Laurent Nguyen rewarded by the AstraZeneca Foundation

Laurent Nguyen won the AstraZeneca prize, awarded by the AstraZeneca Foundation and FNRS, in the field of neurosciences and psychiatry, for his work on polymicrogyria.

Two Telethon fundings for Vincent Seutin of the laboratory of the Neurophysiology

These Telethon fundings concern a project studying the excitability of neurons of the central nervous system involved in the control of the sleep-wake cycle, as part of the Steinert's disease.

Jean-Pierre Bourguignon won the Andrea Prader Prize

The Andrea Prader Prize is an annual Leadership Award given to a member of the Society. It is the most prestigious ESPE senior award and was created to honour lifetime achievement in teaching and research, as well as to recognise outstanding leadership and overall contribution to the field of paediatric endocrinology. It's the annual leadership award of the European Endocrine Society.

GIGA researchers, from everywhere

2014 Key numbers

Members

592 Members
228 PhD Scientists
228 PhD Students
89 Technicians
26 Administratives
21 Platforms Logisticians/Technicians
122 Foreign Researchers
38 Nationalities

FNRS Positions

24 Research Fellows
11 Postdoctoral Researchers
28 Research Associates
8 Senior Research Associates
5 Research Directors
1 Scientific Research Worker
1 Logistician
28 Fellowships
61 Televie Fellowships
36 FRIA Fellowships

Publications

251 Publications
21 Publications with IF > 10
71 Publications with IF between 5 and 10
97 Publications with IF between 3 and 5
62 Publications with IF < 3

28 PhD Thesis
33 Seminars

12 Patent Applications filed
7 Patent Applications published

Research funding

2014 New FNRS Grants

Research Associate
Nor Eddine Sounni (GIGA-Cancer)

Postdoctoral researchers
Juliette Godin (GIGA-Neurosciences)
Carla Gomes da Silva (GIGA-Neurosciences)
Thomas Marichal (GIGA-I3)

MD. PhD Fellow
Pauline Erpicum (GIGA-Cardiovascular Sciences)
Pierre Foidart (GIGA-Cancer)
Martin Moise (GIGA-Neurosciences)

Research Fellow
Kyrylo Bessonov (GIGA-Systems Biology & Chemical Biology)
Céline Laschet (GIGA-Signal Transduction)
Marie Wehenkel (GIGA-Neurosciences)

FNRS

2014 TELEVIE funded projects

Impact of demethylating agents on graft-versus-host disease (GvHD) and graft-versus-leukemia (GvL) effects in humanized mice | Frédéric BARON, Yves BEGUIN

Revisiting Th17 cells in the setting of allogeneic stem cell transplantation and graft-versus-host disease | Frédéric BARON, Yves BEGUIN, Sophie SERVAIS

Hematopoietic stem cell transplantation in children with malignant or nonmalignant disorders | Yves BEGUIN, Christiane VERMYLEN, Eric SARIBA

Mesenchymal stromal cell therapy in the context of hematopoietic stem cell transplantation | Yves BEGUIN, Frédéric BARON

Study of carbonyl stress contribution to the development and progression of human gliobastoma | Akeila BELLAHCÈNE, Vincent CASTRONOVO

Roles of carbonyl stress and mitochondrial dysfunction induced by methylglyoxal in tumoral progression | Akeila BELLAHCÈNE, Vincent CASTRONOVO

Role of Myoferlin in Mitochondrial Function of Cancer Cell | Vincent CASTRONOVO, Andrei TURTOI

Implication of ADAM28 in lung cancer development and the establishment of a tumour-prone inflammatory microenvironment | Didier CATALDO

Role of ADAM/ADAMTS proteases in the establishment of premetastatic niches | Didier CATALDO

Rôle of PINB in EGFR-dependent signaling pathways | Alain CHARIOT

Characterization of HPIP E3 ligases: Insights into mechanisms underlying ERalpha degradation and tumor development in the mammary gland | Alain CHARIOT

Unraveling the signaling and dimerization properties of CXCR3 isoforms with CXCR7 and impact on cancer biology | Andy CHEVIGNÉ, Julien HANSON

Study of Elp3 functions in melanoma | Pierre CLOSE

ADAMTS2, 3 and 14 in angiogenesis and tumour progression | Alain COLIGE

Determination of the specific functions of metalloproteases implicated in different steps of angiogenesis and tumor progression by identification of their substrate repertoire | Alain COLIGE, Agnès NOËL, Didier CATALDO

Personalizing radiotherapy through a novel approach for the deformable registration of medical images | Philippe COUCKE, Pierre GEURTS, Sebastien JODOGNE, Philippe MARTINIVE

Role of alternative NF-kB pathway in chronic hepatitis-mediated Hepatocellular carcinoma development | Emmanuel DEJARDIN

Squamocolumnar junctions: histologic, cellular, molecular and clinical considerations | Philippe DELVENNE

Evaluation of specific glioblastoma (GBM) biomarkers | Philippe DELVENNE, Felix SCHOLTES

Post transcriptional gene regulatory networks in angiogenesis | Franck DEQUIEDT

RNA-seq reveals cancer driver genomic changes in delta-retrovirus-induced leukemia: novel mechanisms of transcriptome rewiring by chimeric long noncoding RNAs | Michel GEORGES, Philippe MARTIAT, Anne VAN DEN BROEKE

Implication of Epithelial-to-mesenchymal transitions (EMTs) on the formation of vascular nests for Circulating Tumor Cells (CTCs) | Christine GILLES, Cécile OURY, Guy JERUSALEM

Development of a therapeutic approach aiming to inhibit tumor promotion of squamous cell carcinomas by using HMGB1 Inhibitors | Pascale HUBERT

Role of Natural Killer cells in the control of virus-induced tumours (papillomavirus and polyomavirus) | Nathalie JACOBS

Lymphatic vasculature and intravasation process characterization in cervical cancer | Frédéric KRIDELKA, Agnès NOËL

Glioblastoma progression: correlation of tumor genetic profile with clinical aggressiveness | Didier MARTIN, Felix SCHOLTES, Vincent BOURS

Adpatative metabolic response of cancer cells to Histone Deacetylase 5 inhibition | Denis MOTTET

Restoration of fertility for cancerous patients by ovarian cryopreservation, follicular and oocyte maturation, detection and purging of neoplastic cells in ovarian grafts | Michelle NISOLLE, Marie-Madeleine DOLMANS, Isabelle DEMEESTERE

Inhibition of follicular apoptosis due to post-transplant and hypoxia reperfusion injury to enhance the graft ovarian cortex to restore fertility of cancer patients | Michelle NISOLLE, Carine MUNAUT

Role of stromal cells in the tumor adaptation to anticancer treatments with RTKIs | Agnès NOËL, Nor Eddine SOUNNI

Role of MT4-MMP in the progression of triple negative breast cancer | Agnès NOËL, Nor Eddine SOUNNI

Role of myoferlin in the secretion of proangiogenic molecules by cancer cells | Olivier PEULEN, Vincent CASTRONOVO

Development of a topical delivery system containing lipoplexes based on anti-E6/E7 nucleic acids for the treatment of HPV cancers | Géraldine PIEL, Pascale HUBERT

Investigation of the pro-apoptotic role of inositol phosphatase SHIP-1 via its interaction with XIAP in myeloid leukemia | Jacques PIETTE, Sylvie LEGRAND

Insights into the role of the dual-specificity protein phosphatase DUSP3/VHR in tumour metastasis | Souad RAHMOUNI

The EORTC G-SAM project: Stability of Actionable Mutations in Glioblastomas- Is a second surgical resection/biopsy required for personalized medicine of recurrent glioblastoma patients? | Pierre ROBE, Vincent BOURS

The MAS-GPVac Project : Microvesicle Analysis for Specific Peptidic Vaccination againts Glioblastomas | Pierre ROBE, Vincent BOURS, Arsène BURNY

Study of the glioblastoma initiating-cells expressing CXCR4 receptor and their possible role in tumor recurrence | Bernard ROGISTER

Involvement of macrophage migration inhibitory factor in HPV infection in the upper aero-digestive tract cancer | Sven SAUSSEZ, Philippe DELVENNE

Role of EXT-1 in T-cell Acute lymphoblastic leukemia | Jean-Claude TWIZERE

Synthetic lethality as therapy against mesothelioma | Luc WILLEMS

Role of bovine leukemia virus microRNAs | Luc WILLEMS

Characterization of circulating tumor cells in cancer patients | Luc WILLEMS

In Vivo and In Vitro characterization of adult bone marrow neural crest stem cells and their potential implication in hematopoietic support | Sabine WISLET, André GOTHOT

2014 Fonds Léon Fredericq funded projects

The Fonds Léon Fredericq aims to support fundamental and clinical medical research at the University Hospital of Liège (CHU).

Clinical research grant
Laure Noël (GIGA-Cancer)

PhD grants
Benjamin Grobarczyk (GIGA-Neurosciences)
Justine Pirson (GIGA-Development)
Meggy Suarez-Carmona (GIGA-Cancer)
Estefania Tarifeno (GIGA-Development)
Priscilla Van den Ackerveken (GIGA-Neurosciences)
Julie Vignisse (GIGA-Neurosciences)

Travel grants
Guillaume Drion (GIGA-Neurosciences)
Olivier Ek (GIGA-Development)
Charlotte Erpicum (GIGA-Cancer)

Operating subsidies
Muriel Hannon (GIGA-I3)
Laurent Lhomme (GIGA-Signal Transduction)
Virginie Neirinckx (GIGA-Neurosciences)
Mélissa Garcia (GIGA-Cancer)
Juliette Godin (GIGA-Neurosciences)
Roy Heusschen (GIGA-I3)
Sandra Huysseune (GIGA-Neurosciences)
Elise Peyre (GIGA-Neurosciences)
Francesca Rapino (GIGA-Signal transduction)
Natacha Rocks (GIGA-Cancer)
Sophie Servais (GIGA-I3)
Renaud Vandenbosch (GIGA-Neurosciences)

Specific awards

ACIIRT award
Pauline Erpicum (GIGA-Sciences Cardiovasculaires)

Bourse du département des sciences biomédicales et précliniques
Sylvain Hansen (GIGA-Cancer)

Bourse de la ligue belge de la sclérose en plaques
Valérie Dion (GIGA-Neurosciences)

Bourse Monsieur et Madame Joseph Darmont-Delmotte
Grégory Ehx (GIGA-I3)

Astrazeneca award
Christophe Desmet (GIGA-I3)

Prix Chevremont-Comhaire
Renaud Vandenbosch (GIGA-Neurosciences)

Prix étudiant
Florence Rogister (GIGA-Neurosciences)

Frederic Van Den Brule award
Muriel Hannon (GIGA-I3)

Nicolas Jacquet award
Andrei Turtoi (GIGA-Cancer)

Awards of Foundations linked to the Fonds Léon Fredericq

Fondation Jaumain
Sophie Servais (GIGA-I3)

Fondation Lejeune Lechien
Olivier Malaise (GIGA-I3)

Fondation pour vaincre le cancer
Catherine Polese (GIGA-Signal Transduction)

Fondation Van Beirs
Nicolas Gillet (GIGA-Cancer)

Fondation Jean Gol
Michael Herfs (GIGA-Cancer)

Fondation Bonjean-Oleffe
Elodie Hendrick (GIGA-Signal Transduction)

Winners of the «Centre Anticancéreux près de l'Université de Liège»
Marilène Binsfeld (GIGA-I3)
Meriem Boukerroucha (GIGA-Genetics)
Nicolas Bovy (GIGA-Cancer)
Maude Gabriel (GIGA-Cancer)
Natacha Leroi (GIGA-Cancer)
Céline Pirlot (GIGA-Signal transduction)
Nassim Bouznad (GIGA-Cardiovascular Sciences)
Jonathan Cimino (GIGA-Systems Biology)
Stéphanie Herkenne (GIGA-Cancer)
Michael Herfs (GIGA-Cancer)
Laurie Henry (GIGA-Cancer)
Pamela Maris (GIGA-Cancer)

Fellowships from the Foundation Against Cancer

Fondation contre le Cancer

The Foundation Against Cancer distributed 17 million euros for research in December. Several GIGA members were rewarded.

This is the occasion to focus on translational research (link between basic research and clinical research), which is supported by the Foundation and particularly active in the GIGA.

On Decemberv 1, in the presence of Her Majesty Queen Mathilde, the Foundation Against Cancer distributed 17 million euros. This amount was shared between 67 research teams and, for the first time, to 8 winners who will benefit from postdoctorate mandates. These 8 physicians will have the chance, for 5 years, to combine a medical career in university with a half time researcher work. Among these 8 laureates, Jo Caers, hematologist with the University Hospital and researcher in the Laboratory of Hematology (GIGA-I3).

GIGA laureates

Regarding the basic research, Agnès Noël was rewarded with a fellowship (grant) for her project «Interfering with tumor metabolism to overcome adaptation to molecular targeted therapies», on resistance to anti-cancer treatment, and Didier Cataldo, as part of research on asbestos cancer with his project «Mechanisms of resistance to therapy in mesothelioma».

Regarding the translational and clinic research, the projects of Frédéric Kridelka, Vincenzo Castronovo and Yves Beguin were selected.
Frédéric Kridelka : «Searching for new prognostic markers of nodal extension : a crucial step toward cervical cancer optimization and personalization».
Vincenzo Castronovo : «Development of TGFBI as a novel armed antibody for therapy of liver metastases»
Yves Beguin : «Improving MSC immunosuppressive therapy for acute GVHD after hematopoietic cell transplantation»

Translational research

The occasion to remember that translational research is particularly active in the GIGA. Translational research is when basic research (by academics in laboratories) develops constant links with clinical research (by physicians at the bedside of patients).

The cooperation between researchers and physicians from the University Hospital in which the GIGA is located is essential. Not less than forty clinicians share their time between medical activities and research in the GIGA, in many medical specialties : cardiology, hematology, genetics, gynecology, endocrinology, gastroenterology, pneumology, pediatrics, rheumatology, neurology, ENT, anatomopathology

Jo Caers, laureate of a postdoctorate mandate

Jo Caers studied medecine at the VUB, and has a specialty in internal medicine and hematology. He is one of the 8 belgian physicians awarded with a postdoctorate mandate from the Foundation against Cancer. This mandate aims at allowing the physicians to combine their clinical activity and research in cancerology.

The opportunity to ask him a few questions on his point of view about translational research.

As a physician, is it important to be involved in research ?
We are often described as «links» between research and clinic and I believe this definition summarizes properly our work. I think it is useful that physicians be involved in research projects, first to try to suppress the gap between research and clinic and also to ensure a project remains pertinent in the fast evolution of medicine.

Have you always wanted to be involved as much on both medical and research levels ?
Since my studies in medicine, I've been involved in research projects. In our hematology staff, there is a long history of translational research, established by Professors Fillet, Beguin and Baron. As soon as I arrived in the staff, I've always had research activities.

What is the main advantage of this mandate ?
This mandate will fund half-time research for 5 years, beside my physician work at the University Hospital. The function of clinician-researcher is not much supported by the government. There are a few mandates and quite a lot of competition with other medical specialties. Regarding cancerology, only one or two physicians active in cancerology receive a FNRS fellowship every year. This new fellowship from the Foundation against Cancer is actually a real opportunity.

Do you think the location of the GIGA in the premises of the University Hospital is a particular asset regarding the translational research ?
Definitely. It is very convenient to be able to switch directly from consultations and patients bedside to the laboratory. I've worked in other universities and I'm very impressed by the complementarity between the research laboratories and the platforms which does not exist elsewhere in Belgium. I'm also very happy with the many exchanges between the laboratories, enhanced by the structure of the GIGA. The concept and the location of the GIGA are ideal to undertake translational research.

GIGA-Cancer

The researchers of the GIGA-Cancer are studying molecular and cellular mechanisms involved in cancer genesis, cancer progression and metastatic dissemination.

They are exploring the functions of novel regulators of different steps of cancer growth and invasion. A special emphasis is given on the identification of predictive, prognostic and diagnostic markers of cancers with putative interest to develop personalized treatments or overcome tumor resistance or adaptation to therapies currently used in clinic. With this aim advanced epigenetic, genomic, proteomic and metabolomic technologies are applied to human samples or sophisticated in vitro and in vivo models.

To achieve their goals, the GIGA-cancer researchers have developed close collaborations with clinicians in departments of the University Hospital (CHU of Liege). These experimental and translational approaches allow an in-depth investigation of intrinsic features of primary tumor cells, metastatic tumor cells and circulating tumor cells (CTC).

In addition, the complex interactions occurring between cancer cells and their molecular and cellular environments are studied with a special focus on extracellular matrix, immune cells, inflammatory cells and endothelial cells of blood or lymphatic vessels. In order to get new insights into abnormal tissue remodeling, impaired vessel functions and excessive inflammation, the URT members are also investigating other disorders sharing these abnormal features such as ocular diseases, lung inflammatory disorders, preeclampsia, endometriosis and embryonic implantation.

The ultimate goal of the URT is to develop safer and more efficient treatments with a specific interest in developing a personalized medicine.

Laboratories

- Laboratory of Cellular and Molecular Epigenetics (CME)
  Luc Willems
- Laboratory of Human Genetics (HG)
  Vincent Bours
- Laboratory of Tumor and Development Biology (LBTD)
  Didier Cataldo, Agnès Noel, Jean-Michel Foidart
- Laboratory of Connective Tissues Biology (LBTC)
  Alain Colige
- Laboratory of Experimental Pathology (LEP)
  Philippe Delvenne
- Metastases Research Laboratory (MRL)
  Vincent Castronovo
- Laboratory of Molecular Angiogenesis Laboratory (LAM)
  Ingrid Struman

Head

Agnès Noël

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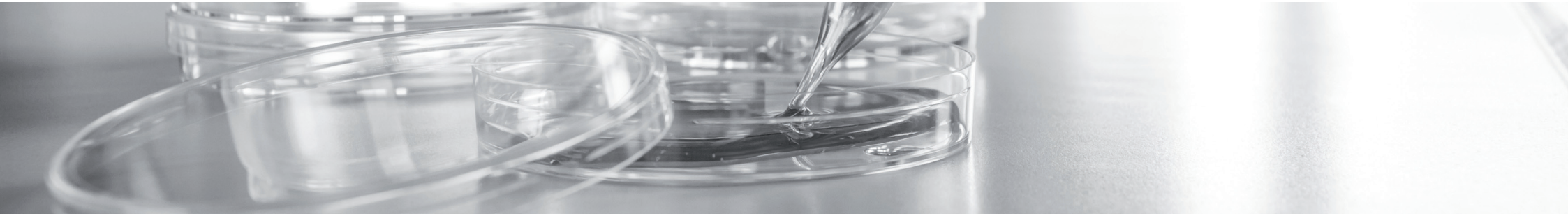
39 Scientists

65 PhD Students

19 Technicians



PAI-1 mediates the antiangiogenic and profibrinolytic effects of 16K prolactin

Bajou K, Herkenne S, Thijssen VL, D'Amico S, Nguyen NQ, Bouche A, Tabruyn S, Srahna M, Carabin JY, Nivelles O, Paques C, Cornelissen I, Lion M, Noel A, Gils A, Vinckier S, Declerck PJ, Griffioen AW, Dewerchin M, Martial JA, Carmeliet P and Struman I.

Nature medicine. 2014;20:741-7.

The N-terminal fragment of prolactin (16K PRL) inhibits tumor growth by impairing angiogenesis, but the underlying mechanisms are unknown. Here, we found that 16K PRL binds the fibrinolytic inhibitor plasminogen activator inhibitor-1 (PAI-1), which is known to contextually promote tumor angiogenesis and growth. Loss of PAI-1 abrogated the antitumoral and antiangiogenic effects of 16K PRL. PAI-1 bound the ternary complex PAI-1-urokinase-type plasminogen activator (uPA)-uPA receptor (uPAR), thereby exerting antiangiogenic effects. By inhibiting the antifibrinolytic activity of PAI-1, 16K PRL also protected mice against thromboembolism and promoted arterial clot lysis. Thus, by signaling through the PAI-1-uPA-uPAR complex, 16K PRL impairs tumor vascularization and growth and, by inhibiting the antifibrinolytic activity of PAI-1, promotes thrombolysis.

Blocking lipid synthesis overcomes tumor regrowth and metastasis after antiangiogenic therapy withdrawal

Sounni NE, Cimino J, Blacher S, Primac I, Truong A, Mazzucchelli G, Paye A, Calligaris D, Debois D, De Tullio P, Mari B, De Pauw E and Noel A.

Cell metabolism. 2014;20:280-94.

The molecular mechanisms responsible for the failure of antiangiogenic therapies and how tumors adapt to these therapies are unclear. Here, we applied transcriptomic, proteomic, and metabolomic approaches to preclinical models and provide evidence for tumor adaptation to vascular endothelial growth factor blockade through a metabolic shift toward carbohydrate and lipid metabolism in tumors. During sunitinib or sorafenib treatment, tumor growth was inhibited and tumors were hypoxic and glycolytic. In sharp contrast, treatment withdrawal led to tumor regrowth, angiogenesis restoration, moderate lactate production, and enhanced lipid synthesis. This metabolic shift was associated with a drastic increase in metastatic dissemination. Interestingly, pharmacological lipogenesis inhibition with orlistat or fatty acid synthase downregulation with shRNA inhibited tumor regrowth and metastases after sunitinib treatment withdrawal. Our data shed light on metabolic alterations that result in cancer adaptation to antiangiogenic treatments and identify key molecules involved in lipid metabolism as putative therapeutic targets.

EGFR activation and signaling in cancer cells are enhanced by the membrane-bound metalloprotease MT4-MMP

Paye A, Truong A, Yip C, Cimino J, Blacher S, Munaut C, Cataldo D, Foidart JM, Maquoi E, Collignon J, Delvenne P, Jerusalem G, Noel A and Sounni NE.

Cancer research. 2014 Dec 1;74(23):6758-70.

MT4-MMP (MMP-17) is a glycosylphosphatidyl inositol-anchored matrix metalloprotease expressed on the surface of cancer cells that promotes tumor growth and metastasis. In this report, we identify MT4-MMP as an important driver of cancer cell proliferation through CDK4 activation and retinoblastoma protein inactivation. We also determine a functional link between MT4-MMP and the growth factor receptor EGFR. Mechanistic experiments revealed direct association of MT4-MMP and its positive effects on EGFR phosphorylation in response to TGFα and EGF in cancer cells. Notably, the effects of MT4-MMP on proliferation and EGFR activation did not rely on metalloprotease activity. Clinically, MT4-MMP and EGFR expressions were correlated in human triple-negative breast cancer specimens. Altogether, our results identify MT4-MMP as a positive modifier of EGFR outside-in signaling that acts to cooperatively drive cancer cell proliferation.

Altered alpha-defensin 5 expression in cervical squamocolumnar junction: implication in the formation of a viral/tumour-permissive microenvironment

Hubert P, Herman L, Roncarati P, Maillard C, Renoux V, Demoulin S, Erpicum C, Foidart JM, Boniver J, Noel A, Delvenne P and Herfs M.

The Journal of pathology. 2014;234:464-77.

Human papillomavirus (HPV) infection, particularly type 16, is causally associated with cancer of the uterine cervix, which mainly develops at the squamocolumnar (SC) junction. The progression of cervical HPV infections into (pre)neoplastic lesions suggests that viral antigens are not adequately recognized by innate immunity or presented to the adaptive immune system. Members of the defensin family have recently been found to inhibit viral and bacterial pathogens, to stimulate the migration of immune cells and to play a role in anticancer responses. In the present study, we focused on the poorly characterized human α-defensin 5 (HD-5) and its possible role in these processes. We showed that HD-5 was able to prevent HPV virion entry into cervical keratinocytes and to influence adaptive immunity. Indeed, this peptide specifically induced the chemoattraction and proliferation of both activated T lymphocytes and immature dendritic cells in a CCR2/CCR6-dependent manner and stimulated the infiltration of these professional antigen-presenting cells in a (pre)neoplastic epithelium transplanted in vivo in immunodeficient mice. No chemotactic effect was observed with plasmacytoid dendritic cells, macrophages or natural killer cells. Proliferative and angiogenic effects of HD-5 were also assessed in vitro and in vivo. However there was a striking regional disparity in expression of HD-5, being prominent in ectocervical, vaginal and vulvar neoplasia, while absent, or nearly so, in the cervical SC junction. Taken together, these results suggest one possible explanation for why the SC junction is uniquely vulnerable to both high-risk HPV infection (via reduced HD-5 expression and viral entry) and progression of neoplasia (via altered cell-mediated immune responses and altered microenvironment).

Triple negative tumors accumulate significantly less methylglyoxal specific adducts than other human breast cancer subtypes

Chiavarina B, Nokin MJ, Durieux F, Bianchi E, Turtoi A, Peulen O, Peixoto P, Irigaray P, Uchida K, Belpomme D, Delvenne P, Castronovo V and Bellahcene A.

Oncotarget. 2014 Jul30;5(14):5472-82.

Metabolic syndrome and type 2 diabetes are associated with increased risk of breast cancer development and progression. Methylglyoxal (MG), a glycolysis by-product, is generated through a non-enzymatic reaction from triose-phosphate intermediates. This dicarbonyl compound is highly reactive and contributes to the accumulation of advanced glycation end products. In this study, we analyzed the accumulation of Arg-pyrimidine, a MG-arginine adduct, in human breast adenocarcinoma and we observed a consistent increase of Arg-pyrimidine in cancer cells when compared with the non-tumoral counterpart. Further immunohistochemical comparative analysis of breast cancer subtypes revealed that triple negative lesions exhibited low accumulation of Arg-pyrimidine compared with other subtypes. Interestingly, the activity of glyoxalase 1 (Glo-1), an enzyme that detoxifies MG, was significantly higher in triple negative than in other subtype lesions, suggesting that these aggressive tumors are able to develop an efficient response against dicarbonyl stress. Using breast cancer cell lines, we substantiated these clinical observations by showing that, in contrast to triple positive, triple negative cells induced Glo-1 expression and activity in response to MG treatment. This is the first report that Arg-pyrimidine adduct accumulation is a consistent event in human breast cancer with a differential detection between triple negative and other breast cancer subtypes.

DeltaNp63 isoform-mediated beta-defensin family up-regulation is associated with (lymph)angiogenesis and poor prognosis in patients with squamous cell carcinoma

Suarez-Carmona M, Hubert P, Gonzalez A, Duray A, Roncarati P, Erpicum C, Boniver J, Castronovo V, Noel A, Saussez S, Peulen O, Delvenne P and Herfs M.

Oncotarget. 2014;5:1856-68.

Beside a role in normal development/differentiation, high p63 immunoreactivity is also frequently observed in squamous cell carcinoma (SCC). Due to the complexity of the gene, the role of each p63 isotype in tumorigenesis is still confusing. Constitutively produced or induced in inflammatory conditions, human beta-defensins (HβDs) are cationic peptides involved in host defenses against bacteria, viruses and fungi. Here, we investigated both the role of p63 proteins in the regulation of HβDs and the implication of these antimicrobial peptides in tumor (lymph)angiogenesis. Thus, in contrast to TAp63 isotypes, we observed that ΔNp63 proteins (α, β, γ) induce HβD1, 2 and 4 expression. Similar results were observed in cancer tissues and cell lines. We next demonstrated that ΔNp63-overexpressing SCC are associated with both a poor prognosis and a high tumor vascularisation and lymphangiogenesis. Moreover, we showed that HβDs exert a chemotactic activity for (lymphatic) endothelial cells in a CCR6-dependent manner. The ability of HβDs to enhance (lymph)angiogenesis in vivo was also evaluated. We observed that HβDs increase the vessel number and induce a significant increase in relative vascular area compared to negative control. Taken together, the results of this study suggest that ΔNp63-regulated HβD could promote tumor (lymph)angiogenesis in SCC microenvironment.

Connexin 30 expression inhibits growth of human malignant gliomas but protects them against radiation therapy

Artesi M, Kroonen J, Bredel M, Nguyen-Khac M, Deprez M, Schoysman L, Poulet C, Chakravarti A, Kim H, Scholtens D, Seute T, Rogister B, Bours V and Robe PA.

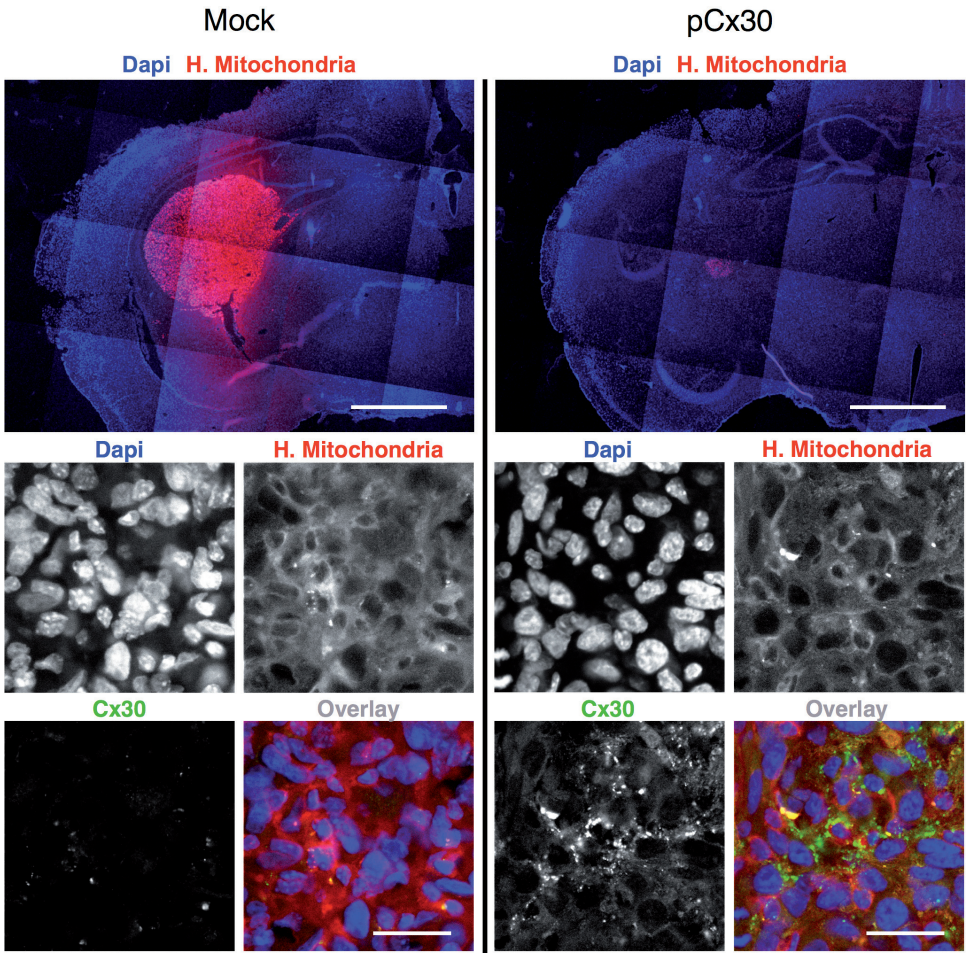
Neuro-oncology. 2014 Aug 25 pii: nou215.

Background
Glioblastomas remain ominous tumors that almost invariably escape treatment. Connexins are a family of transmembrane, gap junction-forming proteins, some members of which were reported to act as tumor suppressors and to modulate cellular metabolism in response to cytotoxic stress.

Methods
We analyzed the copy number and expression of the connexin (Cx)30 gene gap junction beta-6 (GJB6), as well as of its protein immunoreactivity in several public and proprietary repositories of glioblastomas, and their influence on patient survival. We evaluated the effect of the expression of this gap junction protein on the growth, DNA repair and energy metabolism, and treatment resistance of these tumors.

Results
The GJB6 gene was deleted in 25.8% of 751 analyzed tumors and mutated in 15.8% of 158 tumors. Cx30 immunoreactivity was absent in 28.9% of 145 tumors. Restoration of Cx30 expression in human glioblastoma cells reduced their growth in vitro and as xenografts in the striatum of immunodeficient mice. Cx30 immunoreactivity was, however, found to adversely affect survival in 2 independent retrospective cohorts of glioblastoma patients. Cx30 was found in clonogenic assays to protect glioblastoma cells against radiation-induced mortality and to decrease radiation-induced DNA damage. This radioprotection correlated with a heat shock protein 90-dependent mitochondrial translocation of Cx30 following radiation and an improved ATP production following this genotoxic stress.

Conclusion
These results underline the complex relationship between potential tumor suppressors and treatment resistance in glioblastomas and single out GJB6/Cx30 as a potential biomarker and target for therapeutic intervention in these tumors.



In vivo effect of Cx30 expression on human glioma tumor growth. Intracranial implantation of a suspension of U87 cells transfected with a Cx30 expression vector or a control vector in the striatum of immunodeficient mice. Brain slices were stained using a monoclonal antibody to human mitochondria and red-fluorescent dye-coupled secondary antibody. After four weeks, the tumor mass was significantly smaller in Cx30-expressing xenografts in comparison to the mock-transfected ones. Inserts: Immunofluorescence staining for Cx30 (green), human mitochondria (red) and human nuclei (blue). Scale bars: 1100 micrometers (upper panels) and 30 micrometers for lower panels.

GIGA-Cardiovascular Sciences

Cardiovascular disease is the leading cause of death in industrialized countries. Better understanding of the molecular and pathophysiological mechanisms underlying cardiovascular disease requires the elaboration of translational research programs.

The GIGA-Cardiovascular Sciences research Unit is made up of a multi-disciplinary team. Scientists, specialists in cardiology, experts in imaging, cardiovascular surgeons, 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 internationally recognized Centres. The Unit aims at reaching leadership and singular excellence in research and training.

Research projects span over a broad theme of cardiovascular diseases. Correlations between clinical 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 disorders of haemostasis, endothelial dysfunction, atherosclerosis, arterial thrombosis, ischemic heart disease, valvular heart disease, vascular wall disorders, ventriculo-arterial coupling, heart-lung interaction. These studies are mostly based on integrative physiology, cellular and molecular biology, gene expression analysis, hemodynamic evaluation, cardiac imaging techniques and mathematical modelling.

Laboratories

- Valvular heart disorders - Unit of Cardiology, Heart valve clinic
  Patrizio Lancellotti, Raluca Dulgheru, Marie Moonen, Luc Piérard
- Thrombosis Hemostasis - Laboratory of Thrombosis and Hemostasis
  Cécile Oury, André Gothot
- Vascular wall disorders- Unit of Cardiovascular and thoracic surgery
  Natzi Sakalihasan, Jean-Olivier Defraigne, Joël Pincemail
- Hemodynamics- Hemodynamic Research Center Hemoliege
  Bernard Lambermont, Philippe Kohl,Vincenzo d'Orio, Alexandre Ghuysen, Philippe Morimont, Thomas Desaive
- Experimental surgery - Unit of Cardiovascular and thoracic surgery & Unit of Abdominal Surgery and Transplantation
  Jean-Olivier Defraigne, Pierre Drion, François Jouret, Olivier Detry, Natzi Sakalihasan, Jean-Paul Cheramy Bien
- Bioengineering biophysics - Thermodynamics of Irreversible Processes
  Pierre Dauby, Thomas Desaive

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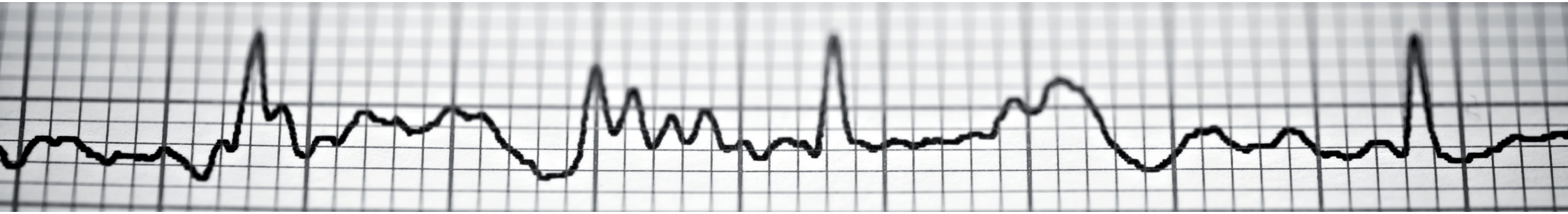
14 PhD Students

5 Technicians



P2X1 expressed on polymorphonuclear neutrophils and platelets is required for thrombosis in mice

Darbousset R, Delierneux C, Mezouar S, Hego A, Lecut C, Guillaumat I, Riederer MA, Evans RJ, Dignat-George F, Panicot-Dubois L, Oury C and Dubois C.

Blood. 2014;124:2575-85.

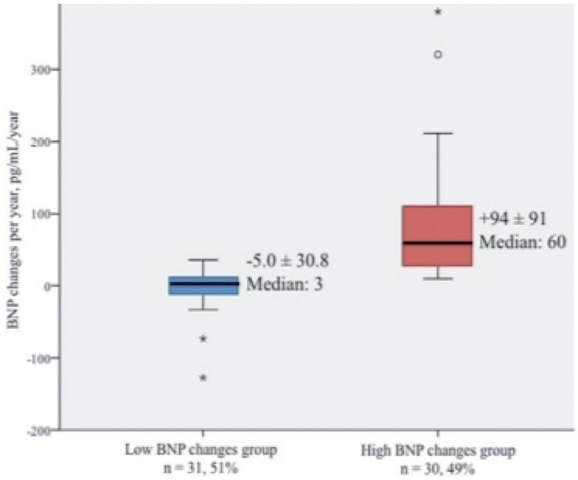
Adenosine triphosphate (ATP) and its metabolite, adenosine, are key regulators of polymorphonuclear neutrophil (PMN) functions. PMNs have recently been implicated in the initiation of thrombosis. We investigated the role of ATP and adenosine in PMN activation and recruitment at the site of endothelial injury. Following binding to the injured vessel wall, PMNs are activated and release elastase. The recruitment of PMNs and the subsequent fibrin generation and thrombus formation are strongly affected in mice deficient in the P2X1-ATP receptor and in wild-type (WT) mice treated with CGS 21680, an agonist of the A2A adenosine receptor or NF449, a P2X1 antagonist. Infusion of WT PMNs into P2X1-deficient mice increases fibrin generation but not thrombus formation. Restoration of thrombosis requires infusion of both platelets and PMNs from WT mice. In vitro, ATP activates PMNs, whereas CGS 21680 prevents their binding to activated endothelial cells. These data indicate that adenosine triphosphate (ATP) contributes to polymorphonuclear neutrophil (PMN) activation leading to their adhesion at the site of laser-induced endothelial injury, a necessary step leading to the generation of fibrin, and subsequent platelet-dependent thrombus formation. Altogether, our study identifies previously unknown mechanisms by which ATP and adenosine are key molecules involved in thrombosis by regulating the activation state of PMNs.

Usefulness of Serial B-type Natriuretic Peptide Assessment in Asymptomatic Aortic Stenosis

Henri C, Magne J, Dulgheru R, Davin L, Laaraibi S, Voilliot D, Kou S, Nchimi A, Oury C, Pierard LA and Lancellotti P.

The American journal of cardiology. 2014;114:441-8.

B-type natriuretic peptide (BNP) level may be a useful prognostic marker for the management of asymptomatic patients with aortic stenosis (AS). The aim of this study was to identify the echocardiographic determinants of BNP changes during follow-up in AS. We studied 61 asymptomatic patients with greater than moderate AS and preserved left ventricular (LV) ejection fraction who underwent rest and exercise Doppler echocardiography with concomitant BNP level measurement at baseline. BNP measurement was repeated after inclusion every 6 months. Patients were divided into 2 groups according to the median of BNP changes during follow-up. According to parameters at rest, patients in the high BNP changes group had significantly higher E/e' ratio. Statistically significant correlations were found between BNP changes and E/e' ratio and indexed left atrial area. According to exercise parameters, patients in the high BNP changes group had significantly lower exercise-induced increase in LV ejection fraction. Statistically significant correlations were found between BNP changes and exercise-induced changes in LV ejection fraction. After adjustment for age, mean aortic pressure gradient, and BNP level at baseline, multivariate analysis identified indexed left atrial area, E/e' at rest, and exercise-induced increase in ejection fraction as independent determinants of BNP changes during follow-up. In conclusion, this study shows that, in asymptomatic patients with preserved LV function and moderate AS, serial BNP measurements may widely vary. Subclinical LV diastolic and systolic dysfunctions are frequently present in patients with higher serial BNP changes.



Annualized BNP changes according to BNP changes group (median) in asymptomatic patients with significant aortic stenosis

Multifactorial relationship between 18F-fluoro-deoxy-glucose positron emission tomography signaling and biomechanical properties in unruptured aortic aneurysms

Nchimi A, Cheramy-Bien JP, Gasser TC, Namur G, Gomez P, Seidel L, Albert A, Defraigne JO, Labropoulos N and Sakalihasan N.

Circulation Cardiovascular imaging. 2014;7:82-91.

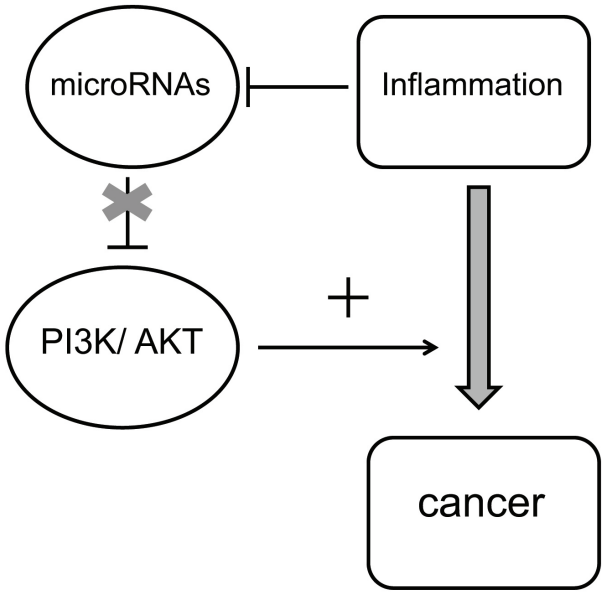
The relationship between biomechanical properties and biological activities in aortic aneurysms was investigated with finite element simulations and 18F-fluoro-deoxy-glucose (18F-FDG) positron emission tomography. The study included 53 patients (45 men) with aortic aneurysms, 47 infrarenal (abdominal aortic) and 6 thoracic (thoracic aortic), who had ≥1 18F-FDG positron emission tomography/computed tomography. During a 30-month period, more clinical events occurred in patients with increased 18F-FDG uptake on their last examination than in those without (5 of 18 [28%] versus 2 of 35 [6%]; P=0.03). Wall stress and stress/strength index computed by finite element simulations and 18F-FDG uptake were evaluated in a total of 68 examinations. Twenty-five (38%) examinations demonstrated ≥1 aneurysm wall area of increased 18F-FDG uptake. The mean number of these areas per examination was 1.6 (18 of 11) in thoracic aortic aneurysms versus 0.25 (14 of 57) in abdominal aortic aneurysms, whereas the mean number of increased uptake areas colocalizing with highest wall stress and stress/strength index areas was 0.55 (6 of 11) and 0.02 (1 of 57), respectively. Quantitatively, 18F-FDG positron emission tomographic uptake correlated positively with both wall stress and stress/strength index (P<0.05). 18F-FDG uptake was particularly high in subjects with personal history of angina pectoris and familial aneurysm. Increased 18F-FDG positron emission tomographic uptake in aortic aneurysms is strongly related to aneurysm location, wall stress as derived by finite element simulations, and patient risk factors such as acquired and inherited susceptibilities.

Identification of a microRNA landscape targeting the PI3K/Akt signaling pathway in inflammation-induced colorectal carcinogenesis

Josse C, Bouznad N, Geurts P, Irrthum A, Huynh-Thu VA, Servais L, Hego A, Delvenne P, Bours V and Oury C.

Am J Physiol Gastrointest Liver Physiol. 2014;306:G229-43.

Inflammation can contribute to tumor formation; however, markers that predict progression are still lacking. In the present study, the well-established azoxymethane (AOM)/dextran sulfate sodium (DSS)-induced mouse model of colitis-associated cancer was used to analyze microRNA (miRNA) modulation accompanying inflammation-induced tumor development and to determine whether inflammation-triggered miRNA alterations affect the expression of genes or pathways involved in cancer. A miRNA microarray experiment was performed to establish miRNA expression profiles in mouse colon at early and late time points during inflammation and/or tumor growth. Chronic inflammation and carcinogenesis were associated with distinct changes in miRNA expression. Nevertheless, prediction algorithms of miRNA-mRNA interactions and computational analyses based on ranked miRNA lists consistently identified putative target genes that play essential roles in tumor growth or that belong to key carcinogenesis-related signaling pathways. We identified PI3K/Akt and the insulin growth factor-1 (IGF-1) as major pathways being affected in the AOM/DSS model. DSS-induced chronic inflammation downregulates miR-133a and miR-143/145, which is reportedly associated with human colorectal cancer and PI3K/Akt activation. Accordingly, conditioned medium from inflammatory cells decreases the expression of these miRNA in colorectal adenocarcinoma Caco-2 cells. Overexpression of miR-223, one of the main miRNA showing strong upregulation during AOM/DSS tumor growth, inhibited Akt phosphorylation and IGF-1R expression in these cells. Cell sorting from mouse colons delineated distinct miRNA expression patterns in epithelial and myeloid cells during the periods preceding and spanning tumor growth. Hence, cell-type-specific miRNA dysregulation and subsequent PI3K/Akt activation may be involved in the transition from intestinal inflammation to cancer.



Model depicting a proposed mechanism linking inflammation and cancer. Carcinogenesis may be triggered by inflammation-induced miRNA dysregulation in colon cells and leukocytes that would impact on proteins involved in the PI3K/Akt signaling pathway, thereby contributing to cancer cell proliferation and tumor growth.

Visualisation of time-varying respiratory system elastance in experimental ARDS animal models

Van Drunen EJ, Chiew YS, Pretty C, Shaw GM, Lambermont B, Janssen N, Chase JG and Desaive T.

BMC pulmonary medicine. 2014;14:33.

Patients with acute respiratory distress syndrome (ARDS) risk lung collapse, severely altering the breath-to-breath respiratory mechanics. Model-based estimation of respiratory mechanics characterising patient-specific condition and response to treatment may be used to guide mechanical ventilation (MV). This study presents a model-based approach to monitor time-varying patient-ventilator interaction to guide positive end expiratory pressure (PEEP) selection. The single compartment lung model was extended to monitor dynamic time-varying respiratory system elastance, Edrs, within each breathing cycle. Two separate animal models were considered, each consisting of three fully sedated pure pietrain piglets (oleic acid ARDS and lavage ARDS). A staircase recruitment manoeuvre was performed on all six subjects after ARDS was induced. The Edrs was mapped across each breathing cycle for each subject. Six time-varying, breath-specific Edrs maps were generated, one for each subject. Each Edrs map shows the subject-specific response to mechanical ventilation (MV), indicating the need for a model-based approach to guide MV. This method of visualisation provides high resolution insight into the time-varying respiratory mechanics to aid clinical decision making. Using the Edrs maps, minimal time-varying elastance was identified, which can be used to select optimal PEEP. Real-time continuous monitoring of in-breath mechanics provides further insight into lung physiology. Therefore, there is potential for this new monitoring method to aid clinicians in guiding MV treatment. These are the first such maps generated and they thus show unique results in high resolution. The model is limited to a constant respiratory resistance throughout inspiration which may not be valid in some cases. However, trends match clinical expectation and the results highlight both the subject-specificity of the model, as well as significant inter-subject variability.

Mesenchymal stromal cell therapy in conditions of renal ischaemia/reperfusion

Erpicum P, Detry O, Weekers L, Bonvoisin C, Lechanteur C, Briquet A, Beguin Y, Krzesinski JM and Jouret F.

Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2014.

Acute kidney injury (AKI) represents a worldwide public health issue of increasing incidence, with a significant morbi-mortality. AKI treatment mostly relies on supportive manoeuvres in the absence of specific target-oriented therapy. The pathophysiology of AKI commonly involves ischaemia/reperfusion (I/R) events, which cause both immune and metabolic consequences in renal tissue. Similarly, at the time of kidney transplantation (KT), I/R is an unavoidable event which contributes to early graft dysfunction and enhanced graft immunogenicity. Mesenchymal stromal cells (MSCs) represent a heterogeneous population of adult, fibroblast-like multi-potent cells characterized by their ability to differentiate into tissues of mesodermal lineages. Because MSC have demonstrated immunomodulatory, anti-inflammatory and tissue repair properties, MSC administration at the time of I/R and/or at later times has been hypothesized to attenuate AKI severity and to accelerate the regeneration process. Furthermore, MSC in KT could help prevent both I/R injury and acute rejection, thereby increasing graft function and survival. In this review, summarizing the encouraging observations in animal models and in pilot clinical trials, we outline the benefit of MSC therapy in AKI and KT, and envisage their putative role in renal ischaemic conditioning.

Early detection of abnormal left ventricular relaxation in acute myocardial ischemia with a quadratic model

Morimont P, Pironet A, Desaive T, Chase G and Lambermont B.

Medical engineering & physics. 2014;36:1101-5.

The time constant of left ventricular (LV) relaxation derived from a monoexponential model is widely used as an index of LV relaxation rate, although this model does not reflect the non-uniformity of ventricular relaxation. This study investigates whether the relaxation curve can be better fitted with a «quadratic» model than with the «conventional» monoexponential model and if changes in the LV relaxation waveform due to acute myocardial ischemia could be better detected with the quadratic model. Isovolumic relaxation was assessed with quadratic and conventional models during acute myocardial ischemia performed in 6 anesthetized pigs. Mathematical development indicates that one parameter (Tq) of the quadratic model reflects the rate of LV relaxation, while the second parameter (K) modifies the shape of the relaxation curve. Analysis of experimental data obtained in anesthetized pigs showed that the shape of LV relaxation consistently deviates from the conventional monoexponential decay. During the early phase of acute myocardial ischemia, the rate and non-uniformity of LV relaxation, assessed with the quadratic function, were significantly enhanced. Tq increased by 16% ($p<0.001$) and K increased by 12% ($p<0.001$) within 30 and 60 min, respectively, after left anterior descending (LAD) coronary artery occlusion. However, no significant changes were observed with the conventional monoexponential decay within 60 min of ischemia. The quadratic model better fits LV isovolumic relaxation than the monoexponential model and can detect early changes in relaxation due to acute myocardial ischemia that are not detectable with conventional methods.

GIGA-Development, stem cells & Regenerative medicine

Developmental biology studies how the various cell types and organs are generated from the zygote. A better understanding of the molecular and cellular processes involved in generating an animal or a human being from a single cell is very important, not only for basic science, but this understanding can also help to imagine and/or to design new therapeutic approaches to cure disease and stimulate regeneration in adulthood after a disease. In a few words: a better knowledge of how we are built can help us to rebuild after a lesion, whatever the etiology is. For this reason, this unit is called "Development, Stem Cells and Regenerative Medicine". It encompasses in three labs about 30 scientists, students and technicians working on several model systems including human and animal stem cell cultures, zebrafish and mouse.

Teams of TRU "Development, Stem Cells and Regenerative Medicine" (GIGA-Development) are involved in several areas of research. One of the topics is to identify molecular mechanisms controlling the generation of pancreatic cells in normal and disease state, using the zebrafish as animal model. Identification and characterization of novel regulatory genes is performed during pancreas development as well as during the regeneration process after beta cell ablation. The function of these genes is determined by analyzing the phenotype of the corresponding mutants, generated through CRISPR-mediated targeted mutagenesis. The study of cartilage and bone development and homeostasis in zebrafish is another powerful research area in GIGA-Development, while an additional project aims at understanding the development of the anterior pituitary in zebrafish. Zebrafish constitutes an important animal model in GIGA-Development and recently, a platform for using the zebrafish as a model system for toxicology and/or pharmacology has been set up. Finally, some studies of the GIGA-Development investigate the role of neural crest stem cells present in the adult bone marrow and their potential use as an autologous grafting material in various neurological diseases.

Laboratories

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

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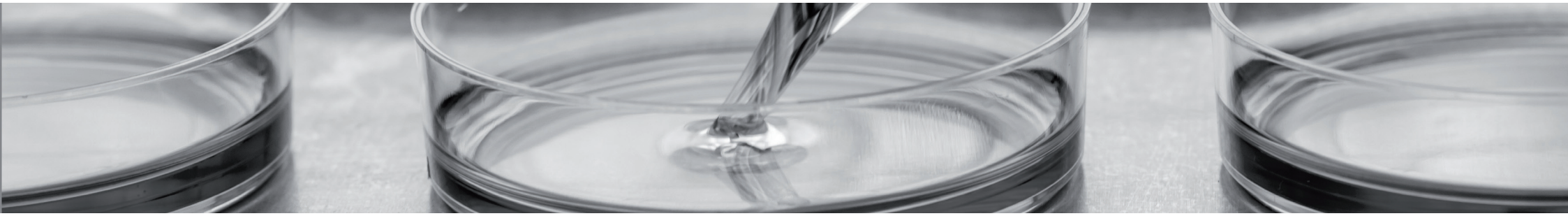
12 Scientists

11 PhD Students

6 Technicians



Detection of nitric oxide by diaminofluorescein visualizes the skeleton in living zebrafish

Renn J, Pruvot B, Muller M

J Appl Ichthyol 2014:30: 701-706.

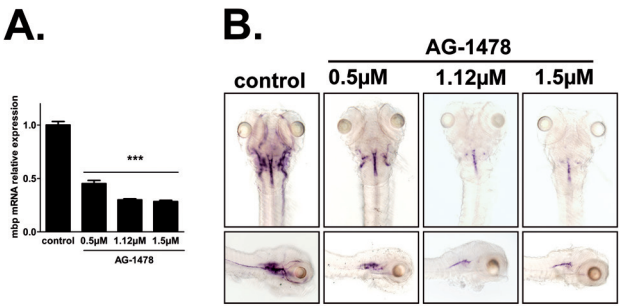
Several in vivo stainings, such as Calcein, Alizarin Red and Quercetin are commonly used to visualize ossification in living teleost specimen. These staining techniques represent important tools for bone research in fish, but do not visualize cartilage. In the present study, we show that nitric oxide (NO) labelling by DAF-FM DA visualizes both bone and cartilage in vivo during zebrafish skeletogenesis. NO detection performed in Tg(osterix:mCherry) or in combination with Alizarin Red in wild-type zebrafish reveals that intense staining through NO labelling colocalizes with the appearance of osteoblasts and characterizes ossified structures. Cartilage structures are clearly distinguished in the living larvae, although the labelling is less intensive when compared to ossified structures. This method is the first and easy to handle alternative to cartilage and bone double stainings on fixed samples. In contrast to most live skeletal stainings, which only stain the mineralized bone structures, this protocol in addition allows in vivo visualization of cartilage.

Developmental defects in zebrafish for classification of EGF pathway inhibitors

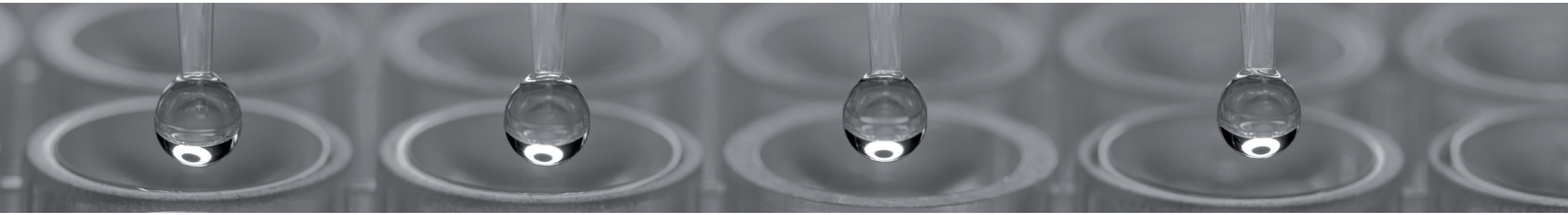
Pruvot B, Cure Y, Djiotsa J, Voncken A and Muller M.

Toxicology and applied pharmacology. 2014;274:339-49.

One of the major challenges when testing drug candidates targeted at a specific pathway in whole animals is the discrimination between specific effects and unwanted, off-target effects. Here we used the zebrafish to define several developmental defects caused by impairment of Egf signaling, a major pathway of interest in tumor biology. We inactivated Egf signaling by genetically blocking Egf expression or using specific inhibitors of the Egf receptor function. We show that the combined occurrence of defects in cartilage formation, disturbance of blood flow in the trunk and a decrease of myelin basic protein expression represent good indicators for impairment of Egf signaling. Finally, we present a classification of known tyrosine kinase inhibitors according to their specificity for the Egf pathway. In conclusion, we show that developmental indicators can help to discriminate between specific effects on the target pathway from off-target effects in molecularly targeted drug screening experiments in whole animal systems.



Myelin basic protein expression in 96hpf zebrafish embryos upon exposure to the EGF inhibitor AG-1478.
*Myelin basic protein gene expression analysis by qRT-PCR (A) and whole mount in situ hybridization (B) upon exposure to AG-1478 at the indicated concentrations from 4hpf to 4dpf. The columns in (A) represent the mean ± SD of three samples; *** statistically different from control (P<0.005).*



Concise review: Spinal cord injuries: how could adult mesenchymal and neural crest stem cells take up the challenge?

Neirinckx V, Cantinieaux D, Coste C, Rogister B, Franzen R and Wislet-Gendebien S.

Stem cells. 2014;32:829-43.

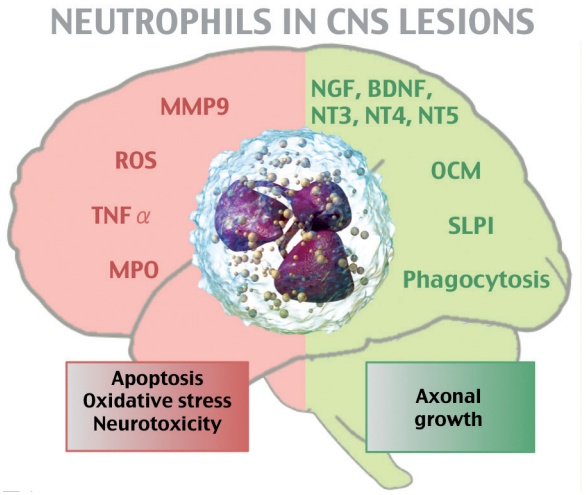
Since several years, adult/perinatal mesenchymal and neural crest stem cells have been widely used to help experimental animal to recover from spinal cord injury. More interestingly, recent clinical trials confirmed the beneficial effect of those stem cells, which improve functional score of patients suffering from such lesions. However, a complete understanding of the mechanisms of stem cell-induced recovery is seriously lacking. Indeed, spinal cord injuries gathered a wide range of biochemical and physiopathological events (such as inflammation, oxidative stress, axonal damage, demyelination, etc.) and the genuine healing process after cell transplantation is not sufficiently defined. This review aims to sum up recent data about cell therapy in spinal cord lesions using mesenchymal or recently identified neural crest stem cells, by describing precisely which physiopathological parameter is affected and the exact processes underlying the observed changes. Overall, although significant advances are acknowledged, it seems that further deep mechanistic investigation is needed for the development of optimized and efficient cell-based therapy protocols.

Neutrophil contribution to spinal cord injury and repair

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

Journal of neuroinflammation. 2014;11:150.

Spinal cord injuries remain a critical issue in experimental and clinical research nowadays, and it is now well accepted that the immune response and subsequent inflammatory reactions are of significant importance in regulating the damage/repair balance after injury. The role of macrophages in such nervous system lesions now becomes clearer and their contribution in the wound healing process has been largely described in the last few years. Conversely, the contribution of neutrophils has traditionally been considered as detrimental and unfavorable to proper tissue regeneration, even if there are very few studies available on their precise impact in spinal cord lesions. Indeed, recent data show that neutrophils are required for promoting functional recovery after spinal cord trauma. In this review, we gathered recent evidence concerning the role of neutrophils in spinal cord injuries but also in some other neurological diseases, highlighting the need for further understanding the different mechanisms involved in spinal cord injury and repair.



Neutrophils are usually depicted as detrimental actors that exacerbate apoptosis, oxidative stress and cell toxicity in the lesioned central nervous system. Recently, new insights in physiopathology of neurological diseases recently showed that neutrophils are responsible for axonal regrowth and tissue repair, especially in spinal cord injuries. Phagocytosis and production of neutrophins, oncomodulin, and secretory leukocyte protease inhibitor are potential pathways underlying neutrophil-associated tissue repair. Unravelling the dual role of neutrophils will help to define new therapeutic ways for promoting regeneration after lesion in the brain and the spinal cord.
(BDNF: Brain-derived neurotrophic factor; CNS: central nervous system; MMP: matrix metalloproteinase; MPO: myeloperoxidase; NGF: nerve growth factor; NT: neurotrophin; OCM: oncomodulin; ROS: reactive oxygen species; SLPI: secretory leukocyte protease inhibitor; TNF: tumor-necrosis factor).

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-infinitesimal 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 glyoblastoma. 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 callipyge sheep: an unsual 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 miRNAs: the team of Anne Van den Broeke continues to study the role of the cluster of miRNAs 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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Comparison of two FFPE preparation methods using label-free shotgun proteomics: application to tissues of diverticulitis patients

Quesada-Calvo F, Bertrand V, Longuespee R, Delga A, Mazzucchelli G, Smargiasso N, Baiwir D, Delvenne P, Malaise M, De Pauw-Gillet MC, De Pauw E, Louis E and Meuwis MA.

Journal of proteomics. 2015. 112:250-261.

Formalin-fixed paraffin-embedded (FFPE) specimens of patients are useful sources of materials for clinical research and have recently gained interest for use in the discovery of clinical proteomic biomarkers. However, the critical step in this field is the ability to obtain an efficient and repeatable extraction using the limited quantities of material available for research in hospital biobanks. This work describes the evaluation of the peptide/protein extraction using FFPE sections treated by the following two methods before shotgun proteomic analysis: a commercial solution (FFPE-FASP) (filter aided sample preparation) and an antigen retrieval-derived protocol (On Slice AR). Their efficiencies and repeatabilities are compared using data-independent differential quantitative label-free analysis. FFPE-FASP was shown to be globally better both qualitatively and quantitatively than On Slice AR. FFPE-FASP was tested on several samples, and differential analysis was used to compare the tissues of diverticulitis patients (healthy and inflammatory tissues). In this differential proteomic analysis using retrospective clinical FFPE material, FFPE-FASP was reproducible and provided a high number of confident protein identifications, highlighting potential protein biomarkers.
BIOLOGICAL SIGNIFICANCE: In clinical proteomics, FFPE is an important resource for retrospective analysis and for the discovery of biomarkers. The challenge for FFPE shotgun proteomic analysis is preparation by an efficient and reproducible protocol, which includes protein extraction and digestion. In this study, we analyzed two different methods and evaluated their repeatabilities and efficiencies. We illustrated the reproducibility of the most efficient method, FFPE-FASP, by a pilot study on diverticulitis tissue and on FFPE samples amount accessible in hospital biobanks. These data showed that FFPE is suitable for use in clinical proteomics, especially when the FFPE-FASP method is combined with label-free shotgun proteomics as described in the workflow presented in this work.

Selection in action: dissecting the molecular underpinnings of the increasing muscle mass of Belgian Blue Cattle

Druet T, Ahariz N, Cambisano N, Tamma N, Michaux C, Coppieters W, Charlier C and Georges M.

BMC genomics. 2014;15:796.

Background
Belgian Blue cattle are famous for their exceptional muscular development or «double-muscling». This defining feature emerged following the fixation of a loss-of-function variant in the myostatin gene in the eighties. Since then, sustained selection has further increased muscle mass of Belgian Blue animals to a comparable extent. In the present paper, we study the genetic determinants of this second wave of muscle growth.

Results
A scan for selective sweeps did not reveal the recent fixation of another allele with major effect on muscularity. However, a genome-wide association study identified two genome-wide significant and three suggestive quantitative trait loci (QTL) affecting specific muscle groups and jointly explaining 8-21% of the heritability. The top two QTL are caused by presumably recent mutations on unique haplotypes that have rapidly risen in frequency in the population. While one appears on its way to fixation, the ascent of the other is compromised as the likely underlying MRC2 mutation causes crooked tail syndrome in homozygotes. Genomic prediction models indicate that the residual additive variance is largely polygenic.

Conclusions
Contrary to complex traits in humans which have a near-exclusive polygenic architecture, muscle mass in beef cattle (as other production traits under directional selection), appears to be controlled by (i) a handful of recent mutations with large effect that rapidly sweep through the population, and (ii) a large number of presumably older variants with very small effects that rise slowly in the population (polygenic adaptation).

Linkphase3: an improved pedigree-based phasing algorithm robust to genotyping and map errors

Druet T, Georges M.

Bioinformatics, in the press (2015).

Many applications in genetics require haplotype reconstruction. We present a phasing program designed for large half-sibs families (as observed in plant and animals) that is robust to genotyping and map errors. We demonstrate that it is more efficient than previous versions and other programs, particularly in the presence of genotyping errors. Availability and implementation: The software LINKPHASE3 is included in the PHASEBOOK package and can be freely downloaded from www.giga.ulg.ac.be/jcms/prod_381171/software. The package is written in FORTRAN and contains source codes. A manual is provided with the package.

A 660-kb deletion with antagonistic effects on fertility and milk production segregates at high frequency in Nordic Red cattle: additional evidence for the common occurrence of balancing selection in livestock

Kadri NK, Sahana G, Charlier C, Iso-Touru T, Guldbrandtsen B, Karim L, Nielsen US, Panitz F, Aamand GP, Schulman N, Georges M, Vilkki J, Lund MS, Druet T.

PLoS Genet. 2014 Jan;10(1):e1004049.

In dairy cattle, the widespread use of artificial insemination has resulted in increased selection intensity, which has led to spectacular increase in productivity. However, cow fertility has concomitantly severely declined. It is generally assumed that this reduction is primarily due to the negative energy balance of high-producing cows at the peak of lactation. We herein describe the fine-mapping of a major fertility QTL in Nordic Red cattle, and identify a 660-kb deletion encompassing four genes as the causative variant. We show that the deletion is a recessive embryonically lethal mutation. This probably results from the loss of RNASEH2B, which is known to cause embryonic death in mice. Despite its dramatic effect on fertility, 13%, 23% and 32% of the animals carry the deletion in Danish, Swedish and Finnish Red Cattle, respectively. To explain this, we searched for favorable effects on other traits and found that the deletion has strong positive effects on milk yield. This study demonstrates that embryonic lethal mutations account for a non-negligible fraction of the decline in fertility of domestic cattle, and that associated positive effects on milk yield may account for part of the negative genetic correlation. Our study adds to the evidence that structural variants contribute to animal phenotypic variation, and that balancing selection might be more common in livestock species than previously appreciated.

A missense mutation accelerating the gating of the lysosomal Cl-/H+-exchanger ClC-7/Ostm1 causes osteopetrosis with gingival hamartomas in cattle

Sartelet A, Stauber T, Coppieters W, Ludwig CF, Fasquelle C, Druet T, Zhang Z, Ahariz N, Cambisano N, Jentsch TJ, Charlier C.

Dis Model Mech. 2014 Jan-Feb;7(1):119-28.

Chloride-proton exchange by the lysosomal anion transporter ClC-7/Ostm1 is of pivotal importance for the physiology of lysosomes and bone resorption. Mice lacking either ClC-7 or Ostm1 develop a lysosomal storage disease and mutations in either protein have been found to underlie osteopetrosis in mice and humans. Some human disease-causing CLCN7 mutations accelerate the usually slow voltage-dependent gating of ClC-7/Ostm1. However, it has remained unclear whether the fastened kinetics is indeed causative for the disease. Here we identified and characterized a new deleterious ClC-7 mutation in Belgian Blue cattle with a severe symptomatology including perinatal lethality and in most cases gingival hamartomas. By autozygosity mapping and genome-wide sequencing we found a handful of candidate variants, including a cluster of three private SNPs causing the substitution of a conserved tyrosine in the CBS2 domain of ClC-7 by glutamine. The case for ClC-7 was strengthened by subsequent examination of affected calves that revealed severe osteopetrosis. The Y750Q mutation largely preserved the lysosomal localization and assembly of ClC-7/Ostm1, but drastically accelerated its activation by membrane depolarization. These data provide first evidence that accelerated ClC-7/Ostm1 gating per se is deleterious, highlighting a physiological importance of the slow voltage-activation of ClC-7/Ostm1 in lysosomal function and bone resorption.

Genome-wide next generation DNA and RNA sequencing reveals a mutation that perturbs splicing of the phosphatidylinositol glycan anchor biosynthesis class h gene (pigh) and causes arthrogryposis in belgian blue cattle

Sartelet A, Li W, Pailhoux E, Richard C, Tamma N, Karim L, Fasquelle C, Druet T, Coppieters W, Georges M, Charlier C.

BMC Genomics, in the press (2015).

Background
Cattle populations are characterized by regular outburst of genetic defects as a result of the extensive use of elite sires. The causative genes and mutations can nowadays be rapidly identified by means of genome-wide association studies combined with next generation DNA sequencing, provided that the causative mutations are conventional loss-of-function variants. We show in this work how the combined use of next generation DNA and RNA sequencing allows for the rapid identification of otherwise difficult to identify splice site variants.

Results
We report the use of haplotype-based association mapping to identify a locus on bovine chromosome 10 that underlies autosomal recessive arthrogryposis in Belgian Blue Cattle. We identify 31 candidate mutations by resequencing the genome of four cases and 15 controls at 10-fold depth. By analyzing RNA-Seq data from a carrier fetus, we observe skipping of the second exon of the PIGH gene, which we confirm by RT-PCR to be fully penetrant in tissues from affected calves. We identify - amongst the 31 candidate variants - a C-to-G transversion in the first intron of the PIGH gene (c211-10C>G) that is predicted to affect its acceptor splice-site. The resulting PIGH protein is likely to be non-functional as it lacks essential domains, and hence to cause arthrogryposis.

Conclusions
This work illustrates how the growing arsenal of genome exploration tools continues to accelerate the identification of an even broader range of disease causing mutations, hence improving the management and control of genetic defects in livestock.

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. The 7 laboratories of the GIGA-I3, independently of each other, 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 2014, members of the GIGA-I3 produced or contributed to 78 significant scientific publications.

The cellular and molecular mechanisms implicated in inflammation, and particularly in chronic inflammation, are extensively studied in the 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), and on persistent inflammatory joint diseases.

The GIGA-I3 is also involved in clinical studies and translational research in the field of hematopoietic stem cell transplantation (HSCT). In this context, the GIGA I3 aims at optimizing HSCT but also evaluates the consequences of HSCT on the immune system.

The GIGA-I3 pays particular attention to the study of viral diseases. The 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 TCRγδ) in anti-tumor and anti-viral responses.

Finally, the GIGA-I3 is particularly involved in research aimed at identifying the relationships between the immune and endocrine systems. In this context, the 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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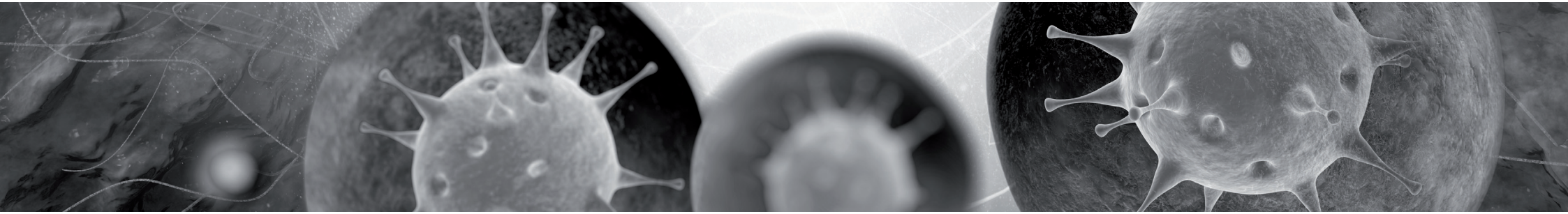


Erythropoietin therapy after allogeneic hematopoietic cell transplantation: a prospective, randomized trial

Jaspers A, Baron F, Willems E, Seidel L, Hafraoui K, Vanstraelen G, Bonnet C and Beguin Y.

Blood. 2014;124:33-41.

We conducted a prospective randomized trial to assess hemoglobin (Hb) response to recombinant human erythropoietin (rhEPO) therapy after hematopoietic cell transplantation (HCT). Patients (N = 131) were randomized (1:1) between no treatment (control arm) or erythropoietin at 500 U/kg per week (EPO arm). Patients were also stratified into 3 cohorts: patients undergoing myeloablative HCT with rhEPO to start on day (D)28, patients given nonmyeloablative HCT (NMHCT) with rhEPO to start on D28, and patients also given NMHCT but with rhEPO to start on D0. The proportion of complete correctors (ie, Hb ≥13 g/dL) before D126 posttransplant was 8.1% in the control arm (median not reached) and 63.1% in the EPO arm (median, 90 days) (P < .001). Hb levels were higher and transfusion requirements decreased (P < .001) in the EPO arm, but not during the first month in the nonmyeloablative cohort starting rhEPO on D0. There was no difference in rates of thromboembolic events or other complications between the 2 arms. This is the first randomized trial to demonstrate that rhEPO therapy hastens erythroid recovery and decreases transfusion requirements when started one month after allogeneic HCT. There was no benefit to start rhEPO earlier after NMHCT.

Minocycline Attenuates HIV-1 Infection and Suppresses Chronic Immune Activation in Humanized NOD/LtsZ-scidIL-2Rgamma mice

Singh M, Singh P, Vaira D, Amand M, Rahmouni S and Moutschen M.

Immunology. 2014; 142:562-72.

More than a quarter of a century of research has established chronic immune activation and dysfunctional T cells as central features of chronic HIV infection and subsequent immunodeficiency. Consequently, the search for a new immunomodulatory therapy that could reduce immune activation and improve T-cell function has been increased. However, the lack of small animal models for in vivo HIV study has hampered progress. In the current study, we have investigated a model of cord blood haematopoietic progenitor cells (CB-HPCs) -transplanted humanized NOD/LtsZ-scidIL-2Rγ(null) mice in which progression of HIV infection is associated with widespread chronic immune activation and inflammation. Indeed, HIV infection in humanized NSG mice caused up-regulation of several T-cell immune activation markers such as CD38, HLA-DR, CD69 and co-receptor CCR5. T-cell exhaustion markers PD-1 and CTLA-4 were found to be significantly up-regulated on T cells. Moreover, increased plasmatic levels of lipopolysaccharide, sCD14 and interleukin-10 were also observed in infected mice. Treatment with minocycline resulted in a significant decrease of expression of cellular and plasma immune activation markers, inhibition of HIV replication and improved T-cell counts in HIV-infected humanized NSG mice. The study demonstrates that minocycline could be an effective, low-cost adjunctive treatment to regulate chronic immune activation and replication of HIV.

Natural killer and dendritic cells collaborate in the immune response induced by the vaccine against uterine cervical cancer

Langers I, Renoux V, Reschner A, Touze A, Coursaget P, Boniver J, Koch J, Delvenne P and Jacobs N.

European journal of immunology. 2014;44:3585-95.

Virus-like particles (VLPs) of human papillomavirus (HPV) are used as a vaccine against HPV-induced cancer, and recently we have shown that these VLPs are able to activate natural killer (NK) cells. Since NK cells collaborate with dendritic cells (DCs) to induce an immune response against viral infections and tumors, we studied the impact of this crosstalk in the context of HPV vaccination. NK cells in the presence of HPV-VLPs enhanced DC-maturation as shown by an upregulation of CD86 and HLA-DR and an increased production of IL-12p70, but not of the immunosuppressive cytokine IL-10. This activation was bidirectional. Indeed, in the presence of HPV-VLPs, DCs further activated NK cells by inducing the upregulation of cell surface activation markers (CD69 and HLA-DR). The function of NK cells was also improved as shown by an increase in IFN-γ secretion and cytotoxic activity against an HPV(+) cell line. This crosstalk between NK cells and DCs needed CD40 interaction and IL-12p70 secretion, whereas NKG2D was not implicated. Our results provide insight into how VLPs interact with innate immune cells and how NK cells and DCs play a role in the immune response induced by this vaccine agent.

Infusion of clinical-grade enriched regulatory T cells delays experimental xenogeneic graft-versus-host disease

Hannon M, Lechanteur C, Lucas S, Somja J, Seidel L, Belle L, Bruck F, Baudoux E, Giet O, Chantillon AM, Delvenne P, Drion P, Beguin Y, Humblet-Baron S and Baron F.

Transfusion. 2014;54:353-63.

Background
We investigated the ability of clinical-grade enriched human regulatory T cells (Treg) to attenuate experimental xenogeneic graft-versus-host disease (GVHD) induced by peripheral blood mononuclear cells (PBMNCs; autologous to Treg) infusion in NSG mice, as well as verified their inability to induce xenogeneic GVHD when infused alone.

Study design and methods
Human Treg were isolated from peripheral blood apheresis products with a cell separation system (CliniMACS, Miltenyi Biotec GmbH) using a two-step procedure (simultaneous CD8 and CD19 depletion followed by CD25-positive selection) in six independent experiments with six different healthy volunteer donors. Sublethally (2.5 Gy) irradiated NSG mice were given 2 × 10(6) cytapheresis (PBMNC) product cells intravenously (IV) without (PBMNC group) or with 1 × 10(6) Treg (PBMNC + Treg group), while other NSG mice received 2 × 10(6) enriched Treg alone (also in IV; Treg group).

Results
The first five procedures were successful at obtaining a relatively pure Treg population (defined as >50%), while the sixth procedure, due to a technical problem, was not (Treg purity, 42%). Treg cotransfusion significantly delayed death from xenogeneic GVHD in the first five experiments, ($p < 0.0001$) but not in the sixth experiment. Importantly, none of the mice given enriched Treg alone (Treg group) experienced clinical signs of GVHD, while, interestingly, the CD4+ cells found in these mice 26 days after transplantation were mainly conventional T cells (median CD25+FoxP3+ cells among human CD4+ total cells were only 2.1, 3.1, and 12.2% in spleen, marrow, and blood, respectively).

Conclusions
Infusion of clinical-grade enriched Treg delayed the occurrence of xenogeneic GVHD without inducing toxicity in this murine model.

Establishment of a murine graft-versus-myeloma model using allogeneic stem cell transplantation

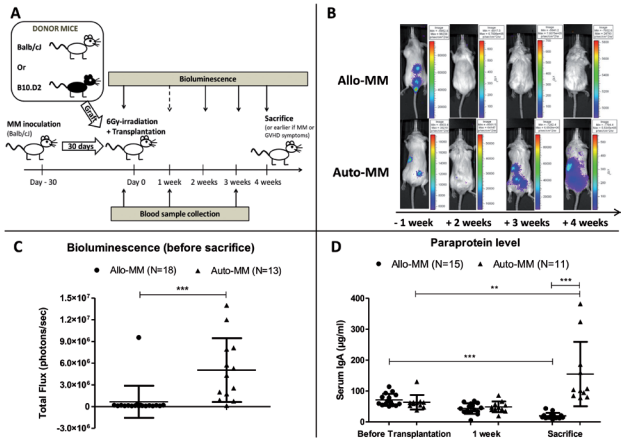
Binsfeld M, Beguin Y, Belle L, Otjacques E, Hannon M, Briquet A, Heusschen R, Drion P, Zilberberg J, Bogen B, Baron F and Caers J.

PloS one. 2014;9:e113764.

Background
Multiple myeloma (MM) is a malignant plasma cell disorder with poor long-term survival and high recurrence rates. Despite evidence of graft-versus-myeloma (GvM) effects, the use of allogeneic hematopoietic stem cell transplantation (allo-SCT) remains controversial in MM. In the current study, we investigated the anti-myeloma effects of allo-SCT from B10.D2 mice into MHC-matched myeloma-bearing Balb/cJ mice, with concomitant development of chronic graft-versus-host disease (GvHD).

Methods and results
Balb/cJ mice were injected intravenously with luciferase-transfected MOPC315.BM cells, and received an allogeneic (B10.D2 donor) or autologous (Balb/cJ donor) transplant 30 days later. We observed a GvM effect in 94% of the allogeneic transplanted mice, as the luciferase signal completely disappeared after transplantation, whereas all the autologous transplanted mice showed myeloma progression. Lower serum paraprotein levels and lower myeloma infiltration in bone marrow and spleen in the allogeneic setting confirmed the observed GvM effect. In addition, the treated mice also displayed chronic GvHD symptoms. In vivo and in vitro data suggested the involvement of effector memory CD4 and CD8 T cells associated with the GvM response. The essential role of CD8 T cells was demonstrated in vivo where CD8 T-cell depletion of the graft resulted in reduced GvM effects. Finally, TCR Vβ spectratyping analysis identified Vβ families within CD4 and CD8 T cells, which were associated with both GvM effects and GvHD, whereas other Vβ families within CD4 T cells were associated exclusively with either GvM or GvHD responses.

Conclusions
We successfully established an immunocompetent murine model of graft-versus-myeloma. This is the first murine GvM model using immunocompetent mice that develop MM which closely resembles human MM disease and that are treated after disease establishment with an allo-SCT. Importantly, using TCR Vβ spectratyping, we also demonstrated the presence of GvM unique responses potentially associated with the curative capacity of this immunotherapeutic approach.



Graft-versus-myeloma effect. (A) Experimental design and monitoring. (B) Tumor burden.
*Representative examples of bioluminescence evolution (dorsal side) for Allo-MM (top row) and Auto-MM (bottom row) mice 1 week before transplantation, and 2, 3 and 4 weeks after transplantation. The mouse in the top row already displayed paraplegia before transplantation, and completely recovered after transplantation. (C) Bioluminescence quantitation. Total flux (photons/sec) measured on the dorsal side just before sacrifice (mean±SD), ***p<0.0001 (Mann-Whitney test). (D) Paraprotein level. Serum IgA quantitation (µg/ml) by ELISA before transplantation, 1 week after and at sacrifice (mean±SD),**p=0.0005 ; ***p<0.0001 (Mann-Whitney test).*

Importance of concomitant local and systemic eosinophilia in uncontrolled asthma

Schleich FN, Chevremont A, Paulus V, Henket M, Manise M, Seidel L and Louis R.

The European respiratory journal. 2014;44:97-108.

Systemic and airway eosinophilia are recognised features of asthma. There are, however, patients who exhibit discordance between local and systemic eosinophilia. In this study, we sought to determine the prevalence and characteristics of patients with concordant and discordant systemic and bronchial eosinophilia.

We conducted a retrospective study on 508 asthmatics with successful sputum induction. We assessed the relationship between blood and sputum eosinophils by breaking down the population into four groups according to blood (≥400 cells per mm3) and sputum (≥3%) eosinophils. Then, we prospectively reassessed the link between eosinophils and asthma control (Asthma Control Questionnaire (ACQ)) and exacerbation rate in a new cohort of 250 matched asthmatics.

In our retrospective cohort, asthmatics without eosinophilic inflammation were the largest group (49%). The group with isolated sputum eosinophilia (25%) was, compared with noneosinophilic asthma, associated with lower forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity ratio and higher bronchial hyperresponsiveness and exhaled nitric oxide fraction (FeNO). Asthmatics exhibiting isolated systemic eosinophilia (7%) had similar characteristics as noneosinophilic asthmatics. The group with concordant systemic and airway eosinophilia (19%) showed remarkable male predominance, and had the lowest airway calibre, asthma control and quality of life, and the highest bronchial hyperresponsiveness, FeNO and exacerbation rate. The prospective cohort confirmed the different subgroup proportions and the higher ACQ and exacerbation rates in cases of diffuse eosinophilia compared with noneosinophilic asthmatics.

Concomitant systemic and bronchial eosinophilic inflammation contribute to poor asthma control.

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 and Malaise MG.

Rheumatology. 2014 Nov10.

Objective
Glucocorticoids are powerful anti-inflammatory compounds that also induce the expression of leptin and leptin receptor (Ob-R) in synovial fibroblasts through TGF-betasignalling 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.
Methods
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-beta1, TNF-alpha 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, alpha-tubulin and glyceraldehyde 3-phosphate dehydrogenase were analysed by western blotting.
Results
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-alpha-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.
Conclusion
CpdA, unlike prednisolone, did not induce leptin or Ob-R in human OA synovial fibroblasts, thereby demonstrating an improved risk:benefit ratio.

Varicella-zoster virus induces the formation of dynamic nuclear capsid aggregates

Lebrun M, Thelen N, Thiry M, Riva L, Ote I, Conde C, Vandevenne P, Di Valentin E, Bontems S and Sadzot-Delvaux C.

Virology. 2014;454-455:311-27.

The first step of herpesviruses virion assembly occurs in the nucleus. However, the exact site where nucleocapsids are assembled, where the genome and the inner tegument are acquired, remains controversial. We created a recombinant VZV expressing ORF23 (homologous to HSV-1 VP26) fused to the eGFP and dually fluorescent viruses with a tegument protein additionally fused to a red tag (ORF9, ORF21 and ORF22 corresponding to HSV-1 UL49, UL37 and UL36). We identified nuclear dense structures containing the major capsid protein, the scaffold protein and maturing protease, as well as ORF21 and ORF22. Correlative microscopy demonstrated that the structures correspond to capsid aggregates and time-lapse video imaging showed that they appear prior to the accumulation of cytoplasmic capsids, presumably undergoing the secondary egress, and are highly dynamic. Our observations suggest that these structures might represent a nuclear area important for capsid assembly and/or maturation before the budding at the inner nuclear membrane.

GIGA-Neurosciences

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 and particularly in the case of epilepsy, Parkinson's and Alzheimer's diseases, autism spectrum disorders, depression, deafness and sexual orientation and gender identity disorder. 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.

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- Molecular regulation of inner ear development and adult neurogenesis
  Brigitte Malgrange, Laurence Delacroix
- Molecular regulation of neurogenesis
  Laurent Nguyen
- Neurophysiology
  Vincent Seutin, Dominique Engel, Jacqueline Scuvée-Moreau
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- Cellular and tissular biology
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- Pathological aging and epilepsies
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MicroRNA targeting of CoREST controls polarization of migrating cortical neurons

Volvert ML, Prevot PP, Close P, Laguesse S, Pirotte S, Hemphill J, Rogister F, Kruzy N, Sacheli R, Moonen G, Deiters A, Merkenschlager M, Chariot A, Malgrange B, Godin JD and Nguyen L.

Cell reports. 2014, 7(4): 1168-83.

The migration of cortical projection neurons is a multistep process characterized by dynamic cell shape remodeling. The molecular basis of these changes remains elusive, and the present work describes how microRNAs (miRNAs) control neuronal polarization during radial migration. We show that miR-22 and miR-124 are expressed in the cortical wall where they target components of the CoREST/REST transcriptional repressor complex, thereby regulating doublecortin transcription in migrating neurons. This molecular pathway underlies radial migration by promoting dynamic multipolar-bipolar cell conversion at early phases of migration, and later stabilization of cell polarity to support locomotion on radial glia fibers. Thus, our work emphasizes key roles of some miRNAs that control radial migration during cerebral corticogenesis.

Glycine receptors control the generation of projection neurons in the developing cerebral cortex

Avila A, Vidal PM, Tielens S, Morelli G, Laguesse S, Harvey RJ, Rigo JM and Nguyen L.

Cell death and differentiation. 2014, 21(11): 1696-708.

The development of the cerebral cortex requires coordinated regulation of proliferation, specification, migration and differentiation of cortical progenitors into functionally integrated neurons. The completion of the neurogenic program requires a dynamic interplay between cell intrinsic regulators and extrinsic cues, such as growth factor and neurotransmitters. We previously demonstrated a role for extrasynaptic glycine receptors (GlyRs) containing the α2 subunit in cerebral cortical neurogenesis, revealing that endogenous GlyR activation promotes interneuron migration in the developing cortical wall. The proliferative compartment of the cortex comprises apical progenitors that give birth to neurons directly or indirectly through the generation of basal progenitors, which serve as amplification step to generate the bulk of cortical neurons. The present work shows that genetic inactivation of Glra2, the gene coding the α2 subunit of GlyRs, disrupts dorsal cortical progenitor homeostasis with an impaired capability of apical progenitors to generate basal progenitors. This defect results in an overall reduction of projection neurons that settle in upper or deep layers of the cerebral cortex. Overall, the depletion of cortical neurons observed in Glra2-knockout embryos leads to moderate microcephaly in newborn Glra2-knockout mice. Taken together, our findings support a contribution of GlyR α2 to early processes in cerebral cortical neurogenesis that are required later for the proper development of cortical circuits.

Forkhead pathway in the control of adult neurogenesis

Genin EC, Caron N, Vandenbosch R, Nguyen L and Malgrange B.

Stem cells. 2014, 32, 1398-407.

New cells are continuously generated from immature proliferating cells in the adult brain in two neurogenic niches known as the subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus and the sub-ventricular zone (SVZ) of the lateral ventricles. However, the molecular mechanisms regulating their proliferation, differentiation, migration and functional integration of newborn neurons in pre-existing neural network remain largely unknown. Forkhead box (Fox) proteins belong to a large family of transcription factors implicated in a wide variety of biological processes. Recently, there has been accumulating evidence that several members of this family of proteins play important roles in adult neurogenesis. Here, we describe recent advances in our understanding of regulation provided by Fox factors in adult neurogenesis, and evaluate the potential role of Fox proteins as targets for therapeutic intervention in neurodegenerative diseases.

Relationships between rapid changes in local aromatase activity and estradiol concentrations in male and female quail brain

Dickens MJ, de Bournonville C, Balthazart J and Cornil CA.

Hormones and behavior. 2014;65:154-64.

Estradiol-17β (E2) synthesized in the brain plays a critical role in the activation of sexual behavior in many vertebrate species. Because E2 concentrations depend on aromatization of testosterone, changes in aromatase enzymatic activity (AA) are often utilized as a proxy to describe E2 concentrations. Utilizing two types of stimuli (sexual interactions and acute restraint stress) that have been demonstrated to reliably alter AA within minutes in opposite directions (sexual interactions=decrease, stress=increase), we tested in Japanese quail whether rapid changes in AA are paralleled by changes in E2 concentrations in discrete brain areas. In males, E2 in the pooled medial preoptic nucleus/medial portion of the bed nucleus of the stria terminalis (POM/BST) positively correlated with AA following sexual interactions. However, following acute stress, E2 decreased significantly (approximately 2-fold) in the male POM/BST despite a significant increase in AA. In females, AA positively correlated with E2 in both the POM/BST and mediobasal hypothalamus supporting a role for local, as opposed to ovarian, production regulating brain E2 concentrations. In addition, correlations of individual E2 in POM/BST and measurements of female sexual behavior suggested a role for local E2 synthesis in female receptivity. These data demonstrate that local E2 in the male brain changes in response to stimuli on a time course suggestive of potential non-genomic effects on brain and behavior. Overall, this study highlights the complex mechanisms regulating local E2 concentrations including rapid stimulus-driven changes in production and stress-induced changes in catabolism.

Neural activation during mental rotation in complete androgen insensitivity syndrome: the influence of sex hormones and sex chromosomes

van Hemmen J, Veltman DJ, Hoekzema E, Cohen-Kettenis PT, Dessens AB and Bakker J.

Cerebral cortex. 2014. Dec 1. pii:bhu280.

Sex hormones, androgens in particular, are hypothesized to play a key role in the sexual differentiation of the human brain. However, possible direct effects of the sex chromosomes, that is, XX or XY, have not been well studied in humans. Individuals with complete androgen insensitivity syndrome (CAIS), who have a 46,XY karyotype but a female phenotype due to a complete androgen resistance, enable us to study the separate effects of gonadal hormones versus sex chromosomes on neural sex differences. Therefore, in the present study, we compared 46,XY men (n = 30) and 46,XX women (n = 29) to 46,XY individuals with CAIS (n = 21) on a mental rotation task using functional magnetic resonance imaging. Previously reported sex differences in neural activation during mental rotation were replicated in the control groups, with control men showing more activation in the inferior parietal lobe than control women. Individuals with CAIS showed a female-like neural activation pattern in the parietal lobe, indicating feminization of the brain in CAIS. Furthermore, this first neuroimaging study in individuals with CAIS provides evidence that sex differences in regional brain function during mental rotation are most likely not directly driven by genetic sex, but rather reflect gonadal hormone exposure.

Expression pattern of synaptic vesicle protein 2 (SV2) isoforms in patients with temporal lobe epilepsy and hippocampal sclerosis

Crèvecoeur J, Kaminski RM, Rogister B, Foerch P, Vandenplas C, Neveux M, Mazzuferi M, Kroonen J, Poulet C, Martin D, Sadzot B, Rikir E, Klitgaard H, Moonen G and Deprez M.

Neuropathol Appl Neurobiol. 2014;40:191-204.

Synaptic vesicle proteins 2 (SV2) are neuronal vesicles membrane glycoproteins that appear as important targets in the treatment of partial and generalized epilepsies. Therefore, we analysed the expression of SV2 isoforms in the hippocampus of patients with temporal lobe epilepsy (TLE).

Methods
SV2A, SV2B and SV2C immunostaining and QuantiGene branched DNA assay were performed on biopsies from 31 consecutive TLE patients with mesial temporal sclerosis (MTS) and compared with 10 autopsy controls. SV2 expression was further compared with Timm's staining, and synaptophysin, Zinc transporter 3 (ZnT3), dynorphin, vesicular glutamate transporter 1 (VGLUT1) and vesicular GABA transporter (VGAT) expression.

Results
In TLE patients, SV2A and SV2B expression was decreased in areas of synaptic loss. SV2C, which is weakly expressed or absent in the hippocampus of controls, was overexpressed in 10/11 cases with classical MTS1A and mossy fibre sprouting but not in cases with other types of MTS. SV2C staining was located in the inner molecular layer of the dentate gyrus and colocalized with dynorphin, ZnT3 and VGLUT1, suggesting selective expression in presynaptic glutamatergic Zn(2+) -rich terminals of abnormal sprouting fibres. SV2 expression patterns correlated with histological subtypes of MTS, but not with clinical features or therapeutic regimens in this patient cohort.

Conclusion
In classical MTS1A, the expression of SV2 isoforms is altered with a marked decrease of SV2A and SV2B paralleling synaptic loss and a selective increase of SV2C in sprouting mossy fibres. These findings suggest a different physiology of sprouting synapses and the possibility to target them with SV2C-specific strategies.

Concomitant manipulation of murine NMDA- and AMPA-receptors to produce pro-cognitive drug effects in mice

Vignisse J, Steinbusch HW, Grigoriev V, Bolkunov A, Proshin A, Bettendorff L, Bachurin S and Strekalova T.

European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2014;24:309-20.

Bifunctional drug therapy targeting distinct receptor signalling systems can generate increased efficacy at lower concentrations compared to monofunctional therapy. Non-competitive blockade of the NMDA receptors or the potentiation of AMPA receptors is well documented to result in memory enhancement. Here, we compared the efficacy of the low-affinity NMDA receptor blocker memantine or the positive modulator of AMPA receptor QXX (in C57BL/6J at 1 or 5mg/kg, ip) with new derivatives of isothiourea (0.5-1 mg/kg, ip) that have bifunctional efficacy. Low-affinity NMDA blockade by these derivatives was achieved by introducing greater flexibility into the molecule, and AMPA receptor stimulation was produced by a sulfamide-containing derivative of isothiourea. Contextual learning was examined in a step-down avoidance task and extinction of contextual memory was studied in a fear-conditioning paradigm. Memantine enhanced contextual learning while QXX facilitated memory extinction; both drugs were effective at 5 mg/kg. The new derivative IPAC-5 elevated memory scores in both tasks at the dose 0.5 mg/kg and exhibited the lowest IC_{50} values of NMDA receptor blockade and highest potency of AMPA receptor stimulation. Thus, among the new drugs tested, IPAC-5 replicated the properties of memantine and QXX in one administration with increased potency. Our data suggest that a concomitant manipulation of NMDA- and AMPA-receptors results in pro-cognitive effects and supports the concept bifunctional drug therapy as a promising strategy to replace monofunctional therapies with greater efficacy and improved compliance.

Mechanism of the medium-duration afterhyperpolarization in rat serotonergic neurons

Alix P, Venkatesan K, Scuvee-Moreau J, Massotte L, Nguyen Trung ML, Cornil CA and Seutin V.

The European journal of neuroscience. 2014;39:186-96.

Most serotonergic neurons display a prominent medium-duration afterhyperpolarization (mAHP), which is mediated by small-conductance Ca(2+) -activated K(+) (SK) channels. Recent ex vivo and in vivo experiments have suggested that SK channel blockade increases the firing rate and/or bursting in these neurons. The purpose of this study was therefore to characterize the source of Ca(2+) which activates the mAHP channels in serotonergic neurons. In voltage-clamp experiments, an outward current was recorded at -60 mV after a depolarizing pulse to +100 mV. A supramaximal concentration of the SK channel blockers apamin or (-)-bicuculline methiodide blocked this outward current. This current was also sensitive to the broad Ca(2+) channel blocker Co(2+) and was partially blocked by both ω-conotoxin and mibefradil, which are blockers of N-type and T-type Ca(2+) channels, respectively. Neither blockers of other voltage-gated Ca(2+) channels nor DBHQ, an inhibitor of Ca(2+)-induced Ca(2+) release, had any effect on the SK current. In current-clamp experiments, mAHPs following action potentials were only blocked by ω-conotoxin and were unaffected by mibefradil. This was observed in slices from both juvenile and adult rats. Finally, when these neurons were induced to fire in an in vivo-like pacemaker rate, only ω-conotoxin was able to increase their firing rate (by ~30%), an effect identical to the one previously reported for apamin. Our results demonstrate that N-type Ca(2+) channels are the only source of Ca(2+) which activates the SK channels underlying the mAHP. T-type Ca(2+) channels may also activate SK channels under different circumstances.

Alteration of rat fetal cerebral cortex development after prenatal exposure to polychlorinated biphenyls

Naveau E, Pinson A, Gerard A, Nguyen L, Charlier C, Thome JP, Zoeller RT, Bourguignon JP and Parent AS.

PloS one. 2014;9:e91903.

Polychlorinated biphenyls (PCBs) are environmental contaminants that persist in environment and human tissues. Perinatal exposure to these endocrine disruptors causes cognitive deficits and learning disabilities in children. These effects may involve their ability to interfere with thyroid hormone (TH) action. We tested the hypothesis that developmental exposure to PCBs can concomitantly alter TH levels and TH-regulated events during cerebral cortex development: progenitor proliferation, cell cycle exit and neuron migration. Pregnant rats exposed to the commercial PCB mixture Aroclor 1254 ended gestation with reduced total and free serum thyroxine levels. Exposure to Aroclor 1254 increased cell cycle exit of the neuronal progenitors and delayed radial neuronal migration in the fetal cortex. Progenitor cell proliferation, cell death and differentiation rate were not altered by prenatal exposure to PCBs. Given that PCBs remain ubiquitous, though diminishing, contaminants in human systems, it is important that we further understand their deleterious effects in the brain.

GIGA-Signal Transduction

The shared interest among the STU laboratories is to gain novel insights into the properties and interactions of different cellular signaling pathways under normal and pathological conditions. A better understanding of these processes forms the basis for the development of novel diagnostic and therapeutic strategies. Given the diversity and complexity of cellular signaling pathways, this objective is achieved by bringing together a multifaceted and multidisciplinary group of researchers that bring in their unique expertise and technologies. The STU achieves this goal by establishing an interactive environment in which 8 laboratories share their complementary expertise to build up fruitful interactions.

More specifically, examples of projects undergoing in the STU laboratories are :
- Understanding the molecular events and biological outcomes associated with activation of classical and alternative NF-κB signaling
- Characterization of the roles of key proteins such as Elp3, PINB, BCL-3 and IKK-related kinases in signaling pathways associated with tumor emergence and progression up to metastasis
- Identification and Characterization of covalent modifications targeting important signaling intermediates in health and disease
- Identification and characterization of specific cellular signaling cascades involved in photodynamic therapy-induced necroptosis, DNA damage response, bacterial product tolerance and modulation of inflammatory responses by fatty acids
- Investigating the role of the dual-specificity phosphatase DUSP3/VHR in innate immunity, cancer and thrombosis
- Understanding the upstream activating and downstream signaling events associated with orphan and uncharacterized G-coupled receptors (GPCR) in physiological and pathological contexts
- Reverse genetic characterization of key genes involved in the control of inositide metabolism and signaling
- Identification and characterization of signaling pathways converging on chromatin during specific gene expression programs involved in health and diseases
- Perturbations of protein-protein interactions associated with pathological conditions

Through this consortium, the laboratories of the STU have access to a broad range of cellular and molecular techniques as well as to relevant genetically modified cellular and in vivo (mouse and Zebrafish) models, and patient material, to perform translational approaches. The unit also includes a unique interactome biology lab, which is instrumental to analyze cross-talks between signaling pathways.

Laboratories

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

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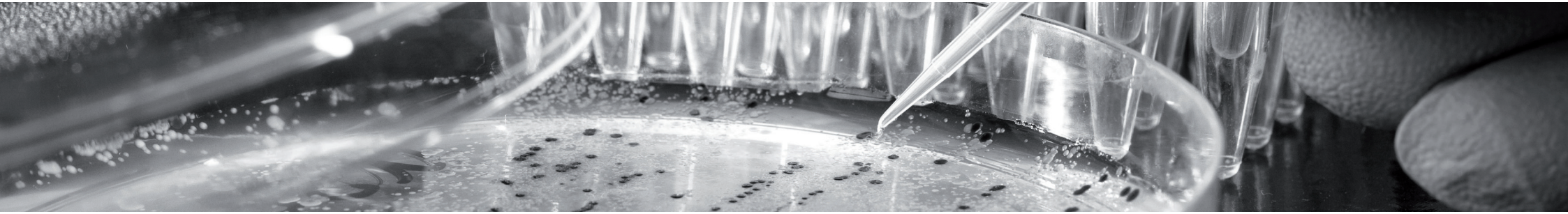


Predicting interactome network perturbations in human cancer: application to gene fusions in acute lymphoblastic leukemia

Hajingabo LJ, Daakour S, Martin M, Grausenburger R, Panzer-Grumayer R, Dequiedt F, Simonis N and Twizere JC.

Molecular biology of the cell. 2014;25:3973-85.

Genomic variations such as point mutations and gene fusions are directly or indirectly associated with human diseases. They are recognized as diagnostic, prognostic markers and therapeutic targets. However, predicting the functional effect of these genetic alterations beyond affected genes and their products is challenging because diseased phenotypes are likely dependent of complex molecular interaction networks. Using as models three different chromosomal translocations-ETV6-RUNX1 (TEL-AML1), BCR-ABL1, and TCF3-PBX1 (E2A-PBX1)-frequently found in precursor-B-cell acute lymphoblastic leukemia (preB-ALL), we develop an approach to extract perturbed molecular interactions from gene expression changes. We show that the MYC and JunD transcriptional circuits are specifically deregulated after ETV6-RUNX1 and TCF3-PBX1 gene fusions, respectively. We also identified the bulk mRNA NXF1-dependent machinery as a direct target for the TCF3-PBX1 fusion protein. Through a novel approach combining gene expression and interactome data analysis, we provide new insight into TCF3-PBX1 and ETV6-RUNX1 acute lymphoblastic leukemia.

Rasa3 controls megakaryocyte Rap1 activation, integrin signaling and differentiation into proplatelet

Molina-Ortiz P, Polizzi S, Ramery E, Gayral S, Delierneux C, Oury C, Iwashita S and Schurmans S.

PLoS genetics. 2014;10:e1004420.

Rasa3 is a GTPase activating protein of the GAP1 family which targets Ras and Rap1. Ubiquitous Rasa3 catalytic inactivation in mouse results in early embryonic lethality. Here, we show that Rasa3 catalytic inactivation in mouse hematopoietic cells results in a lethal syndrome characterized by severe defects during megakaryopoiesis, thrombocytopenia and a predisposition to develop preleukemia. The main objective of this study was to define the cellular and the molecular mechanisms of terminal megakaryopoiesis alterations. We found that Rasa3 catalytic inactivation altered megakaryocyte development, adherence, migration, actin cytoskeleton organization and differentiation into proplatelet forming megakaryocytes. These megakaryocyte alterations were associated with an increased active Rap1 level and a constitutive integrin activation. Thus, these mice presented a severe thrombocytopenia, bleeding and anemia associated with an increased percentage of megakaryocytes in the bone marrow, bone marrow fibrosis, extramedular hematopoiesis, splenomegaly and premature death. Altogether, our results indicate that Rasa3 catalytic activity controls Rap1 activation and integrin signaling during megakaryocyte differentiation in mouse.

MDM2 restrains estrogen-mediated AKT activation by promoting TBK1-dependent HPIP degradation

Shostak K, Patrascu F, Goktuna SI, Close P, Borgs L, Nguyen L, Olivier F, Rammal A, Brinkhaus H, Bentires-Alj M, Marine JC and Chariot A.

Cell death and differentiation. 2014 May;21 (5):811-24.

Restoration of p53 tumor suppressor function through inhibition of its interaction and/or enzymatic activity of its E3 ligase, MDM2, is a promising therapeutic approach to treat cancer. However, because the MDM2 targetome extends beyond p53, MDM2 inhibition may also cause unwanted activation of oncogenic pathways. Accordingly, we identified the microtubule-associated HPIP, a positive regulator of oncogenic AKT signaling, as a novel MDM2 substrate. MDM2-dependent HPIP degradation occurs in breast cancer cells on its phosphorylation by the estrogen-activated kinase TBK1. Importantly, decreasing Mdm2 gene dosage in mouse mammary epithelial cells potentiates estrogen-dependent AKT activation owing to HPIP stabilization. In addition, we identified HPIP as a novel p53 transcriptional target, and pharmacological inhibition of MDM2 causes p53-dependent increase in HPIP transcription and also prevents HPIP degradation by turning off TBK1 activity. Our data indicate that p53 reactivation through MDM2 inhibition may result in ectopic AKT oncogenic activity by maintaining HPIP protein levels.

DUSP3/VHR is a pro-angiogenic atypical dual-specificity phosphatase

Amand M, Erpicum C, Bajou K, Cerignoli F, Blacher S, Martin M, Dequiedt F, Drion P, Singh P, Zurashvili T, Vandereyken M, Musumeci L, Mustelin T, Moutschen M, Gilles C, Noel A and Rahmouni S.

Molecular cancer. 2014;13:108.

Background
DUSP3 phosphatase, also known as Vaccinia-H1 Related (VHR) phosphatase, encoded by DUSP3/Dusp3 gene, is a relatively small member of the dual-specificity protein phosphatases. In vitro studies showed that DUSP3 is a negative regulator of ERK and JNK pathways in several cell lines. On the other hand, DUSP3 is implicated in human cancer. It has been alternatively described as having tumor suppressive and oncogenic properties. Thus, the available data suggest that DUSP3 plays complex and contradictory roles in tumorigenesis that could be cell type-dependent. Since most of these studies were performed using recombinant proteins or in cell-transfection based assays, the physiological function of DUSP3 has remained elusive.

Results
Using immunohistochemistry on human cervical sections, we observed a strong expression of DUSP3 in endothelial cells (EC) suggesting a contribution for this phosphatase to EC functions. DUSP3 downregulation, using RNA interference, in human EC reduced significantly in vitro tube formation on Matrigel and spheroid angiogenic sprouting. However, this defect was not associated with an altered phosphorylation of the documented in vitro DUSP3 substrates, ERK1/2, JNK1/2 and EGFR but was associated with an increased PKC phosphorylation. To investigate the physiological function of DUSP3, we generated Dusp3-deficient mice by homologous recombination. The obtained DUSP3-/- mice were healthy, fertile, with no spontaneous phenotype and no vascular defect. However, DUSP3 deficiency prevented neovascularization of transplanted b-FGF containing Matrigel and LLC xenograft tumors as evidenced by hemoglobin (Hb) and FITC-dextran quantifications. Furthermore, we found that DUSP3 is required for b-FGF-induced microvessel outgrowth in the aortic ring assay.

Conclusions
All together, our data identify DUSP3 as a new important player in angiogenesis.

Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA

Lucifora J, Xia Y, Reisinger F, Zhang K, Stadler D, Cheng X, Sprinzl MF, Koppensteiner H, Makowska Z, Volz T, Remouchamps C, Chou WM, Thasler WE, Huser N, Durantel D, Liang TJ, Munk C, Heim MH, Browning JL, Dejardin E, Dandri M, Schindler M, Heikenwalder M and Protzer U.

Science. 2014;343:1221-8.

Current antiviral agents can control but not eliminate hepatitis B virus (HBV), because HBV establishes a stable nuclear covalently closed circular DNA (cccDNA). Interferon-α treatment can clear HBV but is limited by systemic side effects. We describe how interferon-α can induce specific degradation of the nuclear viral DNA without hepatotoxicity and propose lymphotoxin-β receptor activation as a therapeutic alternative. Interferon-α and lymphotoxin-β receptor activation up-regulated APOBEC3A and APOBEC3B cytidine deaminases, respectively, in HBV-infected cells, primary hepatocytes, and human liver needle biopsies. HBV core protein mediated the interaction with nuclear cccDNA, resulting in cytidine deamination, apurinic/apyrimidinic site formation, and finally cccDNA degradation that prevented HBV reactivation. Genomic DNA was not affected. Thus, inducing nuclear deaminases-for example, by lymphotoxin-β receptor activation-allows the development of new therapeutics that, in combination with existing antivirals, may cure hepatitis B.

Free fatty acids as modulators of the NLRP3 inflammasome in obesity/type 2 diabetes

Legrand-Poels S, Esser N, L'Homme L, Scheen A, Paquot N and Piette J.

Biochemical pharmacology. 2014 Nov 1;92(1):131-41.

Free fatty acids (FFAs) are metabolic intermediates that may be obtained through the diet or synthesized endogenously. In addition to serving as an important source of energy, they produce a variety of both beneficial and detrimental effects. They play essential roles as structural components of all cell membranes and as signaling molecules regulating metabolic pathways through binding to nuclear or membrane receptors. However, under conditions of FFAs overload, they become toxic, inducing ROS production, ER stress, apoptosis and inflammation. SFAs (saturated fatty acids), unlike UFAs (unsaturated fatty acids), have recently been proposed as triggers of the NLRP3 inflammasome, a molecular platform mediating the processing of IL-1β in response to infection and stress conditions. Interestingly, UFAs, especially ω-3 FAs, inhibit NLRP3 inflammasome activation in various settings. We focus on emerging models of NLRP3 inflammasome activation with a special emphasis on the molecular mechanisms by which FFAs modulate the activation of this complex. Taking into consideration the current literature and FFA properties, we discuss the putative involvement of mitochondria and the role of cardiolipin, a mitochondrial phospholipid, proposed to be sensed by NLRP3 after release, exposure and/or oxidation. Finally, we review how this SFA-mediated NLRP3 inflammasome activation contributes to the development of both insulin resistance and deficiency associated with obesity/type 2 diabetes. In this context, we highlight the potential clinical use of ω-3 FAs as anti-inflammatory compounds.

Inositol trisphosphate 3-kinase B is increased in human Alzheimer brain and exacerbates mouse Alzheimer pathology

Stygelbout V, Leroy K, Pouillon V, Ando K, D'Amico E, Jia Y, Luo HR, Duyckaerts C, Erneux C, Schurmans S and Brion JP.

Brain : a journal of neurology. 2014;137:537-52.

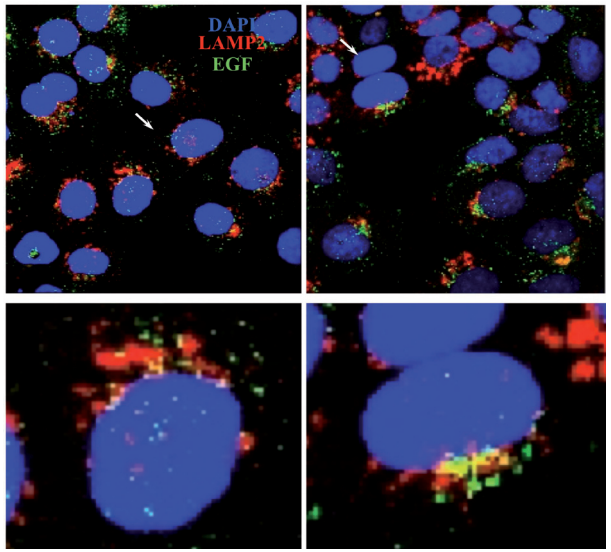
ITPKB phosphorylates inositol 1,4,5-trisphosphate into inositol 1,3,4,5-tetrakisphosphate and controls signal transduction in various hematopoietic cells. Surprisingly, it has been reported that the ITPKB messenger RNA level is significantly increased in the cerebral cortex of patients with Alzheimer's disease, compared with control subjects. As extracellular signal-regulated kinases 1/2 activation is increased in the Alzheimer brain and as ITPKB is a regulator of extracellular signal-regulated kinases 1/2 activation in some hematopoietic cells, we tested whether this increased activation in Alzheimer's disease might be related to an increased activity of ITPKB. We show here that ITPKB protein level was increased 3-fold in the cerebral cortex of most patients with Alzheimer's disease compared with control subjects, and accumulated in dystrophic neurites associated to amyloid plaques. In mouse Neuro-2a neuroblastoma cells, Itpkb overexpression was associated with increased cell apoptosis and increased β-secretase 1 activity leading to overproduction of amyloid-β peptides. In this cellular model, an inhibitor of mitogen-activated kinase kinases 1/2 completely prevented overproduction of amyloid-β peptides. Transgenic overexpression of ITPKB in mouse forebrain neurons was not sufficient to induce amyloid plaque formation or tau hyperphosphorylation. However, in the 5X familial Alzheimer's disease mouse model, neuronal ITPKB overexpression significantly increased extracellular signal-regulated kinases 1/2 activation and β-secretase 1 activity, resulting in exacerbated Alzheimer's disease pathology as shown by increased astrogliosis, amyloid-β40 peptide production and tau hyperphosphorylation. No impact on pathology was observed in the 5X familial Alzheimer's disease mouse model when a catalytically inactive ITPKB protein was overexpressed. Together, our results point to the ITPKB/inositol 1,3,4,5-tetrakisphosphate/extracellular signal-regulated kinases 1/2 signalling pathway as an important regulator of neuronal cell apoptosis, APP processing and tau phosphorylation in Alzheimer's disease, and suggest that ITPKB could represent a new target for reducing pathology in human patients with Alzheimer's disease with ITPKB expression.

NF-κB-induced KIAA1199 promotes survival through EGFR signalling

Shostak K, Zhang X, Hubert P, Goktuna SI, Jiang Z, Klevernic I, Hildebrand J, Roncarati P, Hennuy B, Ladang A, Somja J, Gothot A, Close P, Delvenne P and Chariot A.

Nature communications. 2014;5:5232.

Constitutive activation of EGFR- and NF-κB-dependent pathways is a hallmark of cancer, yet signalling proteins that connect both oncogenic cascades are poorly characterized. Here we define KIAA1199 as a BCL-3- and p65-dependent gene in transformed keratinocytes. KIAA1199 expression is enhanced on human papillomavirus (HPV) infection and is aberrantly expressed in clinical cases of cervical (pre)neoplastic lesions. Mechanistically, KIAA1199 binds Plexin A2 and protects from Semaphorin 3A-mediated cell death by promoting EGFR stability and signalling. Moreover, KIAA1199 is an EGFR-binding protein and KIAA1199 deficiency impairs EGF-dependent Src, MEK1 and ERK1/2 phosphorylations. Therefore, EGFR stability and signalling to downstream kinases requires KIAA1199. As such, KIAA1199 promotes EGF-mediated epithelial-mesenchymal transition (EMT). Taken together, our data define KIAA1199 as an oncogenic protein induced by HPV infection and constitutive NF-κB activity that transmits pro-survival and invasive signals through EGFR signalling.



KIAA1199 deficiency enhances EGFR degradation by lysosomes upon stimulation by EGF in transformed keratinocytes. The number of yellow dots, which mark EGFR in lysosomes, is increasing in KIAA1199-depleted cells (right panels). LAMP2 (red dots) marks lysosomes whereas green dots mark EGF.

GIGA-Systems Biology & Chemical Biology

The goal is to make advances in the fields of Systems Biology and Chemical Biology and to foster synergies between both. The teams comprised in this thematic research unit are highly interdisciplinary and cover a broad range of disciplines: engineering, computer science, mathematics, biology, chemistry, statistical genetics, chemistry, physics, and bioinformatics, to name but a few.

Laboratories

- Laboratory of Molecular Biomimetic and Protein Engineering
  Cécile Van de Weerdt
- Laboratory of Histology
  Marie-Claire de Pauw-Gillet
- Laboratory of Mass Spectrometry
  Edwin de Pauw
- Laboratory of Systems and Modeling
  > Machine learning and bioimage informatics
  Louis Wehenkel, Pierre Geurts, Raphael Maree
  > BIO3 – biostatistics, biomedicine, bioinformatics
  Kristel Van Steen

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21 PhD Students

6 Technicians

Polymer topology revealed by ion mobility coupled with mass spectrometry

Morsa D, Defize T, Dehareng D, Jerome C and De Pauw E.

Analytical chemistry. 2014;86:9693-700.

Hyperbranched and star shaped polymers have raised tremendous interest because of their unusual structural and photochemical properties, which provide them potent applications in various domains, namely in the biomedical field. In this context, the development of adequate tools aiming to probe particular three-dimensional features of such polymers is of crucial importance. In this present work, ion mobility coupled with mass spectrometry was used to experimentally derive structural information related to cationized linear and star shaped poly-ε-caprolactones as a function of their charge state and chain length. Two major conformations were observed and identified using theoretical modeling: (1) near spherical conformations whose sizes are invariant with the polymer topology for long and lightly charged chains and (2) elongated conformations whose sizes vary with the polymer topology for short and highly charged chains. These conformations were further confirmed by collisional activation experiments based on the ejection thresholds of the coordinated cations that vary according to the elongation amplitude of the polymer chains. Finally, a comparison between solution and gas-phase conformations highlights a compaction of the structure with a loss of specific chain arrangements during the ionization and desolvation steps of the electrospray process, fueling the long-time debated question related to the preservation of the analyte structure during the transfer into the mass spectrometer.

Exploiting snp correlations within random forest for genome-wide association studies

Botta V, Louppe G, Geurts P and Wehenkel L.

PloS one. 2014;9:e93379.

The primary goal of genome-wide association studies (GWAS) is to discover variants that could lead, in isolation or in combination, to a particular trait or disease. Standard approaches to GWAS, however, are usually based on univariate hypothesis tests and therefore can account neither for correlations due to linkage disequilibrium nor for combinations of several markers. To discover and leverage such potential multivariate interactions, we propose in this work an extension of the Random Forest algorithm tailored for structured GWAS data. In terms of risk prediction, we show empirically on several GWAS datasets that the proposed T-Trees method significantly outperforms both the original Random Forest algorithm and standard linear models, thereby suggesting the actual existence of multivariate non-linear effects due to the combinations of several SNPs. We also demonstrate that variable importances as derived from our method can help identify relevant loci. Finally, we highlight the strong impact that quality control procedures may have, both in terms of predictive power and loci identification. Variable importance results and T-Trees source code are all available at www.montefiore.ulg.ac.be/~botta/ttrees/ and github.com/0asa/TTree-source respectively.

Practical aspects of genome-wide association interaction analysis

Gusareva ES and Van Steen K.

Human genetics. 2014;133:1343-58.

Large-scale epistasis studies can give new clues to system-level genetic mechanisms and a better understanding of the underlying biology of human complex disease traits. Though many novel methods have been proposed to carry out such studies, so far only a few of them have demonstrated replicable results. Here, we propose a minimal protocol for genome-wide association interaction (GWAI) analysis to identify gene-gene interactions from large-scale genomic data. The different steps of the developed protocol are discussed and motivated, and encompass interaction screening in a hypothesis-free and hypothesis-driven manner. In particular, we examine a wide range of aspects related to epistasis discovery in the context of complex traits in humans, hereby giving practical recommendations for data quality control, variant selection or prioritization strategies and analytic tools, replication and meta-analysis, biological validation of statistical findings and other related aspects. The minimal protocol provides guidelines and attention points for anyone involved in GWAI analysis and aims to enhance the biological relevance of GWAI findings. At the same time, the protocol improves a better assessment of strengths and weaknesses of published GWAI methodologies.

Biointerface multiparametric study of intraocular lens acrylic materials

Bertrand V, Bozukova D, Svaldo Lanero T, Huang YS, Schol D, Rosiere N, Grauwels M, Duwez AS, Jerome C, Pagnoulle C, De Pauw E and De Pauw-Gillet MC.

Journal of cataract and refractive surgery. 2014;40:1536-44.

Purpose
To compare hydrophilic and hydrophobic acrylic materials designed for intraocular lenses in a multiparametric investigation in a liquid environment to highlight their properties in terms of adhesion forces, lens epithelial cell (LEC) adhesion, and tissue response as indicators of the risk for posterior capsule opacification (PCO) development.

Methods
The hydrophobicity and surface adhesion force were assessed using contact-angle and atomic force microscopy measurements. The bioadhesiveness of the disks and the tissue response were determined by in vitro experiments using bovine serum albumin and porcine LECs and by in vivo rabbit subcutaneous implantation, respectively.

Results
Increasing surface hydrophobicity led to a greater surface-adhesion force and greater LEC adhesion. After 1 month, the rabbit subcutaneous implants showed a similar thin layer of fibrous capsule surrounding the disks without extensive inflammation. A layer of rounded cells in contact with disks was detected on the hydrophobic samples only.

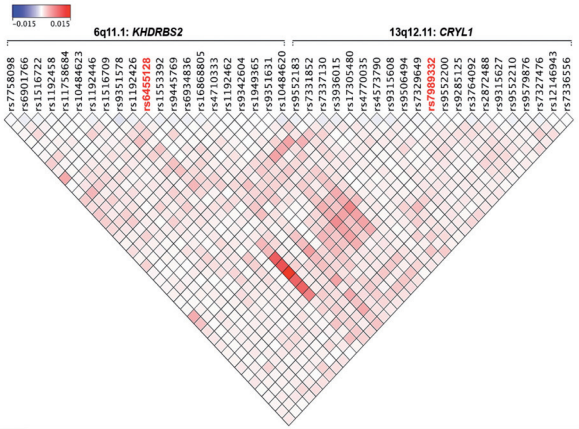
Conclusions
Hydrophobic acrylic disks that have been associated with a reduced risk for PCO in clinical studies showed increased tackiness.

Genome-wide association interaction analysis for Alzheimer's disease

Gusareva ES, Carrasquillo MM, Bellenguez C, Cuyvers E, Colon S, Graff-Radford NR, Petersen RC, Dickson DW, Mahachie John JM, Bessonov K, Van Broeckhoven C, Consortium G, Harold D, Williams J, Amouyel P, Sleegers K, Ertekin-Taner N, Lambert JC and Van Steen K.

Neurobiology of aging. 2014;35:2436-43.

We propose a minimal protocol for exhaustive genome-wide association interaction analysis that involves screening for epistasis over large-scale genomic data combining strengths of different methods and statistical tools. The different steps of this protocol are illustrated on a real-life data application for Alzheimer's disease (AD) (2259 patients and 6017 controls from France). Particularly, in the exhaustive genome-wide epistasis screening we identified AD-associated interacting SNPs-pair from chromosome 6q11.1 (rs6455128, the KHDRBS2 gene) and 13q12.11 (rs7989332, the CRYL1 gene) (p = 0.006, corrected for multiple testing). A replication analysis in the independent AD cohort from Germany (555 patients and 824 controls) confirmed the discovered epistasis signal (p = 0.036). This signal was also supported by a meta-analysis approach in 5 independent AD cohorts that was applied in the context of epistasis for the first time. Transcriptome analysis revealed negative correlation between expression levels of KHDRBS2 and CRYL1 in both the temporal cortex (β = -0.19, p = 0.0006) and cerebellum (β = -0.23, p < 0.0001) brain regions. This is the first time a replicable epistasis associated with AD was identified using a hypothesis free screening approach.



Synergy Disequilibrium (SD) analysis plot for the AD-associated interacting SNP pairs from the KHDRBS2 and CRYL1 genes in France_AD cohort.
The hit SNPs, rs6455128 (6q11.1) and rs7989332 (13q12.11), are highlighted by red fount. The blue dots for a single SNP indicate main effects for particular SNPs (no prominent main effect signals are identified by the SD analysis, hence no intensive blue dots are presented in the plot). The red dots in the SD plot represent large positive synergy between pairs of SNPs (high epistatic interaction). Four SNPs around rs7989332 in the CRYL1 gene also showed evidence for positive synergy with rs6455128, but had not been identified neither by BOOST nor by MB-MDR. Genes: KHDRBS2 - KH domain containing, RNA binding, signal transduction associated 2, CRYL1 – crystallin, lambda 1.

Platforms

Platforms

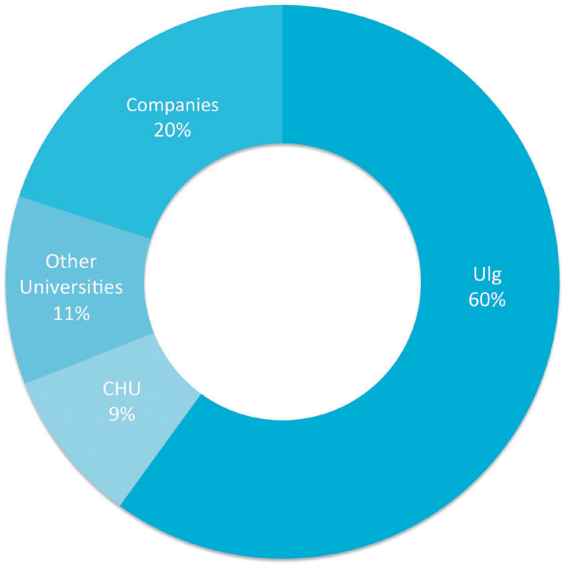
An efficient research requires an access to a broad range of technologies, specific equipment and/or expertise. GIGA-technology platforms have been created to address the needs of the scientists and make up an essential support to the biomedical research.

Each GIGA-technology platform is managed by an expert who is fully dedicated to the platform and can give advice and/or perform the experiments

- is equipped with state-of-the-art equipment under the responsibility of the platform's manager
- offers a broad range of services, from routine to sophisticated services
- is open to academic researchers as well as to the private sector

A quality system is currently implemented under the supervision of a quality manager.

Turnover



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www.giga.ulg.ac.be/platforms

7 Platforms

20 Logisticians & Technicians

52% Use of the platforms by external clients (animal facilities excluded)

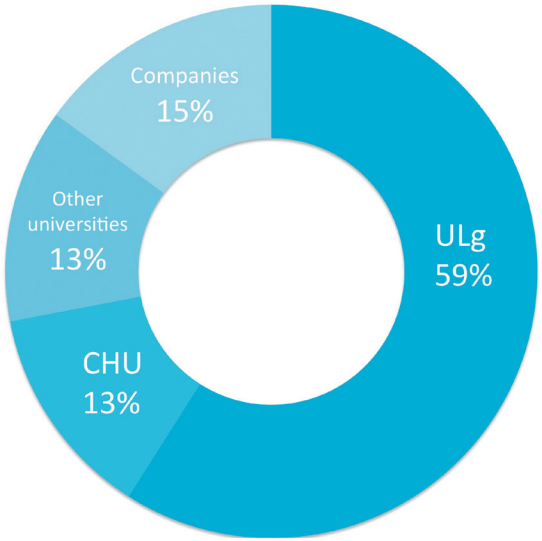
Genomics

Our ability to characterize genome, epigenome and transcriptome of virtually any organism continues to improve at a mindboggling speed, primarily as a result of steady advances in next generation sequencing technology. Streamlined access to genomic "big data" has become essential for both fundamental and translational research projects in the biomedical sciences. The ambition of the GIGA-Genomics platform is to provide access to state-of-the-art genomic technologies and information to academic and corporate users in the Liège region and beyond.

To keep pace with recent technological advances and a growing demand for NGS, the GIGA Genomics platform acquired an Illumina NextSeq500 instrument in the end of 2014, to be added to the already available Illumina HiSeq2000, MiSeq sequencer, Illumina IScan instrument, associated robotic stations, and growing computing facility. The platform's team has concomitantly expanded now counting 8 highly qualified members.

The platform offers expert services in high throughput genomic assays including array-and NGS-based SNP genotyping, variant detection, transcriptome and epigenome analyses.

Turnover



Publications

Shostak K, Zhang X, Hubert P, Göktuna SI, Jiang Z, Klevernic I, Hildebrand J, Roncarati P, Hennuy B, Ladang A, Somja J, Gothot A, Close P, Delvenne P, Chariot A. NF-κB-induced KIAA1199 promotes survival through EGFR signalling. Nat Commun. 2014 Nov 4;5:5232. doi: 10.1038/ncomms6232.

Druet T, Ahariz, N, Cambisano N, Tamma N, Michaux C, Coppieters W, Charlier C, Georges M. Selection in action: dissecting the molecular underpinnings of the increasing muscle mass of Belgian Blue Cattle. BMC Genomics 15:796 (2014)

Sartelet A, Stauber T, Coppieters W, Ludwig C, Fasquelle C, Druet T, Zhang Z, Ahariz N, Cambisano N, Jentsch TJJ, Charlier C. A missense mutation accelerating the gating of the lysosomal Cl-/H+ exchanger ClC-7/Ostm1 causes osteopetrosis with gingival hamartomas in cattle. Dis Model Mech 7: 119-128 (2014)

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46 132 Genotyping

12 559 Sanger Sequencing

3 960 NGS Sequencing

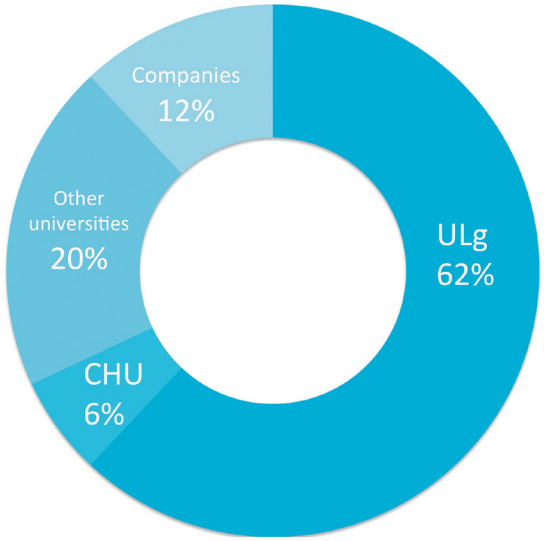
Proteomics

The proteomics platform offers a broad range of services for characterizing and/or quantifying proteins. The majority of these services are based on mass spectrometry. The proteomic platform is therefore working in close vicinity with Mass Spectrometry Laboratory.
Those services includes among others: entire protein mass determination, protein identification from gel or from solution, Multi-Enzymatic Limited Digestion for maximum sequence coverage for identification of pure protein (MELD), label-free differential proteomic analyses by LC-ESI-MS, quantification of peptides or proteins by LC-ESI-MS/MS...

Quality Assurance management on the platform follows the norm ISO17025. Since 2012, the platform has received the agreement of the Federal Agency for Medicines and Health Products (FAMHP) for the qualitative analyses of proteins. The FAMHP agreement makes the platform a good partner for the private sector and guarantees to all users that the samples are tracked by the quality management system.

The platform also continuously develops new applications in collaboration with the Mass Spectrometry Laboratory and with different research groups. One of the technics that is actually developed and optimized is Mass Spectrometry Imaging (molecular histology) that certainly opens new perspectives for biomarkers or drug discovery.

Turnover



Publications

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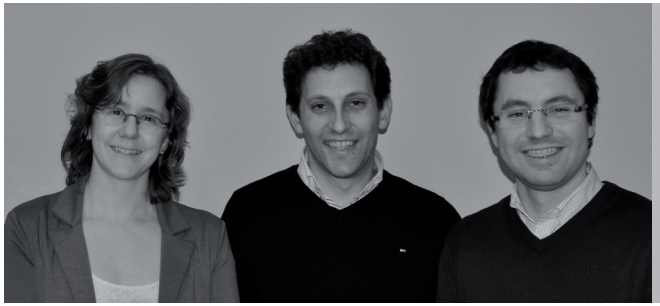

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407 Maldi-Tof protein identification
499 LC-MS/MS protein digest identifications
121 Mass determination by ESI-Q-TOF
109 Label free quantitative differential proteomic analyses
13 Quantitative analysis by LC-MS/MS (triple quadrupole)

Imaging

Confocal imaging and flow cytometry have become, over the last decade, really essential for most biomedical research programs. Quite complex technologies, they allow the fast and accurate study of molecules at the cellular level.

Through detection using fluorochrome-coupled molecules emitting at different wavelengths, confocal microscopy can highlight simultaneously a large number of fluorochromes and can study extremely precisely intracellular localization. Thanks to an thermostatized chamber built on the microscopes, the cells can be maintained in optimal experimental conditions, which allows to record sequential images and track over time the subcellular localization of a protein of interest or cells behavior in response to a stimulus or to given experimental conditions.

Flow cytometry allows qualitative and quantitative analysis of particles, for example monodispersed cells, previously marked with fluorescent probes targeting molecules very diverse like membrane antigens, cytokines, nucleic acids, viral receptors, calcium ions.... This 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. Sorter flow cytometers can also clone cells or sort simultaneously, under sterile conditions, up to 4 cell populations.

Technologies such as high throughput imaging, laser microdissection, intravital imaging or circulating tumor cells analysing are also available in the Imaging and Flow Cytometry platform.

New equipment and upgrades in 2014

In may 2014, the GIGA Flow Cytometry and Cell Imaging core facility acquired a new cell sorter : the FACSAria III (BD Biosciences). This new sorter was purchased to free our FACSAria IIIu that was completely overbooked.

This instrument, with four air-cooled lasers (407, 488, 561 and 633nm), is a digital sorter that offers acquisition rates of up to 70,000 events/second enabling multicolor analysis of up to 15 parameters (15 colors and 2 scatter) and safety high-speed sorting of potentially infected cells (such as unfixed human cells or cells infected by virus). It offers the possibility to sort up to 4 cell populations by sorting in a variety of tube sizes or multiwell plates, with a temperature control. Cell cloning can be performed on microscope slides, Petri dishes or in 6, 24, 48, 96 and 384 multiwell plates. An expanded set of nozzles lets users to sort a wide range of particle sizes. Larger nozzle allows to sort sensitive cells at lower pressure. This new FACSAria III is equipped with a bubble detector which detects air bubbles from the sample tube and stops sample flow when the sample tube is empty.

During 2014 the decision to purchase a new super resolution confocal microscope was taken. This instrument will be installed and operational by the end of 2015!

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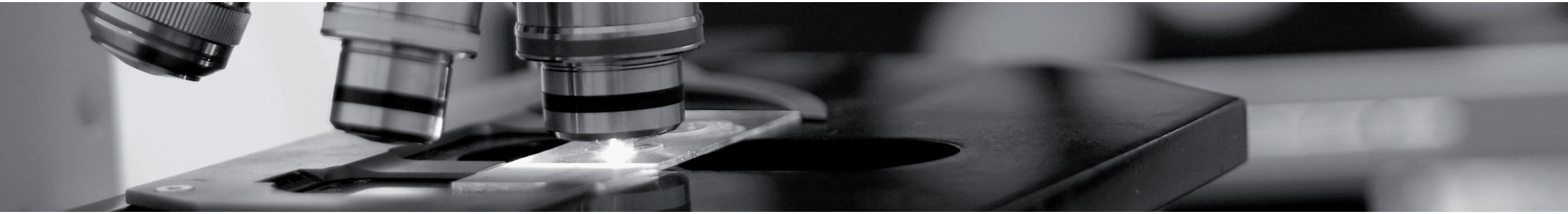
2 073 Confocal analyses

33 Confocal time lapses

468 Epifluorescence analyses

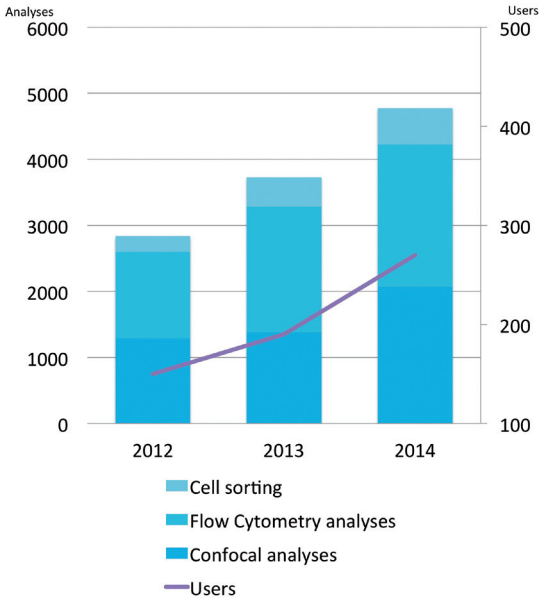


User's opinion

We are interested in the study of copper homeostasis in the alpha proteobacterium Caulobacter crescentus. In order to determine the intracellular copper concentration per bacterium, flow cytometry has been performed in GIGA Cell Imaging and Flow cytometry platform to count precisely the number of bacteria per sample. The flow cytometry platform is very equipped and includes cutting edge technology. The platform's managers are competent and really handful to help you to realize your experiments. We are very satisfied by this platform and we keep using it.

Jean-Yves Matroule, URBM, University of Namur

Number of analyses and users



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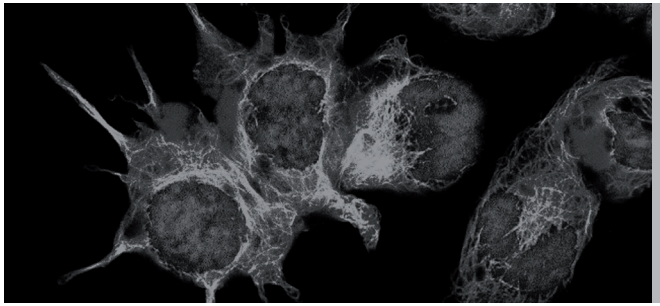
Shostak K, Zhang X, Hubert P, Göktuna SI, Jiang Z, Klevernic I, Hildebrand J, Roncarati P, Hennuy B, Ladang A, Somja J, Gothot A, Close P, Delvenne P, Chariot A. NF-κB-induced KIAA1199 promotes survival through EGFR signalling. Shostak K, Zhang X, Hubert P, Göktuna SI, Jiang Z, Klevernic I, Hildebrand J, Roncarati P, Hennuy B, Ladang A, Somja J, Gothot A, Close P, Delvenne P, Chariot A. Nat Commun. 2014 Nov 4;5:5232.



2154 Flow Cytometry analyses

550 Cell sorting

34 Multiplex Immunoassays

42 Microdissection laser

270 Users

71 Research groups

Viral Vectors

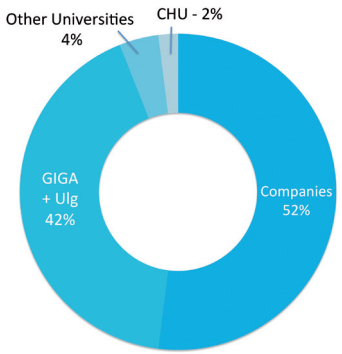
Created in 2012, the Viral Vector platform produces customized lentiviral or retroviral vectors whose production requires to work in Biosafety 2 or 3 labs (BSL2 or BSL3). This platform also trains ULg scientists who need to work in the BSL2 or BSL3 (A3) laboratories of the GIGA. This allows scientists to work into a safe environment with different virus or viral vectors within the respect of biosafety rules. Depending on the request, the platform's staff can help for the design and the cloning into a retro/lentiviral plasmids. These plasmids are then used for production of standard vectors (universal or specific promoters, multicistronic constructs , tagged vectors), imaging Vectors (eGFP, Luciferase, RFP, mCherry, BFP), RNA interference vectors for stable knock-down (shRNA RNAi-vectors polIII promoters or inducible promoters) and alternative pseudotyping (VSV-G, GalV, Measles, Ampho and eco, 10A1 MLV). The viral vectors are produced within two weeks. A titration is performed by RTqPCR and a titer of a minimum 106 transduction units per mililiters (TU/mL) or higher is guaranteed. If needed the produced vectors can be purified and concentrated up to108 TU/mL. Cotransfection with minimum 3 different plasmids is used to produce non-replication competent retroviral particles (non-RCR), this techniques narrows the chance of recombination between the plasmids and prevents the production of hypothetical wild type viruses.

The platform can also transduce cells with these viral vectors. After selection and an amplification of the transduced cells, supernatants are checked for the absence of RCR, which allows using cells into BSL1. The entire process takes approximately 4 weeks. All the produced vectors and cells can be used *in vitro* and *in vivo* (in animals).

The platform also offers production of 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 nondividing cells. Those rAAV vectors are specifically designed to allow an overexpression of the gene of interest without DNA integration into host genome.

Currently the platform is working on the development of Cas9/CRISPR technology. This technology is specifically designed to generate a knockdown or a point mutation in on both alleles through an homologous recombination.

Turnover



Publications

Turtoi A, Blomme A, Debois D, Somja J, Delvaux D, Patsos G, Di Valentin E, Peulen O, Mutijima EN, De Pauw E, Delvenne P, Detry O, Castronovo V.
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Contacts

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400 Lentivirus and retrovirus productions
(300 µL/production, titer: 10^8TU/mL)

15 High concentrated productions
(100µl to 2ml/production,titer 10^9 TU/ml)

50 Users

Immunohistology

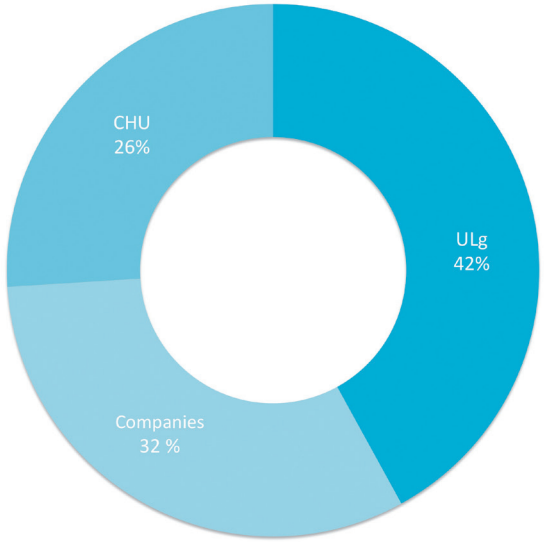
Processing tissues to get high quality sections, optimizing the immunohistochemical detection of antigens that could be weakly expressed can be a long and sometimes difficult process.

Created in 2011, the Immunohistology platform helps the researchers in that task either by giving access and advice to use the equipment or by processing the samples from the embedding to the immunostaining.

The Immunohistology platform is equipped with robotized stations for processing and staining, and with a DISCIOVERY XT System (Ventana, Roche). This DISCOVERY system allows automation of the immunostaining process, ensuring thereby reproducibility of immunohistochemistry or in situ hybridization. Many protocols for human or murine antigens detection have been optimized for the DISCOVERY XT.

Working in close collaboration with the Biobank, the platform is also able to produce Tissue Micrarrays of healthy or pathological tissues. Finally, the slides can be scanned directly by the platform's staff for storage and computer analysis.

Turnover



Publications

Demoulin S, Herfs M, Somja J, Roncarati P, Delvenne P, Hubert P. HMGB1 secretion during cervical carcinogenesis promotes the acquisition of a tolerogenic functionality by plasmacytoid dendritic cells. Int J Cancer. 2014 Dec 9.

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3 792 Paraffin embedding
15 882 Paraffin sections
5 102 Staining
3 033 Immunohistochemistry

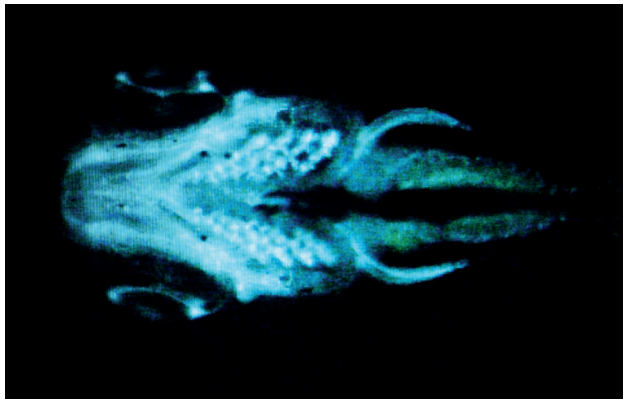
Zebrafish Facility & Trangenics

Over the years, zebrafish gain soaring popularity as animal model for the study of human diseases, developmental genetics and (eco) toxicology.

The zebrafish plateform has provided individually- tailored support for various internal and external projects related to pancreas development and osteogenesis and as a model to unravel the specific role for PP2A in maintaining vascular integrity. Current studies are taking advantage of the zebrafish to help to define the molecular basis of melanoma, hereditary disorders such as galactosemia and mitochondrial diseases.

Zebrafish

Zebrafish constitutes an appropriate tool for various uses in biology. While this model has been used mainly for the characterization of embryo development, it is now broadly used as a model for various issues. The high homology of its genome, together with the ease of use makes it an appropriate model for angiogenesis, cancer, diabetes and toxicology for example.



Publications

Pruvot B, Cure Y, Djiotsa J, Voncken A and Muller M. Developmental defects in zebrafish for classification of EGF pathway inhibitors. Toxicology and applied pharmacology. 2014;274:339-49.

Renn J, Pruvot B, Muller M. Detection of nitric oxide by diaminofluoresceib visualizes the skeleton in living zebrafish. J. Appl. Ichtyol. 2014; 30: 701-706.

Jeanray N, Marée R, Pruvot B, Stern O, Geurts P, Wehenkel L, Muller M. Phenotype classification of zebrafish embryos by supervised learning. PLoS One. 2015; 10(1):e0116989.

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457 Strains housed

168 Adult Zebrafish provided

7 New transgenics or mutant lines obtained

2 gene knock-down by morpholino injection

Mouse Facility & Trangenics

Animal experimental models are of great importance both fundamental and applied research. In fundamental research, the animal models allow to place molecular and cellular observations back into their physiological context.

In applied research, mouse models remain a mandatory step to evaluate the efficiency and the toxicity of potential treatments, before going to clinical trials.

Moreover, KO or KI mice constitute a potent tool for deciphering the role of a gene of interest.

It is thus critical for the scientists to have access to an animal facility of high value.

The GIGA animal facility offers a broad range of (internal and external) services such as housing, management of reproduction, imaging, surgery, experimental behavior recording while monitoring carefully the sanitary status of the housed animals. If needed, experiments can be performed in biosafety level 2or3. Prior any experiment, the experimental protocol has to be approved by the Institutional Animal Care and Use Committee. Additionally, quality procedures have been implemented and the GIGA Mouse facility which is frequently audited by external companies works in GLP-like conditions. For this, standard operating procedures are available as well as a traceability system. GIGA Animal Facility follows the guidelines of the Belgian legislation regarding mandatory training of people involved on the animals (animal caretakers, technicians and researchers).

In 2014, the Mouse Facility & Transgenics platform participates in 5 translational research programs.

Publications

Binsfeld M, Beguin Y, Belle L, Otjacques E, Hannon M, Briquet A, Heusschen R, Drion P, Zilberberg J, Bogen B, Baron F, Caers J. Establishment of a murine graft-versus-myeloma model using allogeneic stem cell transplantation. PLoS One. 2014 Nov 21;9(11):e113764.

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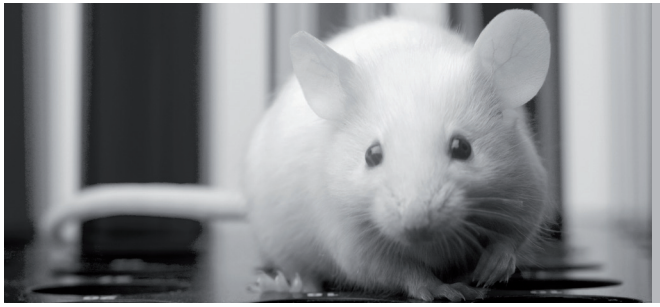

Contact

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581 Mouse embryo assays

221 Colonies housed

5 mES injections + electroporations/selection

5 Lines cryopreservations/revitalisation/sanitisations

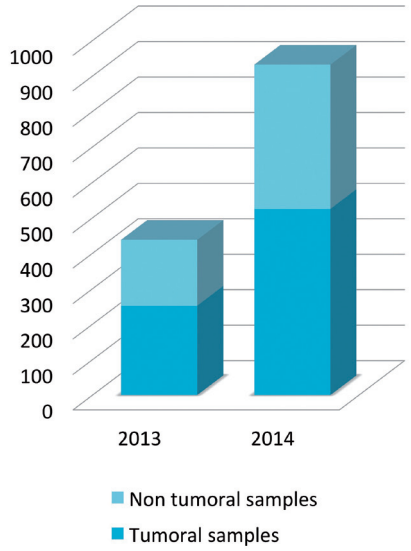
Biobank

The "Biothèque Universitaire de Liège" (BUL) is a biobank 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 fast frozen at -80°C and the corresponding paraffin embedded tissue is available in the pathology department archives.

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... Any sample requested by researchers must have a purpose of scientific research and demonstrate that it will be used in an optimal way.

In 2014, 31 GIGA researchers requested the biobank material. 289 frozen samples and 1627 paraffin samples are provided in the context of experimental studies and 932 frozen samples are collected and characterized (525 tumoral and 407 non tumoral).

Frozen samples collected and characterized



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289 Frozen samples provided

1 627 Paraffin samples provided

932 Frozen samples collected


Business

Business

2014 was an outstanding year for companies located in the GIGA-Business Facilities. Synolyne Pharma has achieved a strategic joint venture with another Biotech from the Liège region, Kytozyme. Mithra Pharmaceuticals has made an 116M€ investment to build its development and production platforms. Xpress Biologics has installed its production facilities in the GIGA tower and three other start-ups have brightly begun their activities in our facilities: Biosourcing, LaCAR MDx Technologies and AmplyCell.

The GIGA-Business Facilities directly related to GIGA-Technology Platforms, with their proximity to the CHU and a wide range of rental possibilities, are more than ever a great place for Biotech's to develop their activities.

New companies

Biosourcing and LaCAR MDx have added their names to the list of companies hosted in the GIGA. Biosourcing (GIGA-Business Area 1) is a reference biotechnology company for the production of biologicals available to animal health. LaCAR MDx (GIGA-Business Area 2) develops projects in the molecular diagnosis of genetic diseases.

LaCAR MDx Technologies

Access to techniques of molecular genetic diagnosis for the medical world

LACAR MDx was created in Liège in December 2013 by different actors from Liège economic and scientific networks. The company's gathered scientific and managerial skills in order to propose new solutions on the molecular genetic diagnosis market. From the beginning of its establishment the company has launched its first project for easy, fast and cost effective detection of SNPs. The applications of this technology offer new applications in the molecular genetic diagnostics market and gives the opportunity to offer genetic testing nearby the patient.

Synolyne Pharma

Chitosan-based medical device to help patients suffering from high impact pathologies

Founded in 2012 with the objective to develop innovative chitosan-based products for the management of osteo-arthritis pain, Synolyne Pharma spent an eventful and challenging year 2014.

The expansion of Synolyne Pharma started up in March 2014 with a capital raised of 3,3 million euros and the spinout of Kitozyme's medical branch of activities. A promising merging of talents and innovative technologies, paired with a solid funding, makes the perfect combination to speed up the growth of this spin-off company of the University of Liège. The main objective of the capital increase was to pursue the development of its treatment against degenerative osteoarthritis and secure animal-free ultrapure chitosan supply, through the spin-out of the biomedical activities from KitoZyme.

First, Synolyne Pharma registered «Vegetech Inside» as an innovative technology platform based on ultrapure animal-free chitosan and finalized a new value proposal which aims at offering safer and highly efficient therapeutic solutions to patients suffering from high impact pathologies.
Meanwhile, Synolyne Pharma refined its strategy and follows now a two-axes valorization strategy, which aims to best answer unmet medial needs identified on the market and optimize the use of its competencies and technologies:
• The first axis is the development of its own products in the field of rheumatology which has been secured thanks to the granting of two patents both in the US and in Europe in relation to its chitosan-

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23 Companies

75 Employees

2 300m² Total occupied area

based microbeads, a component of a promising visco-supplementation product for the slowing down osteoarthritis.
• The second axis consists in offering to B2B partners its expertise in formulating the chitosan and derivatives to develop innovative, safer and highly efficient implants in some specifics markets segments.. This technological support already convinced, among others, two major companies which signed partnerships during 2014, as well as several new feasibility studies in various fields such as ophthalmology, biosurgery and dermatology.

The future objectives of Synolyne Pharma are to support the launch of its propriety products in rheumatology within the next 2 years and to keep promoting and demonstrating the outstanding properties of its unique animal-free "Vegetch Inside" platform.

Xpress Biologics

Protein & DNA for pre-clinical applications

In the next years, close to 40 % of the new treatments against cardiovascular and cancer diseases will be based on protein and DNA molecules called "biologics". Thanks to the high specificity of these molecules, medical approaches known as Personalized Medicine may be developed. The trends is clearly reflected as a high number of the biologics entering in phase I trials are antibody based drugs for example. Despite these great advances, the development of new molecules is still expensive, time consuming and with low success rates. Indeed, more than 80% of the biologics fail the pre-clinical validation (proof of concept and toxicological assays on animals). Among the different reasons, the use of not adapted or optimized manufacturing processes leading to low quantity & quality grade material is one of the critical factor. This particular situation led to the creation of Xpress Biologics in 2014.

Xpress Biologics (XB) is a biotech company proposing contract services for the production of recombinant proteins, antibody fragments and plasmid DNA for preclinical applications specific to the therapeutic and diagnostic markets (human & veterinary). Its mission is to enable the transition of the projects from R&D to clinical manufacturing. The production scale (from 100 mg up to several tens of grams) and the quality of the biologics (R&D and GLP grade material) are adapted for in vitro and in vivo pre-clinical validation of the biologics (proof-of-concept, early safety, potency, efficacy…).

The production processes are all developed in microbial expression systems, mainly Escherichia coli (soluble cytoplasmic, inclusion bodies and periplasmic productions) and Pichia pastoris (secreted protein). XB owns specific equipment for the development of fermentation and purification processes, but also for the development of regulatory compliant quality controls.

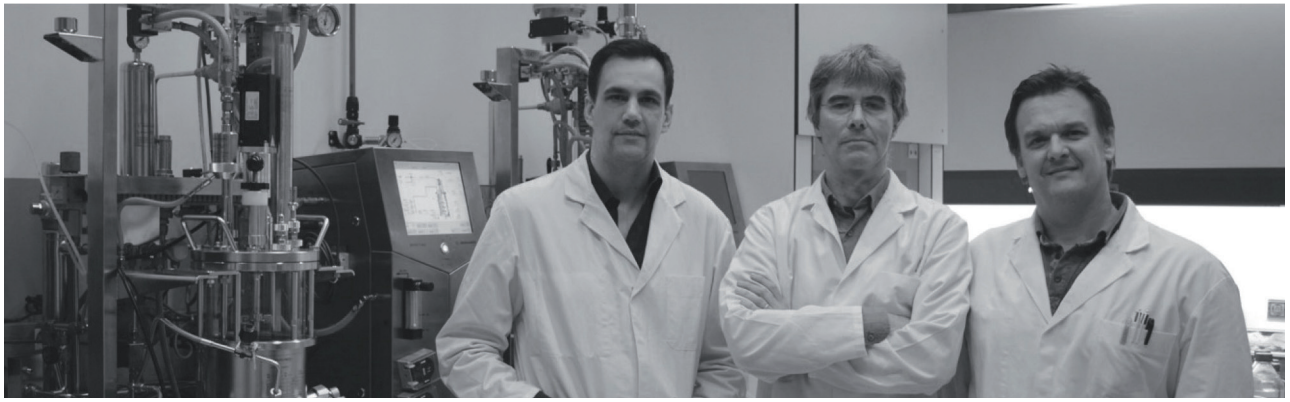
XB has, among others, developed two efficient platforms. One is an optimized P. pastoris service for the production of antibody fragments based on the reformatting of full-length antibody in different types of formats (scFv, Fab, diabodies, minibodies…).

The second is a high yield plasmid production service that generates material for vaccine DNA or therapeutic applications (transfection).

All XB processes are free of charge in terms of license or royalty fees and take into account the industrial and regulatory requirements which greatly facilitates the later transfer of the project to Manufacturing Organizations for the production of GMP grade material needed in clinical trials.

XB acts as One-Stop-Shop and can, through project management with defined subcontractors, take in charge additional services like the outsourcing of GMP production or the organization of pre-clinical studies.

Last but not least, XB also targets the development and co-development of new biologics (biobetters) in order to generate a pipe of innovative molecules.



Mithra Pharmaceuticals

Expert in women's health - Inspired by women

Mithra Pharmaceuticals, a spin-off from the University of Liège specialising in women's health, is today laying the first stone of its development and production platform at the Arbre Saint-Michel industrial estate in Flémalle. This technological platform, built at the heart of Euregio, is available to actors in the pharmaceutical industry and aims to develop the reputation of the region and our country in the pharmaceutical sector, on an international scale.

The creation of this technological platform, known as the "Contract Development and Manufacturing Organisation (CDMO)" will give Mithra Pharmaceuticals the opportunity to expand and enhance its expertise internally and through international, national and regional partnerships.

The platform has 2 main focuses:
• R&D, incorporating innovative projects
• Production

Anchoring and enhancing research and expertise is essential at Mithra Pharmaceuticals in order to preserve the value chain and sustain the group's growth. R&D is the spearhead of the new site at Flémalle. Mithra Pharmaceuticals will conduct its own research projects there, at the same time as exploring new areas.

Beyond developing its own therapeutic and diagnostic solutions, Mithra also wishes to enhance the value of its expertise within the context of external partnerships, particularly in the field of medical polymers, an ever-changing niche market (these polymers are matrices which enable the long-term diffusion of the drug substance in a medicinal product). Mithra Pharmaceuticals boasts rare expertise in this field.

Industrial partners, academics, SMEs and start-ups will be able to benefit from the experience Mithra has built up over the years in a framework facilitating the exchange of ideas and knowledge-sharing, to speed up the market launch of innovative products. Our valuable skills in the regulatory field will also help to open up the European market more quickly to international partners.

Thanks to its integrated technology platform (R&D and production), Mithra will be able to offer therapeutic solutions using medical polymer technology (implants and other polymers), sterile injectable products and IM/SC implants. At a later stage, this platform will also offer a compression and blister packing unit for manufacturing tablets. Therefore production will initially focus on enhancing the value of our assets and will gradually integrate new capabilities as Mithra's international distribution business grows. The platform will comply with strict of European "GMP" (EMA) and US (FDA) requirements in order to meet the specific needs of each partner (volumes, development of production instruments, etc.).

This brand new development platform is built on a 3-hectare site (option on an additional 4 hectares) in Flémalle. A total investment of €116 million. €70 million will be invested between 2014 and 2016, funded by the founder, Intégrale, ING Lease Belgium and public investment companies Meuse-Invest and SRIW. The platform should be operational at the end of 2016.

Amplycell

Optimizing monoclonal antibody production

Located in the GIGA-Business Area 1, AmplyCell is a spin-off emerging from «Centre de Coopération Technique et Pédagogique» (CECOTEPE), a research center associated to the Haute École de la Province de Liège, Belgium. AmplyCell is a Biotech service company of which goal is to help Diagnostic and Pharmaceutical companies to increase the profitability of their antibody production.

Professor Jean Michel Cloes has more than 30 years experience in antibodies producing cells, especially with hybridomas. He brought this technology in the laboratories of the University of Liège in the 80's. After being a scientific consultant, he obtained several grants from the Walloon Region in order to improve hybridoma cells' instability in industrial culture conditions. This is how the Boosting Technology of Amplycell was born.
The CEO of the company is Geoffrey Holsbeek. He is an Engineer in Biotechnology, and a skilled and passionate Entrepreneur, with years of experiences in scientific and industrial sectors. He is the the Chief - Boosting - Executive Officer of the company.

AmplyCell offer cell lines amplification services in order to :
- Improve the stability of cell lines by extending their secretion period.
- Improve their productivity by multiplying the number of antibodies produced by cell and by second

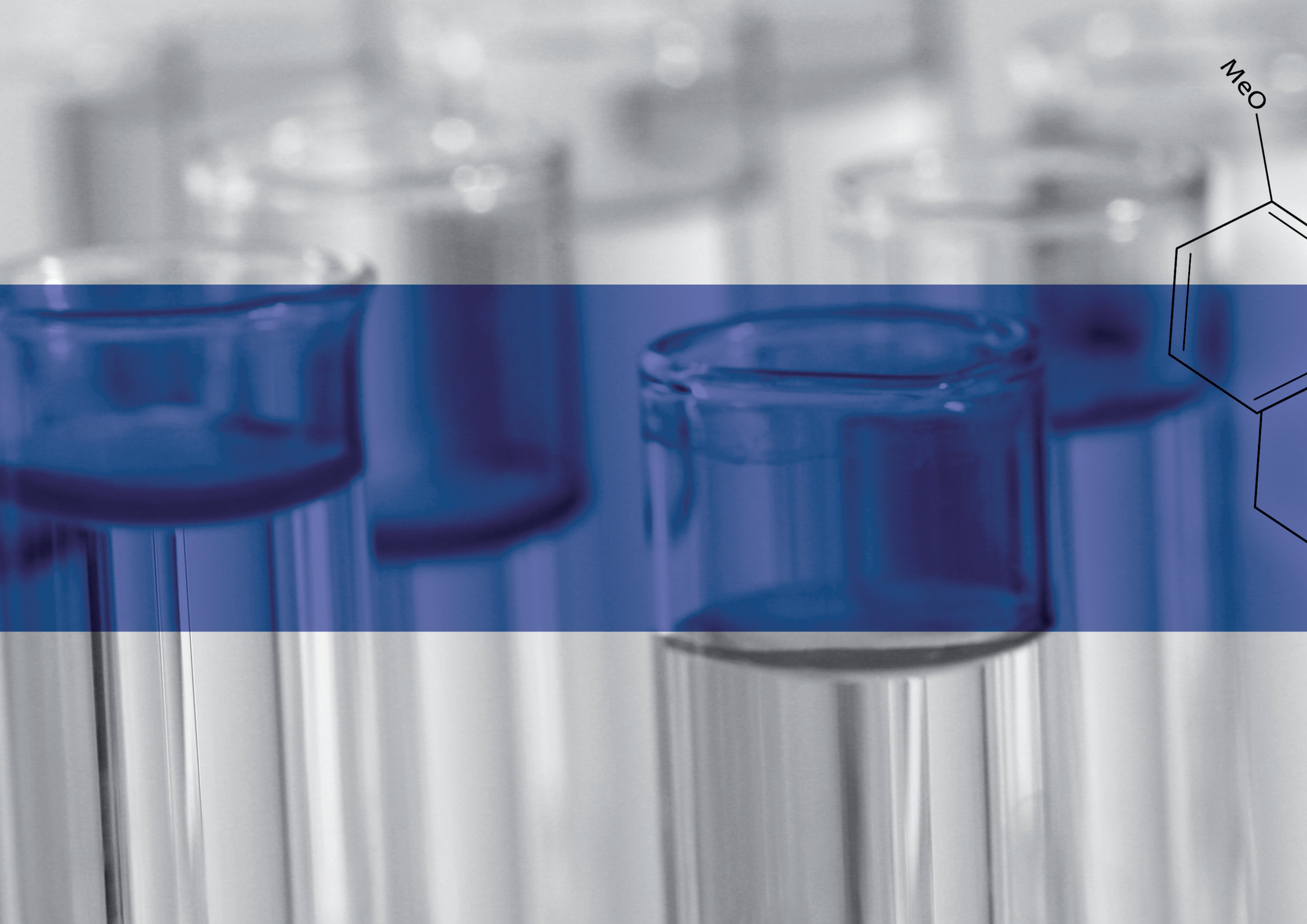
More than 30 year old expertise in the antibody sector allows them to offer consulting services to optimize the development of customer projects.
Various cell lines do secrete antibodies that can be purified and used for medical kits. In theory, most of them should produce immunoglobulins infinitely. But when it comes to the labs, it is not really the case. Most of the cells are unstable, their productivity is poor and/or decrease over time, what makes cultures difficult. Sometimes yield are even not compatible with industrial exploitation. A few alternative exist : successively relaunch new culture, find interresting additives or generate a new cell lines. But while chances of success are relatively low, this is time and money consuming.

In order to answer those issues, AmplyCell has developed the «Special Fitness for cell lines» technology that boost antibody producing cell lines. During the process, best super-producers are selected, sub-cloned and send back to the customer that can directly reintroduce them in the original production process. Currently AmplyCell works maintly on hybridoma cell lines from SMEs and Leaders companies.

The board of AmpliCell is represented by a large panel of high levels Biotech Specialists. In January 2015, new Investors - mainly strategic and financial - joined the development for a second round of investment. This correlates new perspectives according to two axis : adding new skills to increase the team expertise, and extending boosting technologies to various cell lines (CHO, HEK, ...). In the next months and years, AmplyCell wish to become one of the leader into the area of cell lines over-stimulation.

GIGA-Companies

GIGA 1	GIGA 2	GIGA 3	Labhotel
AmplyCell	Arlenda	Neurhumab	Imcyse
Biosourcing	Artialis	ProGenosis	Symbiose
Fabro	Astrea	Sonicbio	
Mithra RDP	Imcyse		
Sproncken Ortho	Labage		
Estetra	LaCAR MDx Technologies		
	Physiol		
	Scinnamic		
	WBC		
	Xpress Biologics		


MeO

Training

Forem-GIGA Biotechnology Training Center

The Forem-GIGA Biotechnology Training Centre 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 programmes 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.
As our new facilities are up-and-running thanks to the ERDF programme, conditions are now optimal for welcoming trainees and reinforcing their skills and expertise.

Highlights 2014

With more than 63,000 hours of training organized for job-seekers, students of technical colleges, and workers from biotech companies, 2014 has been another rewarding year.

Besides our 'standard' training sessions, worth highlighting is our highly successful new Quality Assurance (QA) training programme, which was developed as a 'University Certificate' in close collaboration with the 'Réseau Qualité des Laboratoires' and the Faculty of Medicine of the ULg. At the end of the training session, all 12 trainees have again found a job in this field!

We have also developed in close collaboration with another training centre, Culture in vivo ASBL, a new long-term training program focussed on Regulatory Affairs.

Positive results also for the third session of the new programme 'Biosafety–GLP-GMP. essentials one should know' and the first session focussed on ISO17025.

Don't hesitate to contact us when you need to hire collaborators or set up training programmes for your team, and also if you are willing to welcome trainees.

Results of 2014

1. Job-hunters
In 2014, eight long-term training programmes and four shorter transverse training sessions were organized for 149 people from the entire Walloon Region. Each 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)
- Molecular biology in a biosafety level 1-to-3 environment
- Analytical techniques: HPLC-GC-CE
- Bioinformatics
- Biostatistics
- Project and team management in biotechnology (2 sessions)
- Quality Assurance
- Soft skills in biotechnology
- Regulatory Affairs

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63 300 Hours of training

429 Trainees

73% Job insertion rate

Most of the trainees topped off their training and boosted their chances on the job market with a 2(3)-month internship in a biotech company. According to the final measurement for 2013, the percentage of job insertion was 73 %.

We also pursued our partnership with Culture in vivo ASBL, which organizes two-month biotech training sessions in Nivelles. We set up four 5-day modules focusing on:

- Western blotting
- Animal cell culture
- Real-Time Q-PCR techniques

These modules were designed to strengthen the specific technical skills of 35 job-seekers and should stimulate their professional insertion.

We were also involved in the «BioCell R&D Training Programme» developed through Biowin by the Cefochim skills centre and ULB-Biopark Formation. We organized a module focused on microbiology/bacteriology for 11 trainees.

In December, furthermore, we organized a new session of the CapBio 1 session in Liège. This one-day training session aims to help job-seekers and students discover the biotech field and better understand the required skills. It was organized in collaboration with Biowin and all the training centres operating in Wallonia. This event was attended by a total of 63 job-seekers.

2. Company staff

The following modules were organized for a total of 42 people:

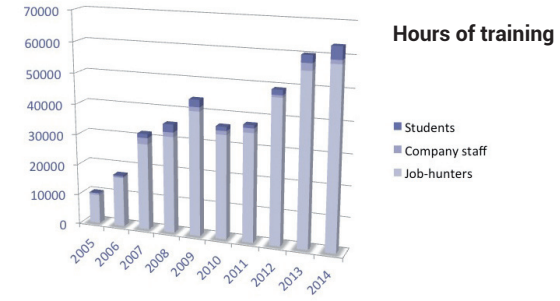
- ISO17025
- Biosafety – GLP - GMP. essentials one should know
- Quality Assurance
- Project Management

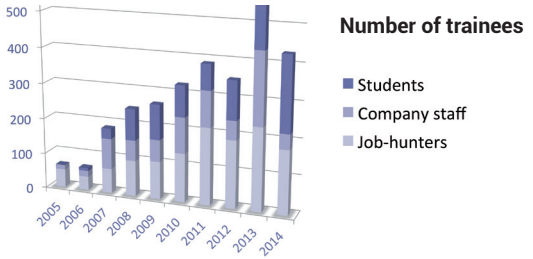
3. Higher education - technical college students

Seven short-term modules specifically designed for 208 students and their teachers were organized in 2014. 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:

- Biosafety
- Molecular biology and PCR
- PCR, advanced
- PCR and immunology
- Practical introduction to HPLC
- GLP, GMP, Validation
- Introduction to project management





Companies' opinion about trainees

Benjamin Brands at Mithra Pharmaceuticals and Sebastien Hoornaert at Immunodiagnostic Systems recently hosted a trainee who completed the University Certificate of Quality Assurance applied to laboratories and chemical, pharmaceutical and biotechnological industries.

Here are their impressions :

Benjamin Brands
Mithra Pharmaceuticals
«*I could release myself with confidence from some of my daily tasks and this allowed me to realize what an additional person would bring to my department*»

Sebastien Hoornaert
Immunodiagnostic Systems
«*It is not our usual practise to host trainees. But in the end, everything went well and we realized that the benefits outweigh the constraints*»


Tech Transfer

Patents

In 2014, GIGA-R has contributed to the filing of 12 patent applications.
And 7 patent applications involving GIGA researchers have been published.

The names of GIGA members are in bold.

A genetic marker test for brachyspina and fertility in cattle

AU2009275988 B2

Michel Georges, **Wouter Coppieters**, **Carole Charlier**, Jorgen Steen Agerholm, Merete Fredholm
GIGA-Genomics

Chitosan biomimetic scaffolds and methods for preparing the same

US 2014/0046236

Abelhafid Aquil, **Alain Colige**, Patrice Filée, Astrid Freichels, Christine Jérôme, **Victor Tchemtchoua Tateu**
GIGA-Cancer

Water soluble curcumin compositions for use in anti-cancer and anti-inflammatory therapy

US 8772265 B

Didier Cataldo, Jacques Delarge, Robert Kiss, Véronique Mathieu, Philippe Neven, **Natacha Rocks**, Didier Serteyn
GIGA-Cancer

Peptide antagonists of the vasopressin-2 receptor

WO2104/041526

Nicolas Gilles, Christiane Mendre, Bernard Mouillac, **Loïc Quinton**, helen Reinfrank, Denis Servent, Ralph Witzgall
GIGA-Systems Biology & Chemical Biology

Biomarkers for osteoarthritis

US 2014/0038841

Dominique de Seny, **Michel Malaise**, Mohammed Sharif
GIGA-Cancer

Method for identifying cows with mastitis by bulk genotyping of tank milk

EP2597159 B1

Michel Georges, **Wouter Coppieters**, Grégoire Blard
GIGA-Genomics

Combination treatment of cancer

WO2014/037316

Agnès Noël, **Alexandra Paye**, **Nor Eddine Sounni**
GIGA-Cancer

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PhD Thesis

Insights into the role of the dual-specificity protein phosphatase 3 in angiogenesis and metastasis formation.
Amand Mathieu, Laboratory of Immunology and Infectious Diseases

Cancer du col utérin de stade débutant et dissémination ganglionnaire : analyse informatique détaillée du réseau vasculaire lymphatique global sur tissus cervicaux humains
Balsat Cédric, Laboratory of Biology of Tumor and Development

Etude multiparamétrique de polymères acryliques, modèles de lentilles intraoculaires : Recherche d'indicateurs de risque de développement de la cataracte secondaire
Bertrand Virginie, Laboratory of Histology

Important roles of SoHo proteins in vascular development: Sorbs1 and Sorbs2 have related but distinct functions in endothelial cell angiogenic properties
Bleuart Anouk, Laboratory of Proteins Signaling and Interactions

Contribution towards understanding the role of myoferlin during breast cancer progression
Blomme Arnaud, Laboratory of Metastasis Research

Insight ino the role of microRNAs in the development of colitis associated cancer
Bouznad Nassim, Laboratory of Thrombosis Hemostasis

Etude du rôle de Cdk4 et Cdk6 dans la neurogenèse postnatale/adulte
Caron Nicolas, Laboratory of Developmental Neurobiology

Study of the role of N-glycosylation sites in the pathogenesis induced by bovine leukemia virus.
De Brogniez Alix, Laboratory of Cellular and Molecular Epigenetics

Etude de la corrélation entre les propriétés biochimiques et biomécaniques du tissu vaginal dans le cadre du prolapsus génital
De Landsheere Laurent, Laboratory of Biology of Tumor and Development

Altérations fonctionnelles des cellules dendritiques dans la cancérisation du col utérin
Demoulin Stéphanie, Laboratory of Experimental Pathology

Proteomic study of primary mithral regurgitation. Implication of autophagy in cellular signalling.
Deroyer Céline, Laboratory of Medical Chemistry

Role of adipose tissue inflammation and NLRP3 inflammasome in the pathogenesis of metabolic syndrome and type 2 diabetes
Esser Nathalie, Laboratory of Virology and Immunology

Les effets anti-tumoraux des inhibiteursd'HDAC dans un modèle in ovo de cancer pancréatique humain sont signicativement améliorés par l'inhibition simultanée de la cyclooxygénase 2.
Gonzalez Arnaud, Laboratory of Metastasis Research

Functional interactions between ADAMTS and VEGF: A specific focus on ADAMTS3
Janssen Lauriane, Laboratory of Connective Tissues Biology

Insights into the role of Elp3 in Wnt-driven tumor initiation and regeneration
Ladang Aurélie, Laboratory of Medical Chemistry

Deciphering the role of Elongator in cerebral cortical progenitors/ Identification du role d Elongator dans les progeniteurs du cortex cerebral
Laguesse Sophie, Laboratory of Developmental Neurobiology

Natural killer and dendritic cells crosstalk in vaccination against human papillomavirus.
Langers Inge, Laboratory of Cellular and Molecular Immunology

Nuclear capsid aggregates of Varicella-Zoster virus : assembly sites or dead-end depot ?
Lebrun Marielle, Laboratory of Virology and Immunology

Understanding random forests : from theory to practice
Louppe Gilles, Laboratory of Systems Biology

Identification of the lung dendritic cell subset responsible for airway allergic sensitization in mice
Mesnil Claire, Laboratory of Cellular and Molecular Immunology

Lung function and airway inflammation monitoring after hematopoietic stem cell transplantation
Moermans Catherine, Laboratory of Pneumology

Régulation des propriétés cellulaires par les signaux mécaniques : leçons d'un modèle expérimental en microgravité
Neutelings Thibaut, Laboratory of Connective Tissues Biology

Immortalité des cellules cancéreuses: rôle d'HDAC5 dans l'homéostasie des télomères
Polese Catherine, Laboratory of Proteins Signaling and Interactions

Cancer characterisation. The intra-tumour heterogeneity bias
Poulet Christophe, Laboratory of Human Genetics

Rôle du facteur de transcription Sox4b dans la différenciation des cellules hypophysaires du zebrafish
Quiroz O'Donova Yobhana, Laboratory of Organogenesis and Regeneration

Diagnosis and clinical interest of asthma inflammatory phenotypes
Schleich Florence, Laboratory of Pneumology

Effets génomiques et non-génomiques de l'oestradiol lors de l'activation du comportement sexuel mâle
Seredynski Aurore, Laboratory of Behavioral Neuroendocrinology

Impact of graft source and graft composition on outcomes after allogeneicstem cell transplantation
Servais Sophie, Laboratory of Hematology

Seminars

Amunts Katrin, Aachen University, Germany
The human brain atlas - challenges and perspectives

Arnal Jean-François, Université de Toulouse, France
Le récepteur des oestrogènes et sa modulation physiologique et pharmacologique : évolution de la structure et des concepts

Baffet Alexandre, Columbia University, New-York, USA
Cell cycle control of "Interkinetic Nuclear Migration" in neuronal progenitors

Baulac Stéphanie, Institut du Cerveau et de la Moelle, Paris, France
Focal epilepsies: from canalopathies to mTORopathies

Belaiche Yohanns, Institut Curie Paris, France
Epithelial morphogenesis: from cell to tissue

Blondeau Caroline, GIGA, Belgium
Tetherin restricts HSV-1 and is antagonized by the glycoprotein gM

Burzio Veronica & Villegas Jaime, Universidad Andres Bello, Santiago, Chile
The antisense non-coding mitochondrial RNAs as targets for diagnostic and therapy in cancer

Cabantous Stéphanie, Université de Toulouse, France
La technolologie « Split-GFP » et ses applications pour la détection intracellulaire et l'étude des interactions protéine-protéine

Chang YoonJeung, Max Planck, Dresden, Germany
Microcephaly proteins during mammalian neurogenesis

Deiters Alexander, University of Pittsburgh, USA
Small Molecules and Light as Tools for the Regulation of Cellular Processes

Faure Philippe, Ecole des Neurosciences, Paris, France
Nicotinic modulation of DA system. Consequences on nicotine addiction

Garel Sonia, INSERM, Paris, France
Wiring the forebrain: atypical roles of cell migration

Giacobini Paolo, Inserm, Lille, France
Semaphorins' signaling in development and function of GnRH neurons: setting the stage for reproduction

Goeman Jelle, Radboud University Medical Center, The Netherlands
Flexible multiple testi

González-Nilo Fernando, Universidad Andrés Bello, Chile
Convergence of bioinformatics and bio-nanotechnology

Huyghe Jeroen, University of Michigan, USA
mRNA-seq analysis of 278 diverse human skeletal muscle biopsies reveals mechanistic insights about type 2 diabetes risk loci

Jacobs-Wagner Christine, Yale University, USA
The surprising cell biology of bacteria and its role in bacterial multiplication

Karoyan Philippe, Université Pierre et Marie Curie, Paris, France
Peptides et Protéines: des études structurales aux outils thérapeutiques anti-microbiens et anti-cancéreux

Korngreen Alon, Université de Bar-Ilan, Israel
Realistic modelling of cortical pyramidal neurons

Loulier Karine, Institut de la vision, Paris, France
Multicolor strategies to probe cell lineage during central nervous system development

Marenne Gaëlle, Sanger Institute, UK
Insight into the genetic architecture of severe childhood onset obesity by analysing whole-exome sequencing data from cases and controls

Muyldermans Serge, VIB, Belgium
Nanobodies as a versatile tool for multiple applications

Servais Laurent, I-Motion Center, Paris and CHR, Liège
From mice to humans through dogs and monkeys: The challenge of bringing science that (really) works to the patient bedside

Soubeyran Philippe, Inserm Marseille, France
Identification of new resistance mechanisms to anticancer therapy by tracking changes in post-translational modifications by ubiquitin and ubiquitin-like proteins

Stevenson Tyler, University of Aberdeen, Scotland, UK
Epigenetic regulation of biological rhythms in reproduction

Stygelbout Virginie, ULB Neuroscience Institute, Belgium
Role of Itpkb and InsP4 in mouse and human Alzheimer disease

Sutton Roger, Texas University, USA
Muscular dystrophy, dysferlin and hypo-stability: Implications for all of the ferlin proteins

Thijssen Victor, VU University, Amsterdam, The Netherlands
Vascular galectins; blood, sugar, sex, magic

Tibaldi Fabian, GSK, Belgium
Modeling the long-term antibody persistence in HPV16 and HPV18 vaccine recipients

Tuoc Tran C., University Göttingen, Germany
Chromatin remodeling BAF complex controls cortical development and epigenetic programs

Van Lishout François, GIGA, Belgium
Detecting interactions in high-dimensional genetic and clinical data

Vivier Eric, Centre d'Immunologie Marseille, France
NK cells: a cytotoxic subset of Innate Lymphoid cells

Wijmenga Cisca, University Medical Center Groningen, The Netherlands
BeMGI Annual Meeting 2014: Genomic Advances in Disease Biology and Diagnostics

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is waiting to be known »

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