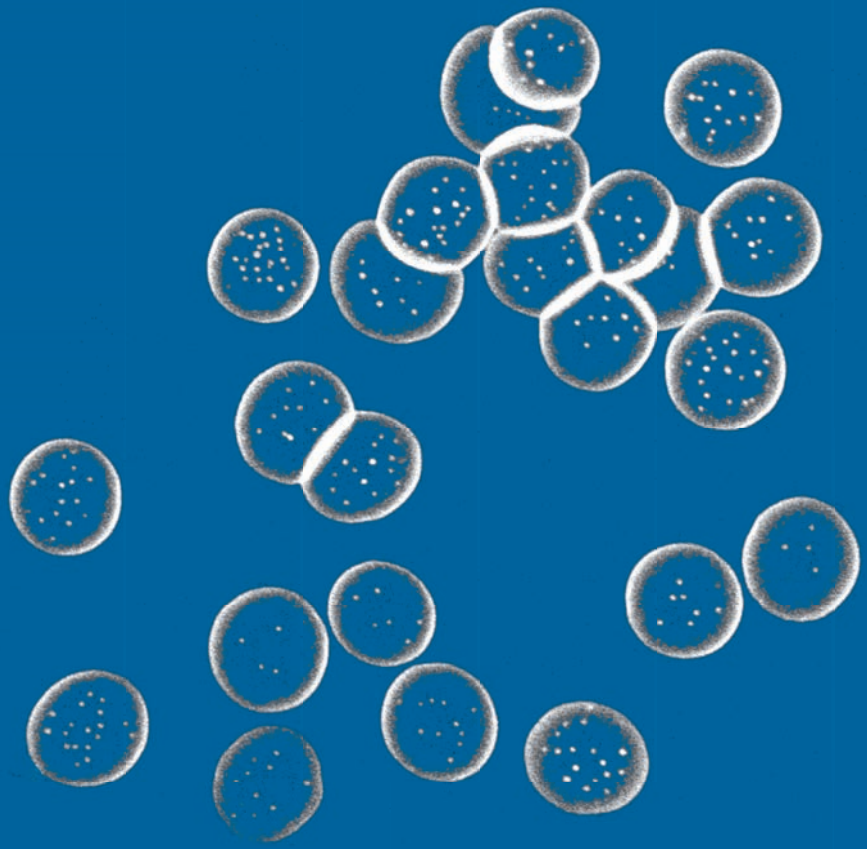
de Duve INSTITUTE

SCIENTIFIC REPORT 2018

de Duve Institute and Ludwig Cancer Research - Brussels

UCLouvain



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Picture: Confocal imaging of lipid domains at the surface of living red blood cells (imaging platform, Tyteca's group)

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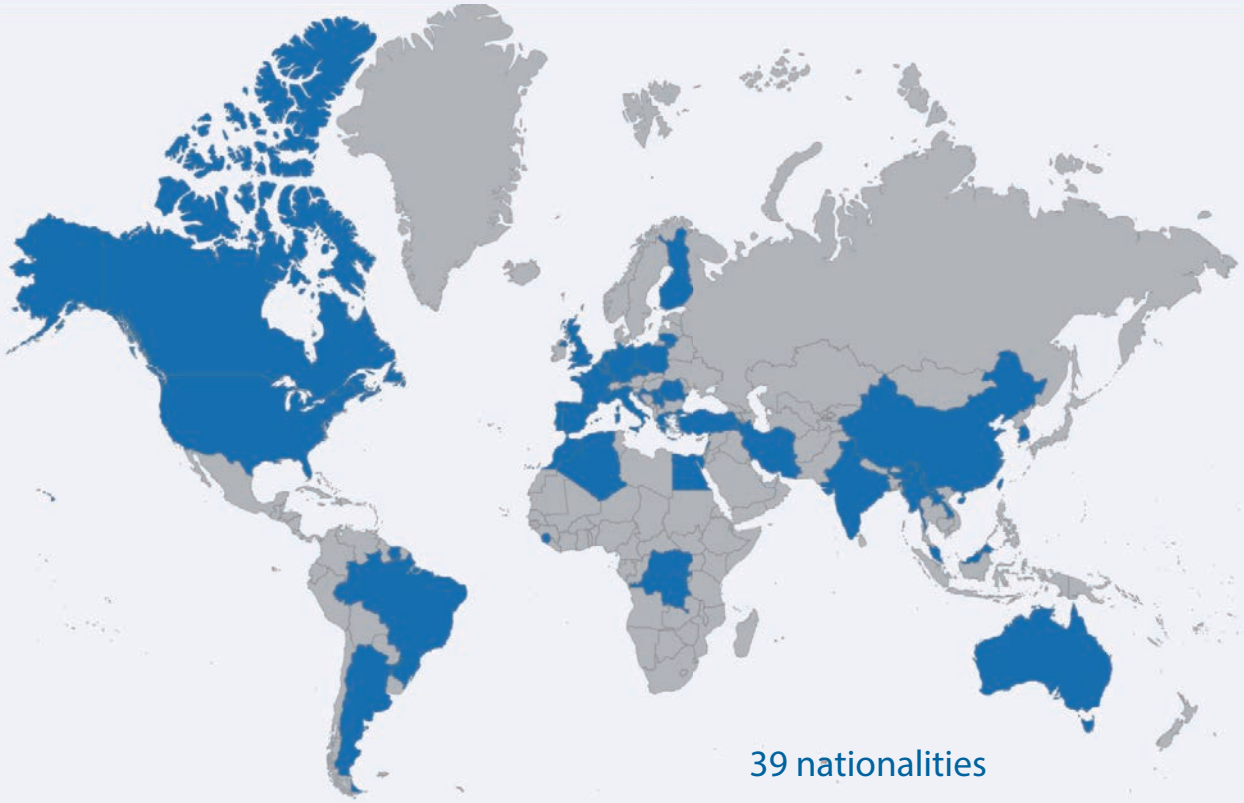


39 nationalities

287 members

45% 55%

100 PhD students

33 postdoctoral students

106 publications

45 international lectures

6 technology platforms

8000 m^2

From the Director

The Nobel Prize in Physiology or Medicine honored last fall two scientists, James P. Allison and Tasuku Honjo, who carried out groundbreaking research on tumor immunology and developed strategies to stimulate our immune system to attack cancer cells. For this therapeutic strategy to work, the immune system must be able to recognize cancer cells as if they were foreign to our body, i.e. cancer cells must display tumor antigens. Thierry Boon and his team, hosted by the de Duve Institute, have played a pioneering role in this research field by being the first to demonstrate the existence of tumor antigens. Not only did they carry out the molecular identification of these antigens, but they also deciphered multiple mechanisms that make virtually all tumor cells bear these potential targets for our immune cells.

Thierry Boon's discovery was in line with Christian de Duve's achievements in cell biology: serendipity played an important role. Intriguing observations made by Thierry Boon while working at the Pasteur Institute in Paris indicated that some mouse tumors were rejected when they were transplanted in syngeneic mice. Hence, tumor immunity might exist! Many years of highly imaginative and brilliantly executed work then followed to provide the molecular proof that tumor immunity indeed exists. The work on tumor immunology is successfully being continued at the de Duve Institute by former collaborators of Thierry Boon: Benoît Van den Eynde (page 19), Sophie Lucas (page 18), Pierre Coulie (page 17), Pierre van der Bruggen (page 20).

The work on cancer immunotherapy perfectly illustrates our philosophy that carrying out fundamental research on disease mechanisms is of utmost importance to understand disease development, and such knowledge is the foundation for improved diagnosis and development of novel therapeutic approaches. The present report further highlights this concept and describes how the Institute's research teams contribute to our understanding of a wide range of disease mechanisms and design of therapeutic strategies. This has also enabled groups of our Institute to obtain additional large grants this year, including those from the European Research Council (to Guido Bommer [page 38] and Géraldine Laloux [page 32]) and the Generet Foundation (to Miikka Vikkula [page 24]).

To foster the development of research on fundamental knowledge, the Institute is closely following the development of biomedical technologies. As increasingly large datasets are generated with cutting-edge high-throughput technologies, the Institute has reinforced its capacity to handle such data. A new group leader, computational biologist Laurent Gatto (page 12), joined the de Duve Institute in 2018. He will be developing novel ways to analyze large datasets, in collaboration with various groups of the de Duve Institute and the Faculty of Medicine of UCLouvain. This will help us stay at the forefront of biomedical research and reinforce our capacity to follow our motto:

"Deeper knowledge for better cures"
(*"Mieux comprendre pour mieux guérir"*)

Emile Van Schaftingen

About the Institute

Originally named International Institute of Cellular and Molecular Pathology (ICP), the de Duve Institute was founded in 1974 by Professor Christian de Duve († 4th of May 2013) to develop basic biomedical research with potential medical applications.

Excellence and freedom of the researchers to choose their line of research are our core values as defined by de Duve. We attract excellent researchers from Belgium and from abroad, and give them the liberty to develop their original ideas in an inspiring environment. Discovery is the endpoint of their efforts and the only element taken into account for their evaluation.

We value collaborative work and interdisciplinary research. The Institute functions in symbiosis with the Faculty of Medicine of the University of Louvain (UCLouvain) and many of its senior members hold a Faculty position and have teaching appointments. The influx of doctoral students and postdoctoral fellows from the University is key to the success, as well as the close collaborations with clinicians of the University Hospital (Cliniques universitaires) Saint-Luc, located within walking distance. In addition we have good contacts and many joint research projects with other research institutions in Belgium and all over the world.

In 1978 the Ludwig Institute for Cancer Research decided to base its Belgian branch within the walls of the de Duve Institute. A fruitful collaboration between the two institutions has been pursued ever since. Even though the two institutes are completely independent, the collaboration between their scientists is extremely close and the sharing of resources considerable.

The de Duve Institute has the ambition of pursuing research projects of high quality under conditions that allow original, long-term projects. Research is funded by public bodies, national and international, as well as by private donations. Most funds are awarded on a competitive basis. The Institute has an endowment, which is a source of key financing for priority issues, such as the creation of new laboratories for promising young researchers. The quality of our researchers, supported by sound organisational approaches, will enable the de Duve Institute to remain at the forefront of European research. We are extremely grateful to all those who support the Institute.

Research Highlights

Controlling the brakes of the immune system

Immune cells are capable of recognizing and killing cancer cells. One of the reasons why this not always happens, is that Tregs inhibit the anti-tumor immune cells. The lab of Sophie Lucas revealed the 3D-structure of a protein complex that is key to the immunosuppressive activity of Tregs. It shows how blocking this complex could restore the immune system's ability to kill cancer cells.

Our immune system is our personal army against foreign invaders. When it faces intruders, it strikes back, fiercely and ruthlessly. In its rage, it can cause considerable collateral damage to healthy cells. To control this, our body is equipped with regulatory T cells, also called Tregs. Tregs dampen the immune response by inhibiting other T cells. People with little or dysfunctional Tregs suffer from auto-immune diseases. Sophie Lucas studies Tregs and how they exert their immunosuppressive function. This is relevant to auto-immune diseases but also to cancer. "In cancer, Tregs inhibit T cells that are supposed to destroy tumors. Inhibiting Treg activity could therefore be a new approach in cancer immunotherapy", she says. A recent discovery of her lab, published in Science, brings such a therapy a step closer.

While studying medicine at UCLouvain, Sophie Lucas quickly knew she wanted to do fundamental research. "The courses on fundamental subjects, like biochemistry and immunology, interested me most. I wanted to understand how things in the human body work at a molecular level." She did her PhD thesis in the tumor immunology lab of Thierry Boon at the de Duve Institute, then called ICP. She joined the lab in an exciting time: "Thierry Boon had just identified the first antigens recognized by T lymphocytes on human tumors. Some of these were present on tumor cells but not on normal, healthy cells. To identify more of these interesting, tumor-specific antigens, we took a completely new approach, starting from the tumor cells themselves to identify genes that are only expressed in tumors. And it worked."

After her PhD degree she went to San Francisco to work as a postdoc at Genentech, where she studied protein messengers, collectively called cytokines, in autoimmune diseases. But in 2004, she wanted to move back to Europe with her family. Thierry Boon offered her to start a new line of research at the de Duve Institute. She decided to focus on Tregs, a still very mysterious type of cells at the time, but which were more and more suspected to play detrimental roles in cancer.

Sophie Lucas' perseverance was severely put to the test in the first years. At the time, little was known about human Tregs. Their close resemblance to other T cells and the difficulty to isolate and study them in vitro made reliable experiments challenging. Things changed when the lab succeeded in obtaining stable clones of human Tregs, providing reliable tools to explore the biology of these cells. Using these tools, the lab discovered that the immunosuppressive actions of Tregs are due to the production of TGF-β1, a powerful cytokine that inhibits neighboring immune cells. They also found that TGF-β1, which is made inside the Tregs in a latent form, is activated outside the cell by GARP, a protein anchored in the Treg membrane. "Latent TGF-β1 is produced by many cells, but only very few cell

"Being able to block TGF-β1 activation by GARP could represent an exquisitely specific way to modulate immunosuppression by Tregs."

types are able to activate it. Even fewer cell types use GARP to do so. Being able to block TGF-β1 activation by GARP could therefore represent an exquisitely specific way to modulate immunosuppression by Tregs, without affecting the many other important functions of TGF-β1", says Sophie Lucas. The lab succeeded to find an antibody that is able to block TGF-β1 activation by GARP. This compound was first licensed by the biotech company argenx and then by the pharmaceutical company AbbVie, for further development as a novel form of cancer immunotherapy.

Still, the fundamentals of TGF-β1 activation by GARP were not completely understood, and the lab wanted to elucidate the 3D structure of the GARP-TGF-β1 complex to tackle this question. They set up a collaboration with Prof. Savvas Savvides at UGent, who is experienced in x-ray crystallography. At first, they could not obtain crystals of the GARP-TGF-β1 complex. They then decided to use a part of the blocking anti-GARP antibody to stabilize the structure. The approach proved successful. "I remember when I first opened the file and saw the image of the complex in three dimensions. I could play with it, turn it around, really see how GARP presents latent TGF-β1. It was one of the best moments of my scientific career", says Sophie Lucas.

The images show how GARP resembles a horseshoe that is straddled by TGF-β1. The blocking antibody glues the two molecules to one another, ensuring that when other molecules pull on one part of the complex, the small, active part of TGF-β1 is not released, and is thus prevented from conveying its inhibitory message. "Visualization of this large molecular complex has not only increased our understanding of how TGF-β1 is released, but also illustrates the feasibility of blocking TGF-β1 activity with antibodies. We now know precisely how this works, which is always better if you want to use a compound in clinical treatments."

Is the research on TGF-β1 and GARP completed now that this structure is elucidated? "Certainly not", says Sophie Lucas. "TGF-β1 activation by GARP also happens on the surface of other cells, like B cells and megakaryocytes. We want to understand precisely when and how this occurs, and know the consequences of it in terms of health and disease. Not only in cancer, but also in autoimmunity or in the context of chronic infections. We are just at the beginning!"

Reference

Liénart S, Merceron R, Vanderaa C, Lambert F, Colau D, Stockis J, van der Woning B, De Haard H, Saunders M, Coulie PG, Savvides SN, Lucas S. Structural basis of latent TGF-β1 presentation and activation by GARP on human regulatory T cells. Science. 2018;362:952-6.

Cracking the bacterial defenses

Most people can't imagine that bacterial infections could become mass killers again, like they were until only seventy years ago. Yet, the increasing resistance of bacteria against antibiotics is a serious threat to today's human health. Jean-François Collet's lab tries to understand the defense mechanisms of bacteria, with the goal to find new ways to fight them.

The outer barrier of a bacterial cell, called the envelope, is more than a bag that keeps the cell content together. It has a well-defined structure built up of multiple layers, which houses many enzymes and other proteins. Besides giving the cell its shape and robustness, it actively transports molecules, transmits signals and protects the cell. Jean-François Collet became acquainted with the bacterial cell envelope as postdoc at the University of Michigan, where he studied a specific protein. When he started his own laboratory at the de Duve Institute in 2006, he decided to fully commit himself to unraveling the envelope's secrets. "It is an intriguing compartment. Its building blocks are made in the cell and then assemble at the surface to form a well-planned structure. Though we have learned a lot about these assembling processes in the last ten, fifteen years, many crucial mechanisms remain unknown. That makes it an attractive subject to study", says Collet. Today, after many publications in top tier journals, his lab is considered one of the leading groups in this field.

Jean-François Collet and the de Duve Institute go a long way back. In the fourth year of secondary school, he first heard of Christian de Duve from his biology teacher. He then read one of his books and thought how nice it would be to work at his institute. Later, during his studies in bio-engineering in Louvain-la-Neuve, he visited Emile Van Schaftingen's lab at the Institute and immediately knew: this is it for me. He did his thesis and PhD in the group of Van Schaftingen, to come back after his postdoc in the US. His laboratory made important contributions to a better understanding of the envelope. They identified two defense systems of bacteria, which save their amino acids from oxidation, and revealed a mechanism that bacteria use to detect membrane damage, to name a few.

Recently, they reported in PLOS Biology a remarkable feature of bacteria with a double membrane, a characteristic of many pathogenic bacteria. The distance between these membranes, they found, is accurately defined and when this distance is enlarged, the bacterium can no longer defend itself against external threats.

It required some first-class cell engineering to get these results. In an attempt to increase the distance between the membranes, Abir Asmar, a former PhD student in Collet's group, used genetic tools to make bacteria produce larger lipoproteins, the helix-shaped molecules that act as pillars between the two membranes. It perfectly gave the desired result. "We couldn't believe our eyes when we saw the first pictures. The distance between the membranes had increased proportionally to the length of the lipoproteins. We could play with the architecture of the cell envelope", says Collet.

The team then showed that the engineered bacteria were no longer able to transmit stress signals, which normally

"The distance between the membranes had increased proportionally to the length of the lipoproteins. We could play with the architecture of the cell envelope."

trigger defensive actions. To find out why, Asmar did some more cell engineering: next to the intermembrane distance she also increased the size of an important signaling protein. These bacteria had regained the capacity to respond to stress. The team concluded that when the intermembrane distance increases, the signaling protein becomes too short to span the envelope, making it unable to transmit signals. Modifying the distance is therefore a potential way to fight pathogenic bacteria. "We are now looking for molecules that can interact with the cell architecture."

Much of Collet's work is about the responses of bacteria when they are attacked by bleach. "This not only happens in our bathrooms, but also in animals and humans, where immune cells release bleach to kill invading bacteria. Bleach harms the bacterial cell by reacting with its proteins, causing them to unfold and then aggregate. Once aggregated, the proteins are lost", explains Collet. In a second recent publication in Molecular Cell, Camille Goemans, another former PhD student of Collet, describes how a molecule called CnoX helps the bacterium to save its proteins from bleach. "CnoX is an abundant compound in *E. coli* bacteria with no function in normal circumstances, but it gets activated in the presence of bleach. It then wraps itself around damaged unfolded proteins and prevents them from aggregating. This so-called chaperone function is also seen in other proteins. However, CnoX has a second way to protect proteins by preventing the irreversible oxidation of the proteins it is wrapped around. Such a dual way of protecting proteins has not been observed before", says Collet. The researchers thus identified a new class of proteins, which they named chaperedoxins. "Chaperedoxins might be present in other bacteria as well, and even in more complex organisms."

Whenever possible, the lab tries to translate their findings to clinical benefits. Since two years, a microbiologist in the group is fully occupied with valorization of the results. This has already led to interesting collaborations with Italian and Swiss companies. Collet's ultimate goal is that his research leads to the development of new antibiotics. "The danger of the increasing number of bacterial strains resistant to antibiotics is underestimated. By 2050, bacteria could be more lethal than cancer. It is urgent to find new antibacterial molecules."

Reference

Goemans CV, Vertommen D, Agrebi R, Collet J-F. CnoX is a chaperedoxin: a holdase that protects its substrates from irreversible oxidation. Mol Cell. 2018;70:614-27.e7.

Tracing the signals

Stefan Constantinescu studies how blood formation is regulated and what goes wrong in hematological cancers. For his work he received the prestigious five-yearly prize for fundamental medical science of the Federal Government of Belgium, awarded by a jury of the Royal Academy of Medicine.

A healthy adult produces several millions new blood cells per second. All these cells are derived from hematopoietic stem cells, which, via several stages, differentiate to many different types of blood cells. The process is controlled through small proteins, called cytokines. Coming from other parts of the body, cytokines tell the blood progenitor cells what to do: differentiate, expand or die. Stefan Constantinescu studies the signaling mechanisms in blood progenitor cells, focusing on the cytokine receptors. Upon binding to a cytokine, the receptors on the blood progenitor membrane undergo a structural change that sets in motion a cascade of signaling reactions towards the cell nucleus. On a molecular level, Constantinescu tries to elucidate the assemblage and structural changes of these complex molecules. "What interests me is the code by which molecular interactions in space are translated into responses in cells. One of the big problems in biology is how proteins fold and change their 3D structure. It is impossible to predict this from the primary amino-acid sequence, because it depends on so many variables. Yet, the 3D interactions of proteins determine whether processes in the cell go right, or wrong."

Romanian-born Stefan Constantinescu was initially trained as a medical doctor in Bucharest and worked briefly in pediatric hematology. During his PhD in virology he detected HIV-1 infections in children, the first cases of pediatric AIDS. It was an impressive experience, he tells: "It was caused by blood transfusion. 12000 children were infected, 6000 of them are still alive, but living with the consequences." In 1991 he left for the US to become a postdoctoral fellow at University of Tennessee Memphis, and then in 1995 at the Whitehead Institute at MIT in Cambridge. There he did his first work on signaling mechanisms, studying an essential receptor in the production of red blood cells. He proved a very talented researcher and started in 2000 his own laboratory at ICP, now called de Duve Institute, under the umbrella of the Ludwig Institute for Cancer Research.

As acknowledged by the award of the five-yearly prize, his lab acquired an international reputation for its contributions to the understanding of Myeloproliferative Neoplasms (MPNs), a group of diseases in which a specific type of blood cells is produced in excess. These chronic diseases may lead to various medical problems, like blurred vision or thrombosis. A small percentage of the patients develops acute myeloid leukemia, a rapidly progressing and lethal cancer. The genetic causes of these diseases have all been identified in just ten years. A first major breakthrough came in 2005, when it was found – and the Constantinescu lab contributed to this – that many MPN patients have a specific mutation in the gene coding for the JAK2 enzyme. JAK2 is a key enzyme in the signaling in blood cells: it is the first intracellular enzyme that gets activated when a cytokine like Epo arrives. In many MPN

"What interests me is the code by which molecular interactions in space are translated into responses in cells."

patients, JAK2 is always in the activated state. The discovery has led to the development of a JAK2-inhibitor that is now approved for use in various diseases. "The drug is beneficial to MPN patients, who feel better and have less symptoms, however, it doesn't cure them. Its efficiency is limited because it inhibits all JAK2 enzymes and not only the mutated ones. It must therefore be used in low doses. We are looking for drugs that specifically inhibit the mutated JAK2 enzyme", says Constantinescu. Unexpectedly, the JAK-inhibitors are now also used for some auto-immune diseases, like graft-versus-host disease. "Here it works better than the standard treatments with cortisones."

After the discovery of the JAK2 mutation, more genetic causes of MPNs were unraveled. The Constantinescu lab found a mutation in the thrombopoietin receptor, which regulates the formation of platelets. The mutation makes the receptor signaling continuously, also when there is no cytokine. The erroneous receptor causes around 5% of the MPNs.

Two years ago, the lab elucidated how the last missing major genetic mutation causing MPNs, discovered by another group, actually works. The mutation leads to a change in a protein called calreticulin. "This was a surprise, as calreticulin was not linked to signaling. It normally has a chaperone function and stays in the endoplasmic reticulum. However, when mutated, it can move to the cell surface and activate the thrombopoietin receptor", says Constantinescu. The remarkable features of this 'delinquent chaperone' gave him the idea to use it in new treatment approaches. "For example, people born with a specific mutation in the thrombopoietin receptor die, because the receptor cannot move to the cell surface. Mutated chaperones might enable this transfer."

Though much is learned about the causes of MPNs, it is still unknown why some of these diseases develop into acute myeloid leukemia. It is the big question Constantinescu would like to resolve with his research. Lately, he has come to work more closely to the clinical practice, since he participates every Monday as an internal consultant in the MPN consultation of University Hospital Saint-Luc's hematology department. "These contacts with physicians and patients are very useful for our research. And it gives me a sense of urgency. Seventy percent of acute myeloid leukemia in children, and 27% of acute myeloid leukemia in adults are cured today. If we want to find new therapies for the other patients, we have to better understand the fundamentals of the disease."

New computational biology group

Modern experimental techniques generate so much data that understanding them has become a discipline on its own. A new group at the Institute, headed by Laurent Gatto, specializes in extracting valuable biological information out of the oceans of data.

Last summer, Laurent Gatto changed Cambridge for Brussels, a city he knows well from his animal biology study at the ULB. He will work on computational biology, the same topic he researched for nine years in Cambridge. There is however one big difference, he says: "One of the attractive features of this position is that I will collaborate intensely with people doing biomedically relevant research. Being so close to experimental groups, here at the Institute, gives me a privileged position."

How does an animal biologist end up in bioinformatics?
"For my master's thesis I studied the genetics of a leaf beetle population. This required significant amounts of data analyses, so I taught myself some programming. But I soon realized that self-teaching didn't work well, and pursued a part-time degree in computer science at the University of Namur. During my PhD project, which was on the genetics of whales and dolphins, my excitement for analysis grew, while my interest in lab work diminished. So I slowly shifted to bioinformatics."

Your group will be the first in the Institute that does no lab experiments. What kind of work will you do?
"We focus on the analysis of data generated by others, especially high throughput data from genomics, proteomics, transcriptomics. We help researchers to identify significant patterns in their data, by developing and applying algorithms and software. For this we use various techniques, such as statistics and machine learning. One noteworthy aspect is controlling the quality of the data throughout the whole analysis process. By using algorithms and visualization, we can see whether there is something wrong with the data. It's important to assure that an analysis reflects the underlying biology. Whichever dataset you analyze, you will always get a result. You must be sure it is not a false positive."

Researchers have always analyzed their data themselves. Why has this become a separate discipline?
"In classical biology, a researcher studies a particular gene or protein in a well-defined system. He designs experiments and analyzes the results, which confirms or contradicts his hypothesis. You can compare it with a box of Lego bricks with clear building instructions. It may take some time, but at the end of the day you have what you wanted to build. In high throughput experiments, you buy a huge Lego box. It contains tons of bricks, many more than you need, while other, important bricks are missing. You know what you want to build – and it's generally pretty complex – but you have no instructions on how to get there. Now you need algorithms to assist you with your construction, which will sort the bricks for you on color and shape. We develop these algorithms."

Where will you get the data from for your projects?
"I am engaged with groups from the whole university's Health Sector. We will develop bespoke methods to analyze their data. Together, by combining our experimental and computational expertise, we will answer their research questions more thoroughly and trustworthy."

Research Groups

Cancer

A cancer starts when cells acquire the ability to grow fast and the body's defence system cannot control them. We study the signaling mechanisms that regulate cell growth and how genetic mutations lead to aberrations in these mechanisms, inducing for example blood cancers or child tumors. Our institute proudly was at the basis of today's cancer immunotherapy treatments. We now investigate how the efficacy of these treatments can be enhanced.

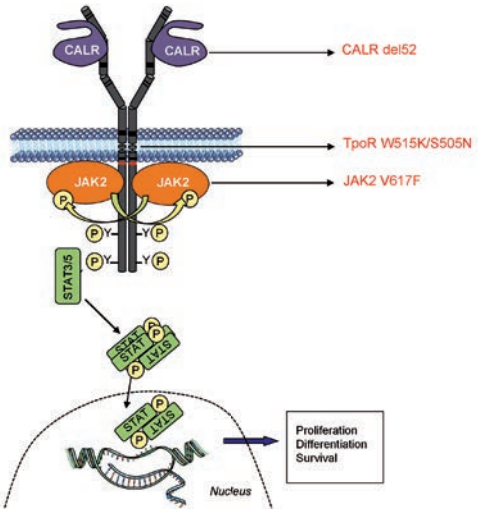
LUDWIG CANCER RESEARCH
Brussels

Stefan Constantinescu

Cell Signaling & Molecular Hematology

We study how blood is formed and how cytokines regulate this process via their membrane receptors, via Janus kinases, STAT proteins and other signaling pathways. We decipher how mutations in cytokine receptors and Janus kinases induce blood cancers.

Formation of blood requires small proteins, denoted as cytokines, such as erythropoietin, thrombopoietin, interleukins or interferons. These proteins transmit information either from distant tissues or from surrounding cells, and induce survival, growth and differentiation of blood precursors. They act by binding on the surface of target cells to 'receptors', which function like 'antennae' that transmit a signal to the cell interior and ultimately to the nucleus, where the choice of expressed genes is made. We study how these specific receptors assemble on the membrane and couple at the cell interior to other proteins, such as Janus Kinases (JAKs), which are absolutely required to transmit a signal. We found that mutations in JAKs or in receptors themselves confuse the cells and make them grow indefinitely, leading to blood cancers, specifically myeloproliferative neoplasms (MPNs). While the excessive blood formation is explained by the activation of JAK2 pathway, it is still a mystery why clones emerge and why disease progresses from the chronic MPN condition to severe acute leukemia. Inhibitors of JAK2 have been isolated by several companies, and one such inhibitor has been approved for the treatment of Myelofibrosis and Polycythemia Vera. Yet, the JAK2 inhibitor does not eliminate the mutated clone and is not very effective. Our hypothesis is that a curative treatment needs a mutant specific inhibitor. To this end, we delineated the circuit of JAK2 kinase activation by the V617F acquired mutation in the pseudokinase domain and aim to target this circuit, which would lead to inhibitors that discriminate between wild type and mutated JAK2. The same strategy is taken for mutants in the Tpo receptor (TpoR/Mpl) that we discovered in 2006, where mutations in W515 in the cytosolic juxtamembrane domain change the structure of the region encompassing the transmembrane domain.



Signals from cytokines are transmitted to the nucleus via JAK2 and STAT proteins. JAK2, CALR or TpoR mutations can lead to blood cancers.

More recently, we discovered that mutations can endow a chaperone protein, calreticulin, with the ability to bind and activate a cytokine receptor, namely Tpo receptor (TpoR/MPL) both in the secretory pathway and at the surface of megakaryocyte progenitors. This closes the circle of major driver mutations in myeloproliferative neoplasms and blood malignancies. The next challenge is the delineation of the pathway by which blood cancer cells evolve to leukemic blasts which are blocked in differentiation and give acute leukemia phenotype.

In order to pursue our aims we use approaches like extensive mutagenesis, functional biological assays as read-outs for structure, biophysics, in vivo transgenesis, microscopy and fractionation, mouse bone marrow transplantation, as well as investigation of primary patient cells.

Staff members

Clinical Investigator: Jean-Philippe Defour • **Senior Investigators:** Didier Colau, Christian Pecquet • **Guest Investigator:** Pierre De Meyts • **Postdoctoral Fellows:** Emilie Leroy, Anita Roy, Leila Varghese • **PhD Students:** Thomas Balligand, Harsh Goyal, Gabriel Levy, Florian Perrin, Gaëlle Vertenoeil • **Research Assistants:** Lidvine Genet, Céline Mouton, Yacine Rahmani, Madeleine Swinarska • **Technical Assistant:** Florin Militaru

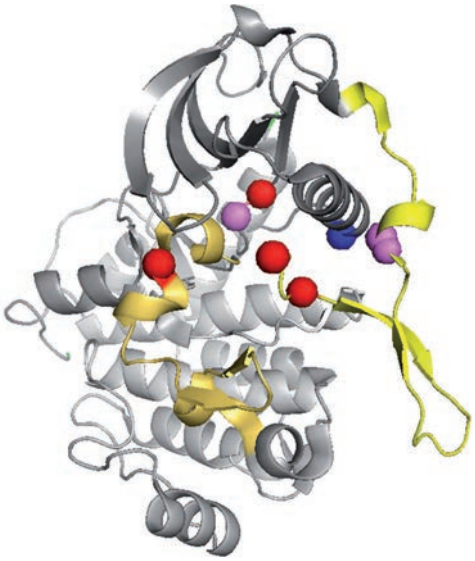
Jean-Baptiste Demoulin

Cancer Signaling

Our team analyzes the signaling pathways that promote cancer cell proliferation. Recently, we made significant progress in understanding infantile myofibromatosis. We showed that these life-threatening tumors are caused by *PDGFRB* gene mutations and identified a treatment.

We have a long-standing interest in platelet-derived growth factors (PDGF), which act via two receptor-tyrosine kinases, namely PDGFRA and PDGFRB. These proteins play important roles in the development of the embryo, as well as in cancer and fibrosis. We analyze signaling cascades activated by these receptors, with a particular interest for transcription factors, such as STAT, FOXO, HBP1 and SREBP. Recently, the role of micro-RNA (miR), as modulators of gene expression and cell proliferation, was also investigated.

PDGF receptors can be aberrantly activated by gene mutation or gene fusion in cancer. Gene fusions involving PDGF receptors cause a rare type of leukemia characterized by proliferation of eosinophils (a blood cell type). Our team has studied the mechanism whereby these fusion products stimulate cell growth and differentiation into eosinophils by introducing mutated receptors in hematopoietic progenitors. In collaboration with the hematology unit of the University Hospital Saint-Luc, we also discovered new fusion genes.



Disease-causing mutations (indicated by colored spheres) in the PDGF receptor kinase domain.

Recently, using deep sequencing, we identified mutations in *PDGFRB* as a cause of childhood soft tissue tumors (infantile myofibromatosis). The disease is characterized by the presence of multiple tumor masses, which can be life-threatening, particularly in young children. The mutations aberrantly activate the kinase domain of the receptor (Figure). Similar mutations were also found in patients suffering from rare congenital disorders, such as Kosaki overgrowth syndrome or Penttinen syndrome. In a preclinical study, we showed that these mutants are sensitive to a drug named imatinib, which potently blocks PDGF receptors. Based on our results, this drug was tested successfully in a child harboring a germline *PDGFRB* mutation.

Finally, dominant *PDGFRB* mutations were also associated with familial brain calcification (Fahr disease). In this case, patients do not develop tumors, but suffer from severe neurological symptoms. We showed that these mutations cause a partial loss of receptor function (in sharp contrast to the mutations described above).

In conclusion, we have shown that alterations of PDGF receptors cause several human diseases. Our promising results suggest that some patients may benefit from PDGF receptor inhibitors. We now aim to understand these diseases in more detail and validate treatments.

Staff members

Clinical Investigator: Violaine Havelange • **Postdoctoral Fellow:** Audrey de Rocca Serra • **PhD Students:** Emeline Bollaert, Guillaume Dachy, Ariane Sablon • **Undergraduate Student:** Maxime Libert • **Research Assistants:** Sandrine Lenglez, Virginie Vandewalle • **Administrative Support:** Geneviève Schoonheydt

Pierre Coulie

Human Tumor Immunology

Cancer immunotherapy is a breakthrough for some but not all cancer patients. We explore important parameters of the very early stages of the development of anti-tumor T cell immune responses, notably antigenicity and inflammation.

Our immune system protects us by destroying foreign substances like bacteria and viruses. T cells, a type of white blood cells, are the effectors of this process as they recognize and destroy foreign cells. T cells can also recognize tumor cells. T. Boon and colleagues at the de Duve Institute discovered the specific markers, called antigens, that are recognized on cancer cells by T cells. It paved the way for clinical applications and remarkable clinical results have been obtained since 2010 with immunostimulatory antibodies that enhance the activity of anti-tumor T cells. However, many patients do not respond to currently available immunotherapies. We try to understand the mechanisms of these limitations to eventually improve cancer immunotherapy.

"Analyzing human tumors at a very early stage, which is possible for example with in situ breast carcinomas, is key to understand why anti-tumor immunity is present or absent in a given patient."

One project focuses on T cells present within human breast tumors. We observed that anti-tumor T cells were often absent from these tumors, the simplest explanation being that T cells have nothing to recognize on breast tumor cells. Indeed, in a tumor that contained many antigens we did find anti-tumor T cells, indicating that the local environment of a breast tumor does not prevent the development of anti-tumor immunity. Now we study the earliest stage of breast cancer, the so-called in situ carcinomas. We wonder whether anti-tumor immunity would not be stronger there than in more advanced tumors. If this is true, immunotherapy should be tried in patients with breast cancer at a much earlier stage than what is done now.

Another project deals with inflammation, which is normally a local response to microbes or various types of cellular stress. Inflammation depends on soluble factors, notably cytokines including IL-1β. Immune responses start only in the presence of some level of local inflammation, which acts as a danger signal. In tumors, and particularly in small ones, inflammatory signals are faint and probably often absent. Increasing them locally could induce or increase anti-tumor T cell responses. In this context, we study the secretion of IL-1β by monocytes, another type of white blood cells and an important source of IL-1β. The process of secretion of IL-1β is completely different from that of most other secreted proteins, and is partly unknown. Monocytes can secrete IL-1β while they die, through a process called pyroptosis, thus releasing their intracellular content. However we have observed that under certain conditions monocytes secrete IL-1β but do not die. We try to understand the mechanism of this secretion. Specifically blocking or increasing this secretion could have important medical applications in chronic inflammatory diseases or cancer, respectively.

Staff members

Senior Investigators: Nicolas Dauguet (Platform Manager), Tiphanie Gomard, Nicolas van Baren • **PhD Students:** Orian Bricard, Walther Brochier, Alix Devaux, Marie-Sophie Dheur, Kevin Missault, Charlotte Six • **Research Assistants:** Gérald Hames, Catherine Muller, Nathalie Remy • **Administrative Support:** Suzanne Depelchin

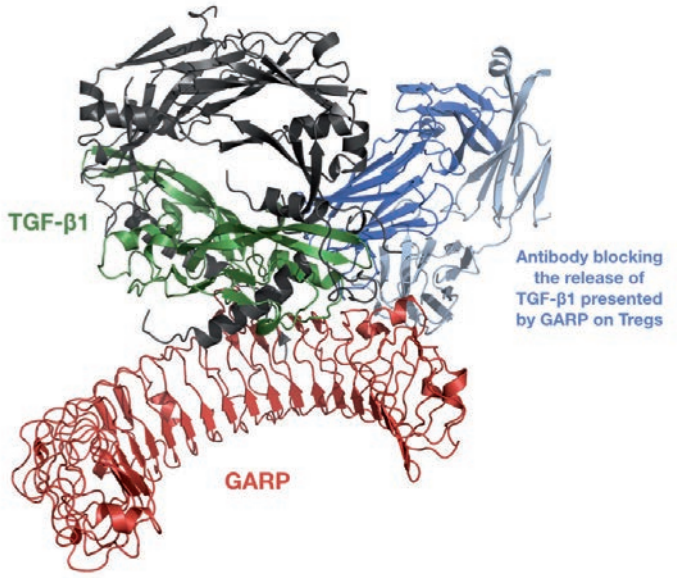
Sophie Lucas

Regulatory T cells & TGF-β

We study how regulatory T cells (Tregs) suppress immune responses. Our long-term goal is to design therapeutic approaches to manipulate immune responses in patients suffering from diseases associated with Treg dysfunction. These include cancer, chronic infections and auto-immunity.

Our immune system protects us against infections and cancer, notably because immune cells are able to kill and eliminate microbial pathogens, infected cells, and tumor cells. But immune cells need to be kept under tight control to avoid aberrant destruction of healthy tissues. Tregs are specialized in the control of immune cells, which they suppress to prevent auto-destructive reactions. Patients with insufficient Tregs suffer from autoimmune diseases. In contrast, excessive Treg function is associated with cancer and chronic infections.

We try to identify the mechanisms by which Tregs suppress immune responses. We found that Tregs produce a protein called TGF-β1, which acts as an inhibitory messenger on immune cells. We also found that production of the immunosuppressive TGF-β1 requires another Treg protein called GARP. In all cell types, production of TGF-β1 is highly regulated and often requires accessory proteins. Tregs are among the very few cell types to produce TGF-β1 in a manner that depends on GARP. We developed tools (e.g. monoclonal antibodies) that bind GARP and block TGF-β1 production by Tregs. We are currently exploring whether these tools could be used as drugs to block Treg immunosuppression in patients suffering from cancer. Our antibodies were licensed to the biotech company argenx, then to the pharmaceutical company AbbVie, for further development toward the clinic. More recently, we used x-ray crystallography to solve the 3D structure of a protein assembly comprising GARP, TGF-β1 and a blocking antibody (Figure). This allowed us to understand how GARP presents TGF-β1 for activation on Tregs, and how our antibody actually blocks this process. We are now studying whether and when cell types other than Tregs also produce TGF-β1 via GARP. This is important to predict potential adverse effects of drugs targeting GARP, but it will also serve to identify non-cancerous diseases, such as autoimmune diseases or chronic infections, in which these drugs could be beneficial.



3D structure of TGF-β1 presented by GARP on Tregs, blocked by an anti-GARP antibody which could serve for the immunotherapy of cancer.

Staff members

Postdoctoral Fellows: Clément Barjon, Mélanie Gaignage • **PhD Students:** Charlotte Bertrand, Grégoire de Streel, Julien Devreux, Fanny Lambert, Sara Lecomte, Stéphanie Liénart, Xuhao Zhang • **Undergraduate Student:** David Lorang • **Research Assistants:** Noora Bleeckx, Amandine Collignon, Maria Panagiotakopoulos • **Administrative Support:** Suzanne Depelchin

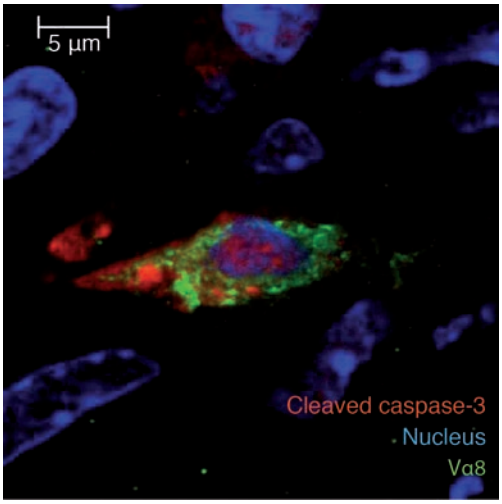
LUDWIG CANCER RESEARCH
Brussels

Benoît Van den Eynde

Cancer immunotherapy is showing clinical benefit in a subset of cancer patients. Our work studies the basic mechanisms of immune recognition and rejection of cancers, aiming to increase the fraction of cancer patients who respond to immunotherapy.

Improving Cancer Immunotherapy

Cancer immunotherapy works by helping the immune system to fight cancer. Its cornerstone is the notion, pioneered at the de Duve Institute, that tumor cells express markers, called 'tumor antigens', which are absent on normal cells and allow the immune system to identify and destroy cancer cells. These tumor antigens are recognized by cytolytic T lymphocytes, which have the capacity to kill tumor cells. However, many tumors manage to resist immune rejection. This can be linked to two mechanisms: they can either lose expression of the tumor antigen, or they can produce immunosuppressive factors that paralyze the immune system. Our group studies these mechanisms, hoping to devise therapeutic strategies able to counteract resistance to immunotherapy.



A T lymphocyte (green) in the tumor microenvironment (blue) is undergoing apoptosis and disappearing (red).

Tumor antigens are made of small protein fragments, named peptides, which are presented at the cell surface by class I molecules of the Major Histocompatibility Complex (MHC, also named HLA in human). These peptides generally come from the degradation of intracellular proteins by the proteasome, a proteolytic particle localized in the cytoplasm and the nucleus. We have characterized different types of proteasomes, which differ in their ability to produce peptides corresponding to tumor antigens. This means that the antigens presented at the surface of cancer cells partly depend on the proteasome composition of these cells, a notion that can explain the variability in tumor antigen expression. We further study how some cancers, while losing expression of classical tumor antigens, unmask other antigens that we are characterizing. We also discovered a new function of the proteasome, which enables the splicing of peptides, i.e. the production of peptides from noncontiguous fragments in the parental protein, following a 'cut and paste' process.

In addition, we are also researching the immunosuppressive mechanisms acting in the tumor microenvironment. We recently observed that tumors can selectively induce the death of T lymphocytes by apoptosis. Furthermore, our previous work showed that tumors are able to paralyze lymphocytes by starving them of a key amino acid, tryptophan. They do so by expressing an enzyme, called indoleamine dioxygenase (IDO), which degrades tryptophan. Several pharmaceutical companies, including our spin-off iTeos Therapeutics, are developing IDO inhibitors, some of which are currently in Phase III clinical trials in combination with immunotherapy.

Staff members

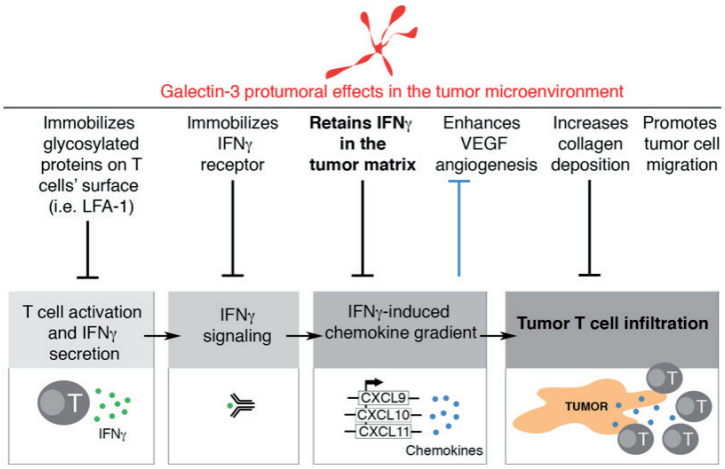
Emeritus: Thierry Boon • **Senior Investigators:** Etienne De Plaen, Christophe Lurquin, Vincent Stroobant • **Postdoctoral Fellows:** Veronica Finisguerra, Wenbin Ma, Stefan Naulaerts, Nathalie Vigneron, Jingjing Zhu • **PhD Students:** Joanna Abi Habib, Tereza Dvorakova, Violette Ferrari, Delia Hoffmann, Simon Klaessens, Julie Lesenfants, Pierre-Florent Petit, Florence Schramme, Marie Solvay, Jiali Yang • **Undergraduate Student:** Aurélie Mazy • **Research Assistants:** Thérèse Aerts, Loubna Boudhan, Rui Cheng, Dominique Donckers, Bernardo Ercoli, Matteo Formenti, Luc Pilotte, Bénédicte Tollet • **Administrative Support:** Auriane Sibille

Pierre van der Bruggen

T Lymphocyte Dysfunction

We study the interactions between cancer cells and the human immune system. We have a particular focus on understanding why tumor-infiltrating lymphocytes (TILs) are unable to kill tumor cells, and finding strategies to overcome this blockage.

We are studying immune responses directed against tumor cells with the aim of improving patients' immune responses to cancer. By a genetic approach, we have identified the first antigen recognized by a cytolytic T lymphocyte on human cancer cells. Gene MAGE-1, which encodes this antigen, is expressed in many tumors, but not in most normal tissues. We have subsequently identified genes with the same expression profiles, such as gene families MAGE, BAGE, and GAGE. We have designed approaches to identify antigenic peptides encoded by these genes and recognized either by CD8 or CD4 T cells, and have set up approaches to measure anti-vaccine T cell responses in vaccinated patients.

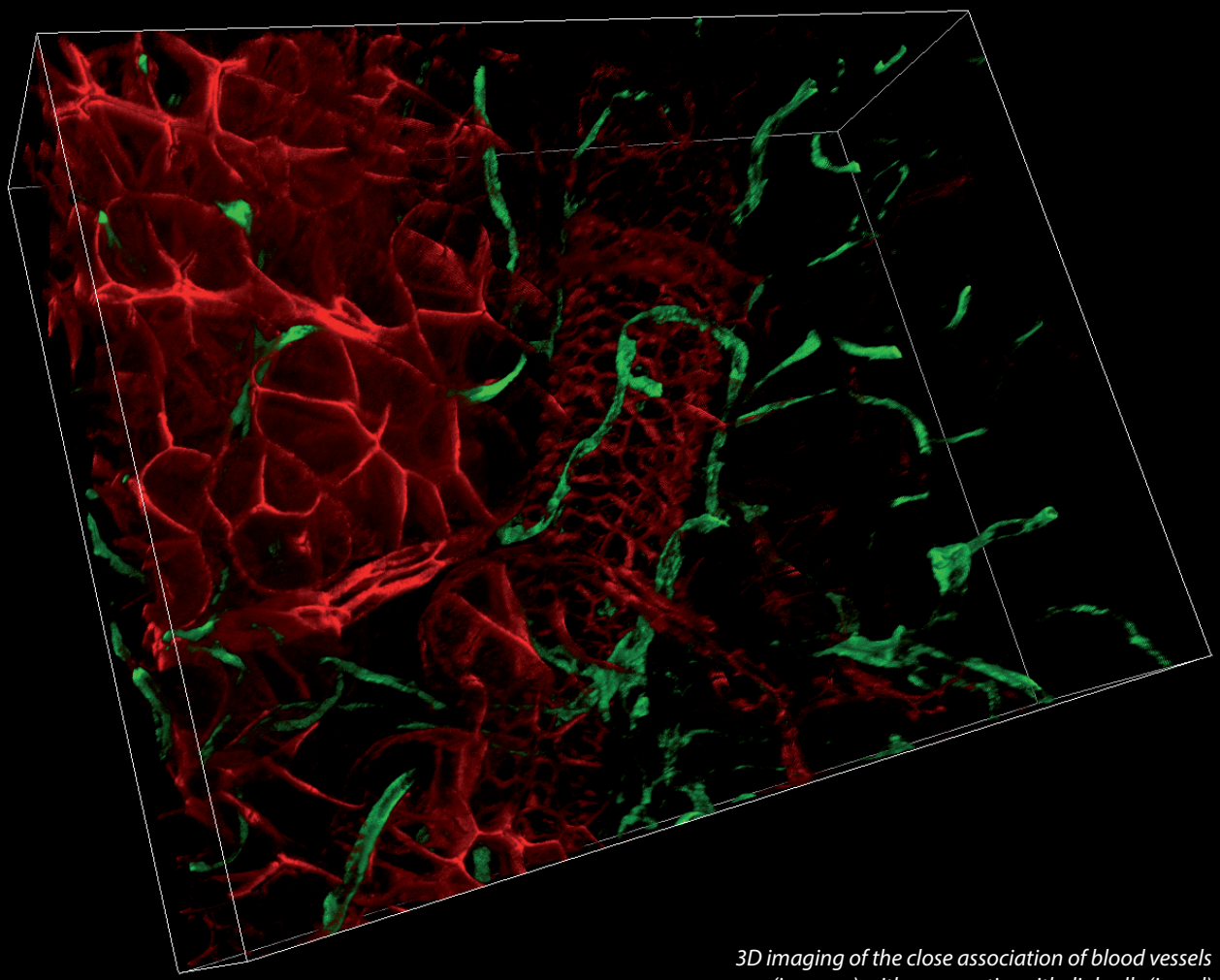


Scheme summarizing the main protumoral effects known for galectin-3 in the tumor microenvironment.

Most tumors are not ignored by the immune system of cancer patients. They contain immune cells and, in particular, T cells directed against tumor antigens. These tumor-infiltrating T cells (TILs) are often dysfunctional. We have decided several years ago to focus our research efforts on TIL dysfunction and a better understanding of the different immunosuppressive mechanisms that operate in human tumors. Galectin-3 is a lectin, i.e. a sugar-binding protein. Galectin-3 is mainly secreted by tumor cells and macrophages. Extracellular galectin-3 binds glycoproteins and forms lattices by oligomerization, thereby blocking functions of human TILs, as treating TILs with an anti-galectin-3 antibody detached galectin-3 from the surface and increased cytokine secretion and cytotoxicity of treated TILs. TILs covered by galectin nevertheless produced cytokines intracellularly upon stimulation, but the cytokines remained trapped inside TILs. The normal secretion process was indeed blocked in TILs due to impaired LFA-1 mobility and impaired actin rearrangement at the secretory synapse. As a result, cytokines and lytic enzymes remain trapped inside TILs, thereby preventing their anti-tumor activity. From a practical standpoint, the new mechanism of T cell dysfunction indicates that evaluating T cell function by intracellular cytokine staining, a widely used immune-monitoring assay, can be highly misleading.

T cell recruitment towards tumors requires a chemokine gradient of IFN-γ-induced chemokines. We observed that galectin-3 binds glycans decorating IFN-γ and the extracellular matrix, thereby reducing IFN-γ diffusion through the matrix and therefore production of a chemokine gradient. A T cell transfer in tumor-bearing mice controls tumor growth only if galectin antagonists are injected. Considering that most human cytokines are glycosylated, galectin secretion could be a another strategy for tumor immune evasion.

Postdoctoral Fellow: Annika Bruger • **PhD Students:** Thibault Hirsch, Mathieu Luyckx, Damien Neyens, Christophe Vanhaver • **Research Assistants:** Alexandre Bayard, Quentin D'Hondt, Claude Wildmann • **Administrative Support:** Julie Klein



3D imaging of the close association of blood vessels (in green) with pancreatic epithelial cells (in red) (imaging platform, Pierreux's group)

All cells of a human body originate from one cell that, directed by the genetic information, divides, grows and differentiates into a fully functional organism. How do our cells develop in the embryo? Which genetic mutations lead to diseases? How do cells maintain themselves during a lifetime and how do they age? How is the expression of genes regulated? Our groups in genetics and development try to elucidate these secrets of life.

Genetics and Development

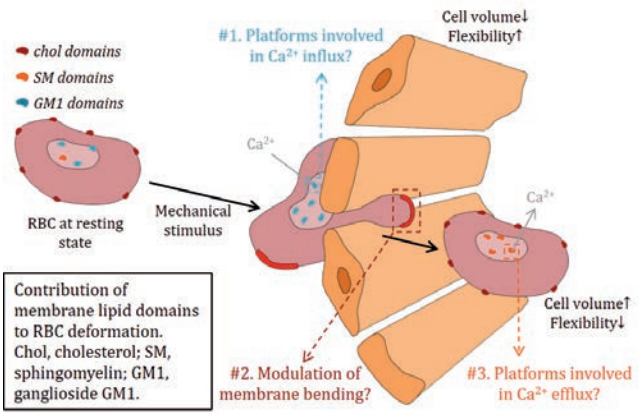
Donatienne Tyteca

Membrane Biology

Cell deformation is critical for numerous pathophysiological processes. Our group explores how plasma membrane biophysical properties contribute with the cytoskeleton and membrane bending proteins to cell deformation and how this interplay is deregulated in diseases.

In their environment, cells face a variety of stimuli and stresses inducing cell deformation. Typical examples are shear stress by squeezing of red blood cells (RBCs) in the narrow pores of spleen sinusoïds, stretching of muscle cells during contraction or pressure exerted by tumors on surrounding cells. Cell deformation is generally attributed to a dynamic cytoskeleton and membrane bending proteins but the contribution of plasma membrane biophysical properties is not understood.

We aim at elucidating how plasma membrane contributes to cell deformation, as a prerequisite towards understanding membrane deformability disorders. We mainly use RBCs, as the simplest and best-characterized human cell model that exhibits remarkable deformability allowing squeezing through narrow splenic pores (> 10,000 times in RBC lifetime). In physiological senescence and genetic membrane deformability disorders (e.g. spherocytosis and elliptocytosis) RBCs fail to deform coordinately.



Contribution of membrane lipid domains to RBC deformation. Chol, cholesterol; SM, sphingomyelin; GM1, ganglioside GM1.

Using high-resolution confocal imaging and atomic force microscopy (coll. D. Alsteens, UCLouvain), we discovered the existence of stable submicrometric lipid domains at the plasma membrane of living RBCs. Three types of domains coexist, showing differential composition, membrane curvature association and lipid order, suggesting control by membrane biophysical properties (Figure, left). One type of domains contributes to RBC deformation through their gathering in highly curved membrane areas. The two others increase in abundance upon calcium influx and efflux respectively, suggesting they could provide platforms for the recruitment and/or activation of proteins involved in calcium exchanges (Figure, right). These hypotheses are under investigation.

In contrast, lipid domains are lost upon RBC senescence, suggesting they could represent sites susceptible to vesiculation. To test for this hypothesis, we isolate and purify vesicles from RBCs upon storage at 4°C to determine their lipid composition, biogenesis and pathophysiological implications (coll. N. Dauguet). In parallel, we examine the importance of the interplay between lipid domains and the cytoskeleton for RBC deformation, using RBCs from patients suffering from genetic red cell disorders (coll. C. Vermylen, University Hospital Saint-Luc). In spherocytosis caused by mutations in ankyrin or β-spectrin genes, lipid domains involved in calcium exchanges are decreased in abundance in a splenectomy-dependent manner, suggesting loss by vesiculation. In elliptocytosis caused by a variant in the α-spectrin gene, lipid domains involved in calcium exchanges show altered properties due to oxidative stress and increased plasmatic sphingomyelinase activity. These data open new avenue for disease treatment. We thus demonstrated that lipid domains contribute to RBC deformation. We now explore their importance for cancer cell migration and invasion.

Staff members

Senior Investigator: Patrick Van Der Smissen (Platform Manager) • **PhD Students:** Anne-Sophie Cloos, Louise Conrard, Mauriane Maja, Hélène Pollet, Sandrine Verstraeten • **Undergraduate Student:** Amaury Stommen • **Research Assistant:** Maxime Lingurski • **Administrative Support:** Aimée-Lys Rusesabagina

Nisha Limaye

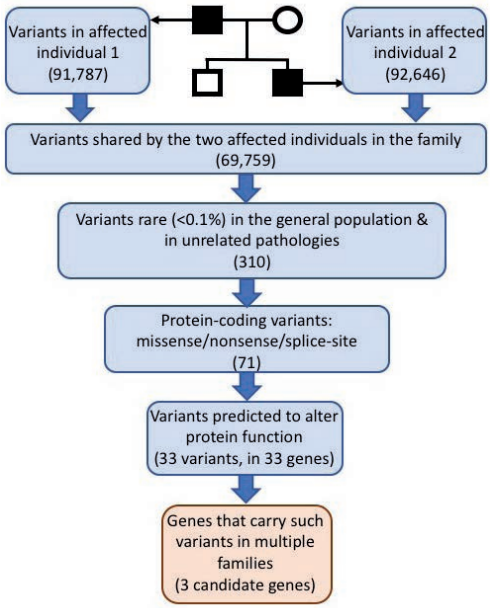
Genetics of Autoimmunity & Cancer

We study genetic factors underlying diseases potentiated by inappropriate immune responses: inadequate (cancers) or excessive (autoimmunity). As extremes of the same spectrum, the insights we gain into disease mechanisms of one have profound implications for the other.

Our immune system, responsible for defending us against harmful pathogens such as certain bacteria and viruses, can sometimes turn on us. It may mistake components of our own cells for foreign invaders, or react too zealously against perceived threats, causing significant collateral damage to our own tissues and organs. The resulting autoimmunity and systemic autoinflammation can be devastating. On the flip-side, inadequate surveillance or responsiveness of the immune system to abnormal 'self' cells can allow for the unchecked growth of cancers.

Our laboratory explores the contribution of genetics to immune imbalances or dysfunction, in rheumatic (autoimmune, autoinflammatory) conditions such as systemic sclerosis and systemic lupus erythematosus, and in certain cancers (primarily Hodgkin lymphoma). In very rare cases, these diseases run in families. By sequencing all genes in multiple members of such families, we identify those variants that are shared by all the affected individuals, but not their healthy relatives. These genes may therefore contribute to disease.

This is no trivial task: we all carry hundreds-of-thousands of genetic variants, i.e., have slightly different 'versions' of each gene, relative to one another. The more closely related we are, the more of these variants we tend to share with each other. A tremendous amount of accumulated information, knowledge-based predictions, and data-processing is therefore required to distinguish the thousands of incidental variants shared by family members, from the one-to-a-few that actually impact disease.



Strategy to identify candidate disease-causative genes, i.e. genes with rare, potentially pathogenic variants that co-segregate with disease in multiple families. Brackets: number of variants retained after each filtering step.

Once we identify a gene that causes disease, we explore how and why it does so: we induce cells to express the faulty version of the gene, study how this changes their appearance, behavior and function, and test the ability of drugs to prevent or reverse these changes. We also screen patients with non-inherited ('sporadic') forms of the same disease for the gene, to assess for how widespread a role it plays. Ultimately, by understanding the genetic and molecular bases of these rare diseases, we seek to better predict, prevent, and treat them.

Staff members

Clinical Investigators: Bernard Lauwerys (Rheumatologist), Hélène Antoine-Poirel (Hematologist) • **Guest Investigator:** Gaëlle Tilman • **PhD Student:** Elsa Khoury

Miikka Vikkula

Human Genetics

Our aim is to understand the mechanisms that underlie disorders of the cardiovascular and skeletal systems, as well as certain cancers. We especially evaluate the contribution of genetic variation to human disease. We also generate models to test novel molecular therapies.

The bases of many disorders remain unknown, and treatments are often aimed at alleviating symptoms. We try to identify the primary causes of vascular tumors and vascular malformations, lymphedema, and cleft lip and palate. We also collaborate in studies on various cancers: (angio)sarcoma, breast cancer and pheochromocytomas. This research is based on blood and tissue samples collected from patients in collaboration with clinical centers worldwide, and especially with the University Hospital Saint-Luc. We analyze the genome using high-throughput sequencing. For these analyses we develop and implement specialized bioinformatics tools via our Highlander software. We also maintain the UCLouvain Genomics Platform and an important computational cluster.

"We demonstrated that rapamycin can control expansion of lesions."

Vascular anomalies are a heterogeneous group of disorders in which the lesions are localized and composed of masses of malformed vessels. They can affect any organ, causing pain, dysfunction and decreased quality of life. We have identified several genes causing familial forms and discovered that the much more common non-hereditary forms can be due to somatic mutations.

In venous malformations, somatic mutations activate the TIE2/PI3K/AKT signaling pathway. We demonstrated that the mTOR inhibitor rapamycin can control expansion of lesions. We have since undertaken phase II clinical trials demonstrating effectiveness in patients. A phase III trial is currently being run by Prof. L. Boon at the University Hospital Saint-Luc.

In parallel, we have recently discovered a second gene causing capillary malformations associated with arterio-venous malformations (CM-AVM2): EPHB4. The proteins encoded by the two discovered genes regulate the RAS/MAPK signaling pathway. We are now generating a mouse model to test for potential therapies.

A large part of our efforts is dedicated to understanding primary lymphedema, which causes chronic swelling, dysfunction and predisposition to infections. We recently discovered mutations in two genes, *VEGFC* and *ADAMTS3*. Altogether, we now know 28 genes to cause primary lymphedema, explaining about 30% of the cases.

The mechanisms leading to cleft lip (CL) with or without cleft palate (CP) are as variable as those causing primary lymphedema. Using whole exome sequencing, we identified an inherited mutation in 10% of the cases. Yet, each time the gene was different. We currently develop novel bioinformatics algorithms to study such complex diseases.

Understanding the primary causes of these diseases allows the development of molecular approaches, resulting in more specific treatments. As we have demonstrated in venous malformations, such a molecular approach may provide great hope for patients.

Staff members

Clinical investigators: Laurence Boon (Plastic Surgeon), Daniel Manicourt (Rheumatologist) • **Senior Investigators:** Pascal Brouillard (Platform Manager), Raphaël Helaers • **Guest Investigator:** Claudia Masini d'Avila-Lévy • **Postdoctoral Fellows:** Ha-Long Nguyen, Angela Queisser • **PhD Students:** Mirta Basha (Dentist), Simon Boutry, Elodie Fastré, Peyman Ranji, Nassim Homayun Sepehr, Matthieu Schlögel, Cedric van Marcke de Lummen • **Research Assistants:** Dominique Cottem, Audrey Debue, Liliana Niculescu, Delphine Nolf • **Technical Assistants:** Mourad El Kaddouri, Christian Miserez • **Administrative Support:** Liliana Niculescu

Charles De Smet

Epigenetics in Cancer

Epigenetic mechanisms are essential to maintain proper gene expression programs in human tissues. Dysregulation of these mechanisms can lead to disease, including cancer. Studies in our group explore the causes and consequences of epigenetic alterations in tumors.

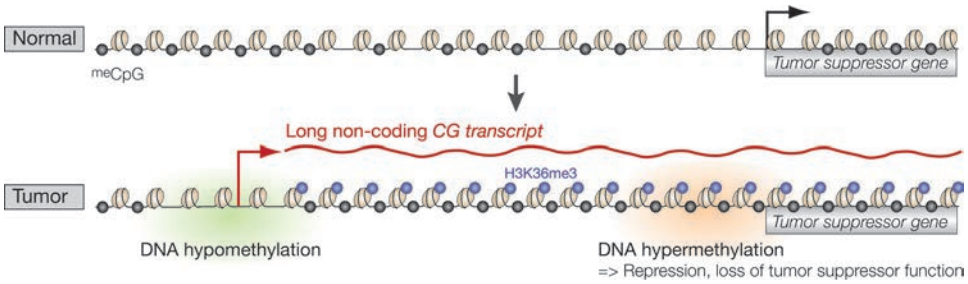
Maintenance of gene expression programs is essential to ensure proper functioning of the various cell types that make up the body. To this end, cells have evolved "epigenetic" regulatory mechanisms, based on the addition of chemical modifications on defined genes. Among such modifications, DNA methylation has an essential role in the long-term inactivation of tissue-specific genes.

Importantly, the distribution of DNA methylation marks is profoundly altered in most tumors, and there is evidence that this contributes to cancer progression. The causes and consequences of this epigenetic disruption in tumor cells remain however unclear.

We discovered that DNA methylation alterations often affect a particular group of genes, which normally display specific expression in germline cells. These genes lose methylation in many tumors, and become therefore aberrantly activated. Due to their particular expression profile, such genes were termed "cancer-germline" (CG).

Several CG genes were found to encode proteins that display oncogenic properties, and are therefore considered as potential targets for anti-cancer therapies. It is expected indeed that therapies directed against proteins expressed almost exclusively in tumors and germline cells will have only little side effects in cancer patients.

Our group isolated a CG gene (*CT-GABRA3*) that is not translated into a protein, but carries a clustered pair of miRNAs (miR-105 and miR-767). Aberrant expression of these miRNAs was confirmed in a significant proportion of tumors of different types. These miRNAs were found to promote tumor development, notably by favoring the formation of distant metastases. Current investigation aims at discovering the full spectrum of miR-105 and miR-767 functions in tumor cells.



More recently, we made the surprising observation that transcriptional activation of CG genes in cancer sometimes impacts the regional epigenetic landscape. Indeed, bioinformatics analyses of tumor transcriptomes and epigenomes identified several long non-coding CG transcripts, which overlap downstream promoters and thereby trigger their hypermethylation. The process appears to involve H3K36me3, a histone mark known to be deposited during progression of the transcription machinery and to attract DNMT3A/B DNA methyltransferases. Another consequence of CG activation in tumors is therefore the epigenetic repression of neighboring genes, which include tumor suppressor genes.

Staff members

Senior Investigator: Axelle Loriot • **PhD Students:** Anna Diacofotakis, Jean Fain • **Undergraduate Student:** Marie Van Wynendaele

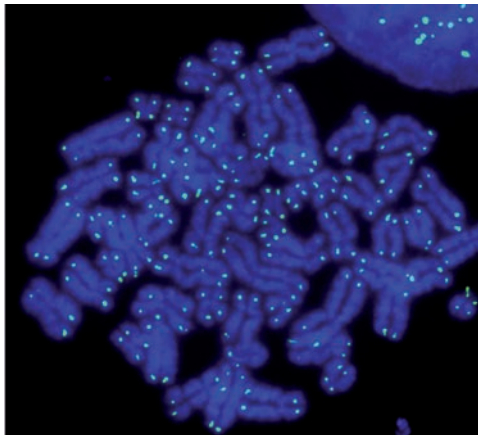
Anabelle Decottignies

Telomeres & Epigenetics

Telomeres are specialized protective structures present at chromosome ends. How to protect telomeres to delay cellular ageing or, conversely, how to damage telomeres to stop cancer cell proliferation, are two aspects of our research.

Telomeres are specialized protein-RNA-DNA structures currently viewed as biological clocks. They prevent linear ends of chromosomes from being recognized as broken DNA. In normal cells, telomeres shorten with successive cell divisions until they get too short to ensure faithful protection of chromosomes, and this triggers entry into cellular senescence.

The current model is that cellular senescence, by triggering a permanent exit from cell cycle, offers a protection against cancer since, with time, cells progressively accumulate mutations that are potentially oncogenic. However, the system is not perfect and some cells escape from the senescence barrier to form tumors. How then do cancer cells avoid the progressive shortening of telomeres when they divide? In 90% of the cases, they acquire mutations that reactivate the telomerase gene expression. Telomerase is the enzyme which, in embryonic stem cells, counteracts telomere shortening, but whose expression is lost upon cell differentiation.



Staining of telomeres in a melanoma cell by Fluorescent Hybridization In Situ using a green probe. The chromosomes are stained in blue.

Sarcomas or central nervous system tumors (including pediatric tumors) frequently activate a telomerase-independent mechanism of telomere maintenance, called ALT (Alternative Lengthening of Telomeres), which relies on homologous recombinations between telomeric sequences. The ALT mechanism is not active in normal cells, thus offering interesting perspectives for cancer therapy. Thanks to a genetic system of cellular hybrids, we discovered new important (epi)genetic features of ALT cells. We are actively working on some of them, with the long-term perspective of identifying new therapeutic targets to kill ALT cancer cells. This may, as well, offer a means to target telomere maintenance in survivor cells that could arise from anti-telomerase treatments that are currently being tested in clinical trials.

Recently, together with the Australian group of Prof. Roger Reddel (CMRI, Sydney), we discovered that some cancer cells do not require the activation of a telomere maintenance mechanism to form aggressive tumors. The unexpected observation that indefinite replicative potential is not a general hallmark of cancer cells is of foremost importance in the context of anti-cancer therapies targeting telomere maintenance.

The second half of our research focuses on the regulation of telomere transcription into non-coding RNA species dubbed TERRA (TElomeric Repeat-containing RNA). TERRA is an important contributor to telomere protection and increasing telomere transcription is likely to delay telomere erosion and cellular senescence. We discovered recently that the AMPK/PGC1-α metabolic pathway, activated by endurance exercise or caloric restriction, promotes human telomere transcription. This discovery fits with the recent suggestion that lifestyle impacts on telomere status.

Staff members

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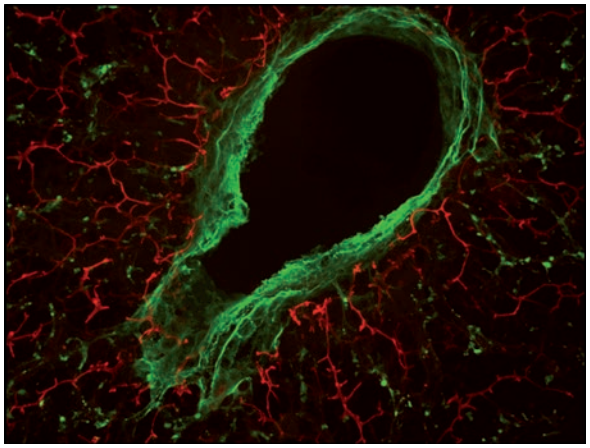
Frédéric Lemaigre &
Patrick Jacquemin

Our group identifies mechanisms that allow cells in liver and pancreas to acquire their mature functions during embryonic development. We also determine how these functions are perturbed in adults, which is essential to understand how diseases, in particular cancer, are initiated.

Cell Differentiation

To develop into a complex organism cells in the embryo need to proliferate, differentiate and organize in three-dimensional tissues. While focusing on liver and pancreas, our group aims at identifying the mechanisms that promote cell differentiation and tissue morphogenesis in the embryo, and those that perturb differentiation in adults and induce liver or pancreatic cancer. We share our data on normal differentiation with collaborators who transpose the information in cell culture protocols aiming at production of hepatic or pancreatic cells for cell therapy. Our findings on disease mechanisms from mouse models are validated using human tissue samples obtained from collaborating clinical research centers.



Section through an embryonic mouse liver illustrating a branch of the portal vein (laminin: green) and the hepatocyte canaliculi (CEACAM: red).

The main cell types of the liver are the hepatocytes, which exert the metabolic functions of the organ, and the cholangiocytes which delineate the bile ducts. We investigate the transcriptional networks that drive hepatocyte and cholangiocyte development in the embryo and identified several regulators of normal hepatocyte and biliary development, e.g. HNF6 – discovered in our laboratory –, and TGFβ signaling. In this context we also recently identified the microRNA miR-337 which controls the dynamics of the hepatic transcriptional networks.

Parallel to our research on development, we investigate the differentiation switches occurring during transition from normal to precancerous and eventually invasive cancer states. In pancreas, we study the cell type of origin of pancreatic ductal adenocarcinoma (PDAC), i.e. acinar or duct cells, and the signaling cascades promoting formation of precancerous lesions and their evolution to cancer. Our results suggest that there is a tight association between defects in primary cilia in duct cells and chronic pancreatitis, a risk factor for PDAC. These observations account for the increased risk to develop PDAC in patients with gene mutations affecting cilia. In our studies of liver cancer, we develop an original mouse model of cholangiocarcinoma which faithfully reproduces the sequential steps of tumorigenesis in humans.

Finally, we address the need of quantitative approaches by using mathematical modeling of the gene networks which we investigate in pancreas and liver. This resulted in the design of a mathematical model that predicts the behaviour and drug response of a gene network involved in hepatocellular cancer.

Staff members
Senior Investigator: Younes Achouri (Platform Manager) • **Postdoctoral Fellows:** Mohamad Assi, Mickaël Di-Luoffo, Claude Gérard • **PhD Students:** Louis Collet, Catalina De Schrevel, Angeline Fages, Lila Gannoun, Nora Meyers, Marie-Albane Minati, Sophie Pirenne, Janne Tys • **Research Assistants:** Sabine Cordi, Katarzyna Konobrocka , Jean-Nicolas Lodewykx • **Undergraduate Student:** Céline Duhamel • **Technical Assistants:** Freddy Abrassart, Mourad El Kaddouri • **Administrative Support:** Marjorie Decroly, Julie Klein

Wen-Hui Lien

Signaling Crosstalk

The goal of our research is to understand how Wnt signaling pathways regulate skin stem cell behavior and tumor development. Our studies provide an integrative view of signaling regulation and extend our knowledge for regenerative medicine and treatment of cancers.

Throughout life, skin epidermis is constantly renewed and its appendage, hair follicles, undergoes cycles of regeneration. Skin epidermal stem cells that can self-renew and differentiate provide the unlimited source of cells required for tissue homeostasis and injury repair. The regeneration of tissues is fine-tuned by signaling cues from their microenvironment. Deregulation of this signaling may contribute to the development of tumors.

In mammals, Wnt signaling pathways, including canonical and non-canonical Wnt signaling, regulate diverse processes, such as cell proliferation, differentiation, migration and polarity. Canonical Wnt signaling, referred to as Wnt/β-catenin signaling, is known as an important regulatory pathway that regulates developmental processes, tissue regeneration and cancers. While Wnt/β-catenin signaling has been extensively studied, the functions of non-canonical Wnt pathways are still underappreciated. Our group uses skin as a model system to investigate the roles of non-canonical Wnt pathways mediated by receptor tyrosine kinase-like orphan receptor 2 (Ror2) in the regulation of stem cells and tumorigenesis.

Wnt signaling is shown to regulate adult stem cells, but exactly how it functions and for what purpose has been a matter of much debate. We conduct loss-of-function approaches by generating mutant mouse models to determine how Ror2-dependent Wnt signaling regulates skin development and hair follicle regeneration. Using cell culture systems, we dissect the mechanism of Ror2 underlying stem cell proliferation and differentiation. By generating double-mutant mouse models, we further investigate the cross-interaction between canonical and non-canonical Wnt signaling pathways in stem cell fate determination.

How non-canonical Wnt signaling regulates tumor development remains elusive. To address this important question, our group collaborates with a surgeon, Dr Benoît Lengele, at University Hospital Saint-Luc, to collect and analyze human non-melanoma skin tumors. Using these human specimens in combination with our mouse models, we investigate the functional significances of Ror2-dependent signaling in carcinogen- and oncogene-induced tumorigenesis. The ultimate goal of our research is to identify the clinical relevance of main regulators involved in non-canonical Wnt signaling pathways and to use them as therapeutic targets to treat cancer and other diseases.

"How non-canonical Wnt signaling regulates skin stem cells and tumor development remains elusive."

Staff members

Postdoctoral Fellow: Chim Kei Chan • **PhD Students:** Gaia Cangiotti, Christopher Lang, Anthony Veltri • **Undergraduate Student:** Justine Bouzet • **Research Assistant:** Daniel Leon da Silva • **Administrative Support:** Aimée-Lys Rusesabagina

Christophe Pierreux

Our group focuses on paracrine communications between epithelial cells and their endothelial environment that govern acquisition of epithelial cell polarity and differentiation during thyroid and pancreas organ genesis, and loss of these characteristics in cancer.

Epithelial Differentiation

Our body is composed of various cell types, among which epithelial cells fulfill different functions: gas exchange in lung alveoli, nutrient absorption in the intestine, digestive enzyme secretion from the pancreas, hormone production by the thyroid, ... To achieve these diverse and essential functions, epithelial cells organize in particular tridimensional structures, like closed spheres in the thyroid. They also gradually specialize by acquisition of specific function(s), e.g. the production of digestive enzymes in the pancreas. This happens during embryonic development through timely and tightly controlled epithelial differentiation programs. Loss or impairment of the tridimensional organization and specialization of these cells is frequently observed in pathological conditions.

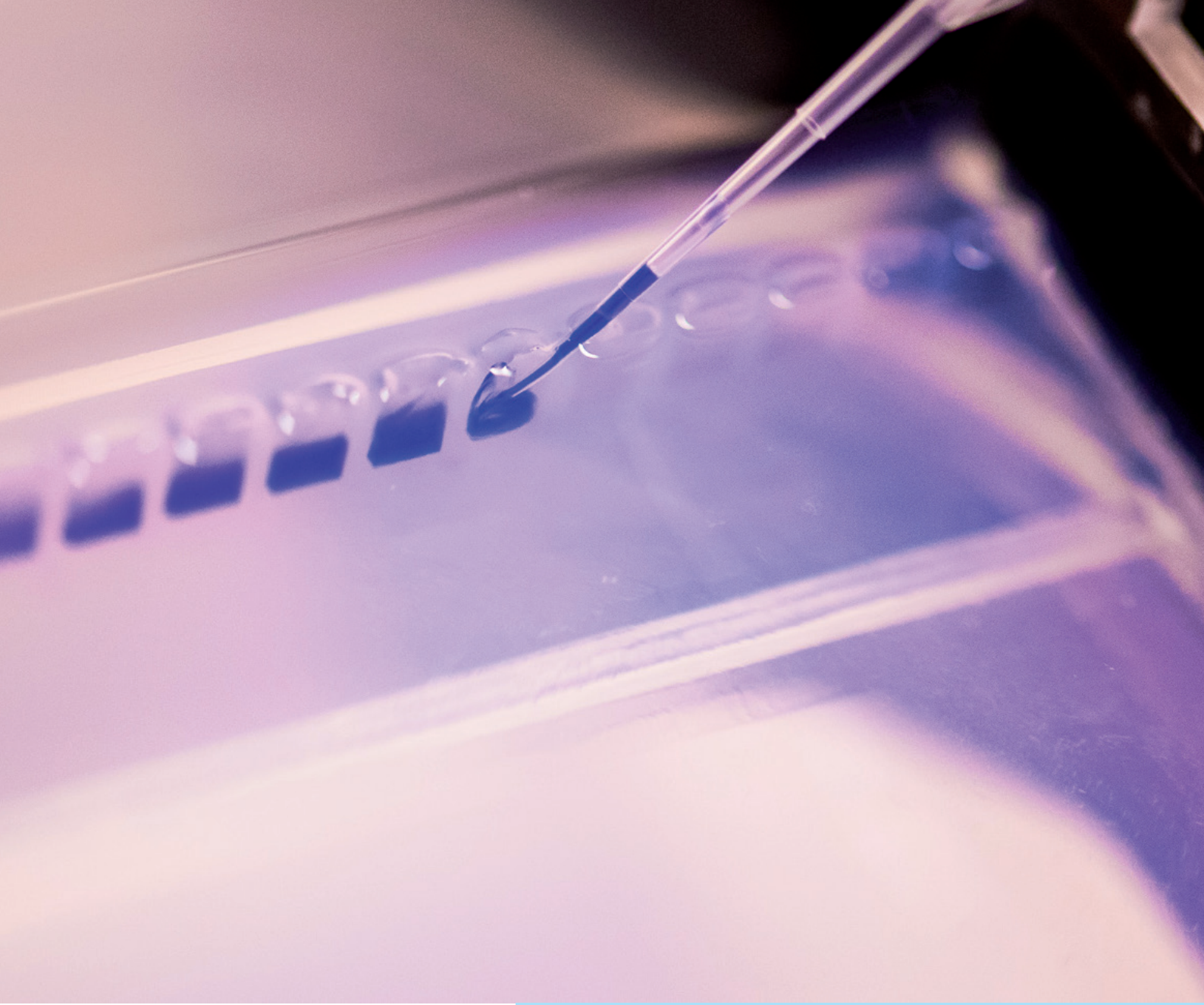
"In-depth characterization of cellular and molecular mechanisms during embryonic development and disease paves the way towards organ bioprinting and therapeutic testing."

Our group aims at understanding how epithelial cells of the thyroid and the exocrine pancreas organize and differentiate in response to signals from their environment. We have shown that thyroid and pancreatic progenitors first form a tridimensional mass of proliferating, non-polarized epithelial cells. Then, epithelial cells polarize and form monolayers that adopt a structure tailored to the organ's function: multiple independent closed spheres, or follicles, in the thyroid, or a single, highly branched network of ducts and acini in the exocrine pancreas. We demonstrated the importance of VEGF signaling during thyroid and pancreas formation and uncovered a perfusion-independent function of blood vessels, mediated by paracrine signals from endothelial cells. Our work on epithelial-endothelial relationship has been instrumental to pave the way towards thyroid bioprinting. We also uncovered the role of extracellular vesicles in intercellular communications. We are now further studying how endothelial cells impact on epithelial cells, and vice versa, in developing and diseased thyroid and pancreas..

We also investigate epithelial homeostasis in adult organs. Current studies focus on the role of class III PI3-kinase/Vps34 in vesicle trafficking to the apical pole in kidney tubules and thyroid follicles. Inactivation of this lipid kinase causes major cellular defects in both organs: mice display kidney tubule dysfunction, referred to as Fanconi syndrome, as well as hypothyroidism. We also addressed the pathophysiology of cystinosis, a multisystemic lysosomal disease due to defective lysosomal membrane cystine/H+ antiporter, cystinosin. This disease first manifests itself by a kidney Fanconi syndrome, and secondly in the thyroid with defective lysosomal generation of thyroid hormones from iodinated-thyroglobulin.

Staff members

Emeritus: Pierre J. Courtoy • **Postdoctoral Fellow:** Manon Moulis • **PhD Students:** Ophélie Delcorte, Laura Glorieux, Léolo Gonay, Charlotte Heymans, Virginie Janssens, Catherine Spourquet • **Undergraduate Student:** Matthieu Baudoin, Louis Lefebvre • **Research Assistant:** Pascale Lemoine • **Technical Assistant:** Abdelkader El Kaddouri • **Administrative Support:** Aimée-Lys Rusesabagina



Infections and Inflammations

Our body deals with viral or bacterial infections by inflammatory responses of the immune system. Our groups investigate how viruses modulate the body's immune reactions, or escape from them. We also address the worrying emergence of bacteria resistant to all available antibacterial agents. When inflammation gets ill-controlled, it can induce inflammatory diseases, like Crohn's disease, asthma or psoriasis, of which we study key mechanisms.

Jean-François Collet

Bacterial Stress Responses

It is urgent to develop new antibiotics against resistant bacteria. Our laboratory wants to contribute to the global effort aiming to prevent the return of untreatable epidemics by better understanding how bacteria respond to different types of environmental stress.

The overuse of antibiotics to treat bacterial infections in human and veterinary medicine has created a global resistance crisis that could lead to a surge in infection-related mortality. A recent report predicted that multidrug resistant bacteria will kill more people than cancer by 2050. A particularly serious threat is the emergence of a new wave of multidrug-resistant Gram-negative bacteria, including *Pseudomonas aeruginosa* and enterobacteria such as *Escherichia coli* and *Klebsiella pneumoniae*. It is therefore urgent to develop new antibiotics against resistant bacteria, which requires a deep understanding of the biology of these microorganisms. Our laboratory wants to contribute to the global effort aiming to prevent the return of untreatable epidemics by better understanding how bacteria respond to the different types of stress to which they are exposed. In particular, we want to understand how bacteria defend themselves against oxidative stress and how they maintain the integrity of their cell envelope despite always changing environmental conditions.

"Proteins involved in envelope biogenesis and maintenance are attractive targets for the design of new antibiotics."

The cell envelope is the morphological hallmark of Gram-negative bacteria. It is composed of two concentric membranes: the inner membrane (IM), which is in contact with the cytoplasm, and the outer membrane (OM), which constitutes the interface with the environment. The IM and the OM are separated by the periplasm, a viscous compartment that contains the peptidoglycan. The cell envelope is essential for bacterial viability. Proteins involved in envelope biogenesis and maintenance are therefore attractive targets for the design of new antibiotics.

The long-term objective of our laboratory is to delineate and ultimately harness the mechanisms underlying the assembly and maintenance of the envelope. Our research will contribute to the global effort to find new antibacterials by identifying proteins that play important roles in envelope assembly and protection, and therefore are attractive targets for new antibiotics.

Since the lab started in 2005, a number of major discoveries were made. In particular, we identified two antioxidant systems that are active in the bacterial envelope. The first system protects single cysteines from oxidation by reactive oxygen species, while the second rescues methionines from oxidative damage. Recently, we also discovered that the lipoprotein RcsF is targeted to the cell surface, in contrast to the general view that OM lipoproteins remain inside the periplasm. We determined that RcsF export is mediated by Bam, the machinery that inserts β-barrel proteins (porins) in the OM. We now want to investigate if additional lipoproteins decorate the cell surface of *E. coli*, which would radically change the model of the cell envelope as it is currently presented in many textbooks.

Staff members

Senior Investigators: Seung Hyun Cho, Pauline Leverrier • **Postdoctoral Fellows:** Abir Asmar, Michaël Deghelt, Alexandra Gennaris, Juliette Létoquart • **PhD Students:** Naemi Csoma, Kilian Dekoninck, Antoine Delhaye, Emile Dupuy, Jessica El Rayes, Camille Goemans, Nahla Hussein, Raquel Rodriguez Alonso • **Undergraduate Student:** Elisa Pierre • **Research Assistant:** Asma Boujtat

Géraldine Laloux

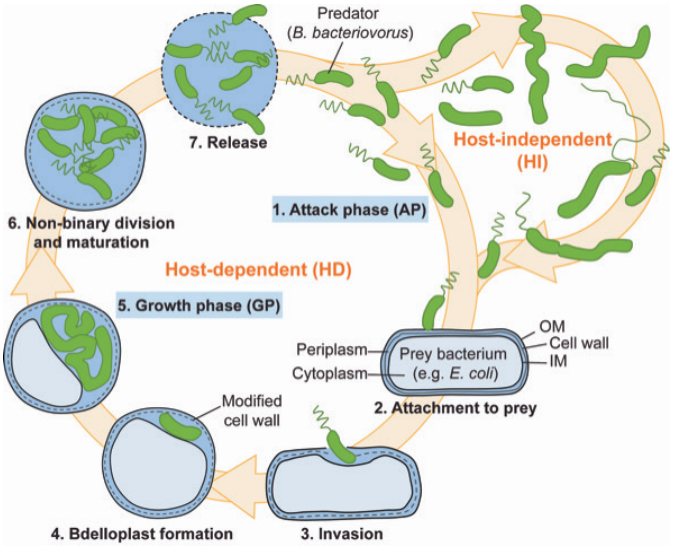
Bacterial Cell Biology

Predatory bacteria kill other bacteria while being inoffensive for eukaryotic cells, hence representing a promising strategy to fight antibiotics-resistant pathogens. We study how these microbes invade and proliferate inside their prey.

In our group, we study how bacteria organize their cellular content in space and time to achieve various and complex lifestyles. Acquiring fundamental knowledge on the cell biology of bacteria is a prerequisite for many clinical applications, including the fight against pathogenic strains, the development of solutions to the rise of antibiotic resistance, and the appropriate use of bacteria with beneficial roles in the human body.

Bacterial cells were long considered as simple bags of randomly distributed molecules, because of their relative small size and the absence of intra-cytoplasmic organelles. Over the past decades, tremendous advances in microscopy and genetic engineering – including the possibility to label proteins of interest with fluorescent molecules – have revealed instead that bacterial cells organize their intracellular content in the most exquisite manner. For instance, specific proteins or gene loci occupy non-random positions inside the cell. Moreover, molecules change place in a highly-regulated manner as the cell cycle progresses. This spatiotemporal organization of the cell is essential for bacterial life and allows bacteria to fulfill their cell cycle (i.e. from 'birth' to the generation of daughter cells) in the most efficient way.

We want to uncover how bacterial cells organize their molecular content in space and time to achieve key steps in their fascinating lifecycles, by using a combination of techniques, including bacterial genetics, molecular biology and live quantitative microscopy at high resolution. We focus on the model predatory bacterium *Bdellovibrio bacteriovorus*, which feeds upon other Gram-negative bacteria, for two main reasons: (i) *B. bacteriovorus* is a promising alternative to antibiotics, since this bacterium kills other Gram-negative bacteria (including antibiotic-resistant and biofilm-forming pathogens), while being harmless for eukaryotic (e.g. human) cells; (ii) *B. bacteriovorus* has an original cell cycle (Figure), which stands in sharp contrast with the textbook knowledge and raises a series of fundamental questions.



During its predatory cell cycle, *B. bacteriovorus* invades and remodels the envelope of a prey bacterium, digests the prey from the inside, grows as a filament, and eventually releases a variable number of daughter cells by non-binary division.

This remarkable bacterium, first discovered in the 1960's, is attracting a revived attention because of its promising 'living antibiotic' potential. However, it remains unknown how cellular processes are orchestrated to govern the non-canonical biology of *B. bacteriovorus*. Yet, discovering the molecular determinants underlying the cell cycle of *B. bacteriovorus* is a prerequisite to understand how it thrives inside its prey and to envision the use of this bacterium as a therapeutic agent.

Staff members

Postdoctoral Fellow: Terrens Saaki • **PhD Students:** Jovana Kaljevic, Ophélie Remy

Jean-Paul Coutelier

The project of our group is to analyze the relationships between infectious agents and the immune microenvironment, as well as their consequences on unrelated diseases that develop concomitantly in the infected host.

Infections & Immunity

The possibility for evoluted organisms to survive infections depends on the ability of their immune system to eliminate the pathogenic agent. Therefore, specialized responses, involving different subsets of immune cells such as cytolytic lymphocytes, T helper and B lymphocytes and macrophages, the molecules that allow those cells to communicate, and the products of those interactions, including antibodies, have been elaborated. Both quantitative and qualitative parameters of these responses will determine the outcome of infections. For instance, infection with *Plasmodium* parasites may result in asymptomatic carriage, mild or severe malaria, depending on this immune response. One of our projects is to determine in patients from Rwanda some of the causative immune events that lead to severe forms of malaria or to asymptomatic persistence of the parasite.

> ***"Modulation of the host immune microenvironment by infections enhanced susceptibility to some diseases (thrombocytopenia, septic shock), but prevented others (autoimmune encephalitis, plasmocytoma development, graft-versus-host disease)."***

Using lactate dehydrogenase-elevating virus (LDV), and other common mouse viruses, we were first to show that viruses triggered a specific type of response, now called Type 1, characterized by increased proportion of IgG2a antibodies that were more efficient to protect mice against a fatal polioencephalomyelitis. LDV-induced response includes also an early production of Type 1 interferon (IFN); transient production of pro-inflammatory cytokines, including IL-6 and IL-12; an enhancement of macrophage phagocytic activity; a transient NK cell activation, characterized by enhanced IFN-γ production and cytolytic activity; and a shift in T helper lymphocyte differentiation towards the Th1 cell subset. Some of these characteristics of the immune responses are found also after infection with intracellular parasites such as *Plasmodium*, whereas helminths, including *Schistosoma*, induce a completely different response. Infections result therefore in a bias in the immune microenvironment of the host, which often leads to alterations of responses elicited against non-infectious antigens and of concomitant diseases with an immune component.

LDV- and *Plasmodium*-modulated immune microenvironment resulted in the exacerbation of some diseases concomitant to the infection, but of unrelated cause, such as septic shock, through macrophage activation leading to enhanced TNF production. Similarly, autoantibody-mediated blood autoimmune diseases, like hemolytic anemia and thrombocytopenia, were aggravated by viral infection, because of enhanced phagocytosis of opsonized erythrocytes and platelets, respectively, by macrophages activated by virally-induced IFN-γ production. This could explain how Immune Thrombocytopenic Purpura develops in children after infection with diverse common viruses. However, modulation of the host immune microenvironment by infections could also protect against immune-mediated diseases such as graft-versus-host response, through type 1 IFN production, and experimental autoimmune encephalitis. Similarly, NK cell activation and IFN-γ production triggered by LDV infection or by ligands of immune receptors that mimick infections resulted in the inhibition of the development of some tumors such as plasmacytoma and mesothelioma.

Staff members

PhD Students: Mohamed Mandour, Jean d'Amour Mutoni, Ella Larissa Ndoricyimpaye, Pyone-Pyone Soe

Thomas Michiels

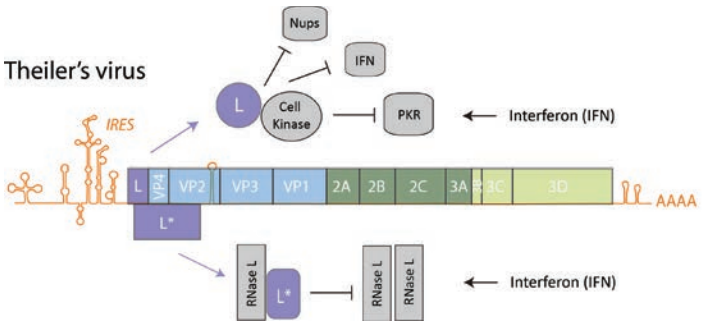
Viral Persistence & Interferon Response

Viruses developed fascinating strategies to hijack cellular signaling pathways and to counteract immune defenses of their host. By studying how viral proteins act, we aim to gain insight into viral infection mechanisms as well as into critical cellular processes.

We are all bearing at least a dozen of viruses, which persist in our body in either a latent or an active form. While some persistent viruses don't cause disease, others, like hepatitis C virus or AIDS virus, can induce serious chronic diseases.

Owing to their rapid multiplication, viruses are likely the fastest evolving organisms. They constantly evolve to adapt to their host and thereby developed many strategies to counteract immune defenses. In particular, persistent viruses were found to express proteins that target key cellular pathways to control their replication rate and to escape the immune system.

Among antiviral immune defenses, the interferon system is likely the most potent one. Interferons are a family of substances secreted by infected cells. They act on neighboring cells and make them resistant to viral infection. Dysfunctions of the interferon system were shown to lead to dramatic viral infections in humans such as herpes virus encephalitis.



Proteins L and L* produced by Theiler's virus interfere with critical cellular processes and with IFN-mediated innate immunity.

Our research focuses on two topics related to the interplay between viral infections and the immune response of the host.

We study Theiler's virus, a mouse picornavirus that has a striking ability to persist in the central nervous system. We currently analyze the function of two viral proteins, named L and L*, which are dispensable for viral replication but critical for establishment of persistent infections of the central nervous system.

- L*: We discovered that protein L* inhibited RNase L, one of the best-characterized effectors of the interferon response. We recently showed that L* competes with RNase L activators called 2-5A for RNase L binding, thus preventing RNase L activation.
- L: The L protein is a very short protein endowed with multiple functions. It notably interferes with IFN production and with activation of PKR, an IFN-inducible protein kinase that blocks mRNA translation in infected cells. Our recent data show that L also interacts with a family of cellular kinases that control critical aspects of cell biology, such as proliferation, motility or mRNA translation. We currently analyze how the recruitment of these kinases by L relates to the different L protein activities.

On the other hand, we analyze the innate immune response against viral pathogens in the particular context of the central nervous system. We focus our analysis on the recently discovered type III interferon (IFN-λ) responses, which are critically important to control viral infections of epithelial barriers such as the lung and the gut. We showed that IFN-λ potently inhibited transmission of acute norovirus strains.

Staff members

Guest Investigator: Eric Freundt • **PhD Students:** Teresa Cesaro, Melissa Drappier, Sophie Jacobs, Belén Lizcano-Perret • **Undergraduate Student:** Abdulai Bah • **Research Assistants:** Stéphane Messe, Fanny Wavreil • **Technical Assistant:** Christian Miserez

Jean-Christophe Renauld &
Laure Dumoutier

Inflammatory Disorders & Cytokines

Inflammation is a response to a variety of aggressions, like infections. It normally heals, but when excessive or ill-controlled, it can induce so-called inflammatory diseases such as Crohn's disease, asthma or psoriasis. We study the key mechanisms in these diseases.

In our laboratory, we try to improve the understanding of the role of cytokines (small signaling proteins) in inflammation. More specifically, we focus our researches on two cytokines, IL-9 and IL-22, which were both discovered by our lab and are crucial players in the inflammatory process.

IL-9 is a double-edged sword depending on the diseases. For instance, IL-9 is involved in the protection against worm infection whereas it plays a detrimental role in asthma. Asthma is a common chronic inflammatory disease of the airways, characterized by reversible airflow obstruction and bronchospasm. We showed that overexpression of IL-9 can cause bronchial hyperresponsiveness upon exposure to various allergens. In addition, we found that asthmatic patients produce increased amounts of IL-9. The potential aggravating role of IL-9 in asthma was confirmed by genetic analyses performed by others and pointing to both IL-9 and the IL-9 receptor genes as major candidate genes for human asthma. We collaborate with pharmaceutical companies to produce molecules that could block IL-9 activity, in order to improve the quality of life of asthmatic patients.

"IL-22 and its receptor are good therapeutic targets in skin inflammatory diseases."

Recently, we investigated the role of IL-22 in psoriasis lesions. Psoriasis is a chronic skin disorder that affects 2% of the world population. It is characterized by dry flakes of skin that result from the unusually rapid proliferation of keratinocytes triggered by immune cells and cytokines. By using experimental psoriasis models, we have shown that administration of an antibody blocking the IL-22 activity is able to decrease some features of the disease such as scaly lesions and redness, demonstrating the deleterious role of this cytokine in psoriasis.

In collaboration with the dermatology department of University Hospital Saint-Luc, we have also shown that IL-22 and cytokine related to IL-22 are highly expressed in various skin diseases such as atopic dermatitis and allergic contact dermatitis. These results strongly suggest that these cytokines are involved in skin inflammatory processes.

In contrast to the skin, we have shown that IL-22 plays a beneficial role in inflammatory bowel disease by protecting the gut mucosa. Crohn's disease and ulcerative colitis are the most common types of inflammatory bowel disease. They affect any part of the digestive tract (Crohn's) or only the colon and rectum (colitis). Crohn's disease is caused by chronic inflammation, in which the immune system of the body attacks the gastrointestinal tract. Currently, there is no cure for this disease and treatments are restricted to controlling symptoms.

In the future, we will investigate the role of other factors that are related to IL-22 and are also up-regulated in some of our experimental models of psoriasis or of colitis. These studies will help to improve the understanding of the inflammatory responses observed in these two diseases and the treatments that are administered to patients.

Staff members
Emeritus: Jacques Van Snick • **Postdoctoral Fellow:** Perrine Cochez • **PhD Students:** Mathilde Choteau, Elisabeth Losdyck, Camille Michiels • **Undergraduate Student:** Léna Puigdevall • **Research Assistants:** Pamela Cheou, Emilie Hendrickx • **Administrative Support:** Geneviève Schoonheydt

Metabolism and Hormones

Our metabolism assures that our cells always dispose of the energy they need, despite a fluctuating demand. We study the amazing networks of metabolic pathways, as well as the enzymes that are involved in it and the genetic mutations that cause a pathway to fail. We also investigate a remarkable example of a dynamic tissue: the uterine mucosa that is substantially destructed and again regenerated during every menstruation.

Emile Van Schaftingen &
Maria Veiga-da-Cunha

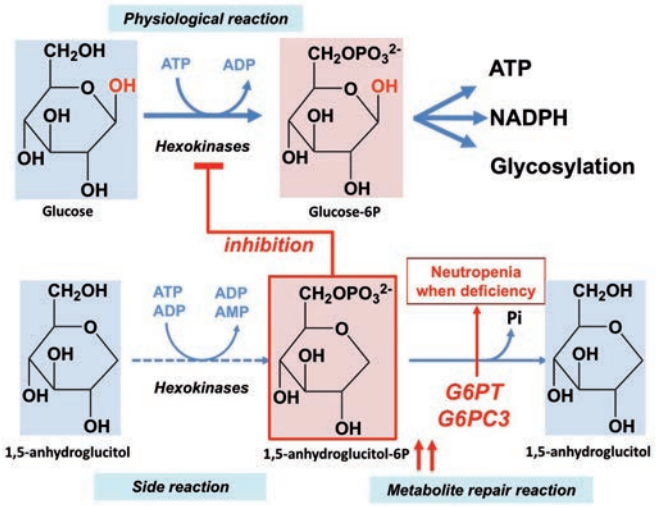
Our work focuses on the discovery of metabolite repair enzymes. Unlike what is usually assumed, enzymes of intermediary metabolism are not absolutely specific, they make significant amounts of side products. Metabolite repair enzymes are indispensable to eliminate these side-products.

Metabolite Repair

Work performed by our group in collaboration with Guido Bommer leads us to revise our ideas about the organization of intermediary metabolism. Intermediary metabolism is the sum of all enzyme-catalyzed reactions that allow cells to produce their own indispensable constituents. Biochemistry textbooks say that these enzyme are extremely specific and that this is important to avoid the formation of useless or even toxic side-products: only useful, non-toxic products are formed.

What the study of L-2-hydroxyglutaric aciduria told us is that, quite to the contrary, enzymes of intermediary metabolism are not absolutely specific, they make significant amounts of side products, but our cells have many, previously unknown enzymes that serve to eliminate these side-products and are therefore named metabolite repair enzymes. Thus, L-2-hydroxyglutarate is made by a side activity of L-malate dehydrogenase; it is normally destroyed by L-2-hydroxyglutarate dehydrogenase, a mitochondrial enzyme, but it accumulates in tissues and causes major neurological problems if L-2-hydroxyglutarate dehydrogenase is deficient due to mutations in its gene.

Our work during the last ten years has been focused on the identification of additional metabolite repair enzymes. One of them, a highly conserved protein called Nit1, degrades a damaged form of glutathione, deaminated glutathione, which results from side activities of transaminases. Mice deficient in this enzyme eliminate deaminated glutathione in urine and therefore lose a substantial amount of cysteine every day.



Another example is a phosphatase destroying erythronate-4-P and L-2-P-lactate, two side-products of two glycolytic enzymes. Erythronate-4-P is a strong inhibitor of 6-P-gluconate dehydrogenase, while L-2-P-lactate inhibits the synthesis of the glycolytic regulator fructose-2,6-bisphosphate. Absence of the phosphatase causes dramatic perturbations of sugar metabolism and is lethal in mice.

The metabolite repair concept led us recently to understand the cause of the congenital neutropenia found in patients deficient in G6PC3, a phosphatase present in the endoplasmic reticulum, or deficient in G6PT (SLC37A4), the glucose-6-phosphate transporter of the endoplasmic reticulum. These two proteins collaborate to destroy 1,5-anhydroglucitol-6-P, an abnormal metabolite made in vivo by side activities of glucose-phosphorylating enzymes. Lack of dephosphorylation of 1,5-anhydroglucitol-6-P leads to its intracellular accumulation and, as a result, to strong inhibition of glucose phosphorylation. This is toxic to neutrophils and explains the patients' neutropenia.

Staff members

Senior Investigator: Elsa Wiame • **Postdoctoral Fellows:** Takfarinas Kentache, Alexandre Marbaix • **PhD Student:** Joseph Dewulf • **Research Assistant:** Nathalie Chevalier • **Technical Assistant:** Karim Acherki • **Administrative Support:** Pauline Leverrier, Marie-Victoire Uwimana

Guido Bommer

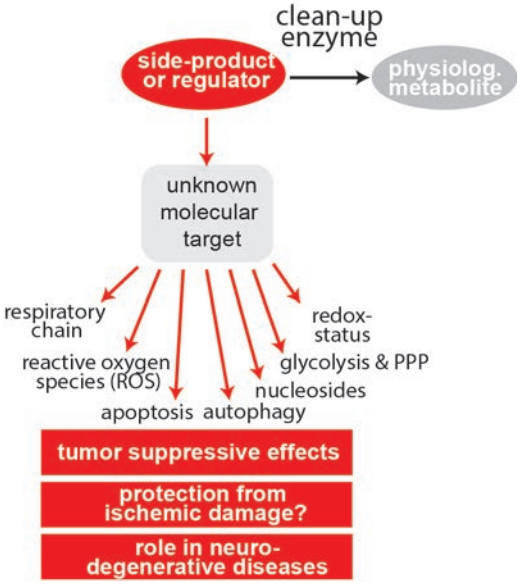
Cancer Metabolism

Cancer cells need to adjust their metabolism to fulfill their continuous need for building blocks and energy. We try to identify vulnerabilities in known or newly-discovered metabolic pathways, which might be targeted by future therapies.

The local 'success' of a cancer cell is measured by its ability to proliferate and survive better with the available nutrients than its neighboring cancerous cells. Like any other cell, a cancer cell needs to maintain cellular integrity and fulfill baseline housekeeping functions. All cell types need to synthesize ATP by breaking down nutrients in pathways such as glycolysis, citric acid cycle and mitochondrial oxidative phosphorylation. In addition, proliferating cells in general and cancer cells in particular need to generate biomass, composed of amino acids, nucleotides and lipids. Synthesis of these components starts with precursors that are intermediary products in the same pathways that are used to synthesize cellular ATP. Several adjustments of the flux through these pathways are needed to reconcile cellular demand for biosynthetic building blocks and for ATP synthesis.

We are investigating the role of a series of enzymes, for which we have reason to believe that they might be involved in the synthesis of regulatory molecules. In these studies, we use a combination of state-of-the-art metabolomics (GC-MS and LC-MS) and genetic manipulation of cell lines to understand the cellular effects of novel regulatory molecules. Classical enzymological studies (in collaboration with the laboratory of Emile Van Schaftingen) on purified proteins are then used to understand the molecular basis of the observed effects.

Eventually, we hope that our work will reveal novel therapeutic targets in cancer. Currently, we are particularly interested in several phosphatases that might serve to eliminate metabolic side-products or metabolic regulators.



Degradation of metabolic side-products and regulators can lead to a variety of cellular effects that might play a role in cancer and other diseases.

While we strive to understand processes involved in cancer biology, we remain very much open to surprising discoveries. As such, we have recently discovered a novel post-translational modification of α-dystroglycan by ribitolphosphorylation (Figure). This modification does not play a role in cancer, but is known to be defective in a group of neuromuscular diseases. Hence, part of our laboratory is currently trying to reveal the remaining molecular machinery to generate this modification.

Staff members
Senior Investigator: Isabelle Gerin • **Postdoctoral Fellow:** Marina Bury, Sven Potelle • **PhD Students:** Mathias Halbout, Isaac Heremans, Stéphanie Paquay, Benoît Ury • **Research Assistant:** Julie Graff

Mark Rider

We study mechanisms that control cell function via protein phosphorylation, particularly in relation to diseases involving metabolic disorders, such as type 2 diabetes.

Protein Phosphorylation

Metformin is the most prescribed drug used for the treatment of type 2 diabetes and its effects can partly be explained by activation of an enzyme, a protein kinase called AMP-activated protein kinase (AMPK), which is the focus of our research.

AMPK acts as a sensor of cellular energy status activated by an increase in the AMP/ATP ratio as occurs during muscle contraction/exercise. The role of AMPK in the cell is to maintain ATP by stimulating ATP-producing pathways and at the same time inhibiting energy-consuming biosynthetic pathways. AMPK has emerged as an attractive therapeutic drug target for treating metabolic disorders. In collaboration with the pharmaceutical company AstraZeneca (Mölndal, Sweden), we investigated whether inhibition of AMP metabolizing enzymes could be a means of achieving or potentiating AMPK activation. Genetic deletion of cytosolic 5'-nucleotidase-1A (NT5C1A) or 5'-nucleotidase-II (NT5C2) did not enhance contraction-induced increases in AMP/ATP ratio, AMPK activation or glucose transport in incubated skeletal muscles. Therefore, these enzymes would not be viable drug targets for the treatment of type 2 diabetes.

"Drug targeting soluble 5'-nucleotidase enzymes in skeletal muscle would not be a viable strategy for the treatment of type 2 diabetes."

We took advantage of a potent small-molecule direct AMPK activator called compound '991' to explore AMPK function. Treatment of skeletal muscles with compound 991 activated AMPK and elicited metabolic effects in muscle appropriate for treating type 2 diabetes by stimulating glucose uptake. Using compound 991, we provided a novel mechanism by which AMPK antagonizes hepatic glucagon signaling, with implications for lowering liver glucose production in diabetes. In addition, AMPK activation could play an anti-cancer role by inhibiting protein synthesis/cell proliferation via increased eukaryotic elongation factor-2 phosphorylation as well as by inhibiting mammalian target of rapamycin complex-1 signalling. In mitogen-stimulated thymocytes, we showed that increased fructose-2,6-bisphosphate levels could be involved in coupling glycolysis to increased protein synthesis required for cell proliferation.

In addition to our work on AMPK, we run the protein mass spectrometry (MS) facility on the Brussels campus of UCLouvain. We developed a MS-based phosphoproteomics strategy and applied the methodology to validate the identification of proteins phosphorylated in brown adipose tissue in the switch from glucose to lipid metabolism during ground squirrel hibernation. The use of MS for our research and collaborations has led to well over 100 publications. The acquisition by the de Duve Institute of a High Resolution/Accurate Mass mass spectrometer of the latest generation will allow us to perform quantitative proteomics and increase our capabilities to study other protein modifications.

Staff members

Emeritus: Louis Hue • **Senior Investigator:** Didier Vertommen (Platform Manager) • **Postdoctoral Fellows:** Manuel Johanns, Sébastien Pyr dit Ruys • **PhD Students:** Sheng-Ju Chuang, Samanta Kviklyte, Nathalie Kyalu Ngoie Zola • **Research Assistants:** Gaëtan Herinckx, Nusrat Hussain, Roxane Jacobs • **Technical Assistant:** Freddy Abrassart • **Administrative Support:** Aimée-Lys Rusesabagina

Etienne Marbaix &
Patrick Henriet

Endometrium Physiopathology

Our group identifies mechanisms controlling physiological degradation and regeneration of the human endometrium at menstruation, with the aim to understand how their dysregulation results in dysfunctional uterine bleeding and endometriosis.

Throughout the reproductive life, the human endometrium – the uterine mucosa – undergoes cyclic remodeling. Changes in endometrial structure condition fertility and must be perfectly orchestrated by sex hormones, namely estrogens and progesterone. Menstruation occurs at the end of every unchallenged menstrual cycle and results from an intense but locally restrained degradation of the endometrium when the circulating concentration of the sex hormones drops. Treatment of two endometrial pathologies, dysfunctional uterine bleeding (DUB) and endometriosis, should benefit from a better understanding of the molecular events surrounding menstruation. On the one hand, DUB results from local menstrual-like breakdown of the endometrium, suggesting inadequate response to sex hormones. On the other hand, endometriosis, a pathology characterized by the presence of endometrial tissue outside the uterus, is believed to often originate from retrograde menstruation, i.e. migration of menstrual endometrial fragments through the fallopian tubes and invasion of the peritoneal cavity, peritoneum and ovaries.

"Treatment of two endometrial pathologies, dysfunctional uterine bleeding (DUB) and endometriosis, should benefit from a better understanding of the molecular events surrounding menstruation."

Twenty-five years ago, our laboratory was the first to show that endometrial tissue breakdown at menstruation is performed by a group of proteolytic enzymes, the matrix metalloproteinases (MMPs). Our subsequent work aimed at characterizing the various molecular mechanisms that ensure the focal nature of progressive tissue lysis by locally tuning the global hormonal control. Our research is focused on three levels of control of MMP activity. In a first axis, we investigate how the different potential sex hormone receptors combine their specific effects to induce or repress MMP expression. In a second axis, we dissect the complex network of local regulators acting between hormone receptors and MMP genes. Our work has highlighted the role of cytokines and growth factors, such as interleukin-1α, TGF-βs and Lefty2, in the control of MMP expression. In a third axis, we explore mechanisms able to discard obsolete MMP activity. We have shown that members of the low density lipoprotein receptor family, LRP-1 and LRP-2, act as endocytic receptors able to bind MMPs complexed with their TIMP inhibitors, in order to induce their lysosomal degradation.

Following up on puzzling data from our previous whole genome transcriptomic analysis of the menstrual endometrium, we also investigate the molecular mechanisms coupling tissue lysis and subsequent scarless regeneration. Indeed, our results highlighted that genes required for early endometrial repair, in particular extracellular matrix components, are expressed concomitantly with MMPs during menstruation.

Staff members
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Guido Bommer

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Technology Platforms

Flow Cytometry and Cell Sorting

Flow cytometry technology allows simultaneous multiparametric analysis of thousands of cells per second, enabling trained users to rapidly analyze complex cell populations based on phenotypic and functional features. High-speed assisted cell sorting services provide researchers with physical separation of identified cell populations, for any downstream characterizations. The platform is managed by Prof. Pierre Coulie and is run by Dr. Nicolas Dauguet.
[W] http://www.deduveinstitute.be/flow-cytometry-and-cell-sorting

Genomics

The genomics platform provides the scientific community with the latest technologies, such as Next Generation Sequencing (Massive Parallel Sequencing). Theses techniques facilitate and speed up data acquisition, which is beneficial for many different fields, such as biology, medicine, agronomy, ... Their use in clinical diagnosis also broadens the spectrum of molecular diagnosis and opens new ways for personalized medicine. The platform is managed by Prof. Miikka Vikkula and is run by Drs. Pascal Brouillard and Raphaël Helaers.
[W] http://www.deduveinstitute.be/genomics-platform

Imaging

The imaging platform trains and provides the scientific community with various confocal and electronic microscopes and a wide range of sophisticated methods of vital confocal microscopy and immunolabeling. It is also a source of advices, collaborations and a «school of morphology» for users, providing them with the necessary expertise at all stages of the experiment, from sample preparation to analysis and interpretation of data. The platform is managed by Prof. Donatienne Tyteca and is run by Dr. Patrick Van Der Smissen.
[W] http://www.deduveinstitute.be/pict-platform-imaging-cells-and-tissues

Laboratory Animals

The platform produces mice under 'SPF' health status for academic research use, with no commercial purpose. It hosts 80 different mouse strains, both non-genetically and genetically modified, available under a very high sanitary status monitored via a sentinel program, for research teams of the University of Louvain and collaborators. The platform is managed by Prof. Sophie Lucas and is run by Dr. Pedro Gomez, with technical help from Lionel Crikeler, Julien Gossiaux, Laurent Hermanns and Quentin Lechien.
[W] http://www.deduveinstitute.be/laboratory-animals

Mass Spectrometry

The platform provides proteomics services principally through gel-free approaches coupled to mass spectrometry. It specializes in the identification and quantification of proteins from complex samples, and can also provide data on the location of post-translational modifications, even in complex samples. The platform is managed by Profs. Jean-François Collet and Mark Rider and is run by Dr. Didier Vertommen, together with Prof. Pierre Morsomme and Dr. Hervé Degand at the Louvain Institute of Biomolecular Science and Technology.
[W] https://www.deduveinstitute.be/mass-spectrometry

Transgenesis

The transgenesis platform offers transgene technology tools to research teams of the University of Louvain and other Belgian universities at the lowest possible cost. It also enables the sharing of expertise in designing and creating transgenic mouse lines and offers training opportunities to PhD students and post-doctoral researchers. The platform is managed by Profs. Patrick Jacquemin and Frédéric Lemaigre, and is run by Dr. Younes Achouri.
[W] http://www.deduveinstitute.be/transgenesis

Prizes, Awards and Honors

Guido BOMMER • Lagast Prize 2017
Awarded every year to a UCLouvain scientist working in basic or clinical research on genetic muscle diseases.

Anabelle DECOTTIGNIES • Officer of the Walloon Merit, category Sciences, 2017
Distinction conferred every year by the Walloon government on a researcher 'whose merit does honor to Wallonia to an exceptional extent and contributes to its influence'.

Anabelle DECOTTIGNIES • Allard-Janssen Prize 2017
Awarded every three years to a UCLouvain scientist working in basic or applied research on cancer.

Ophélie DELCORTE • Mahieu Prize 2017-2018
Awarded every year to a UCLouvain undergraduate student in Biomedical Sciences for the best master thesis.

Elsa KHOURY • Salus Sanguinis Foundation, Fellowship 2018
Granted every year to a UCLouvain PhD student in Health Sciences working on blood diseases.

Wen-Hui LIEN • Distinguished Alumni Award, College of Medicine, National Cheng-Kung University, Taiwan

Sophie LUCAS • Associate Member of the Académie royale de Médecine de Belgique

Christophe PIERREUX • d'Alvarenga, de Piauhy Prize 2017
Awarded every year to a Belgian researcher by the Académie royale de Médecine for the best thesis on a medical topic.

Miikka VIKKULA • Honorary Foreign Member of the Argentinian Medical Association

Miikka VIKKULA • Generet Prize 2018
Awarded for the first time, and every year for the next 20 years, by the King Baudouin Foundation to a Belgian researcher working on rare diseases.

PhD Theses - August 2017 to December 2018

Melissa DRAPPIER • *Antagonism of the antiviral OAS/RNase L pathway by Theiler's virus L* protein: molecular mechanisms and species-specificity* • Promoter: T. Michiels

Maxime BEYAERT • *ATR signalling after DNA damage: from the discovery of a new target to the reevaluation of its function in primary chronic lymphocytic leukaemia cells* • Promoter: F. Bontemps

René BIGIRIMANA • *Antigen persistence alone is sufficient to disarm human specific T lymphocytes* • Promoter: P. van der Bruggen

Julie SOBLET • *Activating TIE2 mutations with distinct features cause a spectrum of venous malformations* • Promoter: M. Vikkula

Ilyas CHACHOUA • *Novel mechanisms for STAT5 activation in myeloid neoplasms and secondary acute myeloid leukemia* • Promoter: S. Constantinescu

Francesca BALDIN • *Metabolite repair in glycolysis: dephosphorylation of three 'abnormal' metabolites made by side-activities of glycolytic enzymes* • Promoter: E. Van Schaftingen

Catherine LEONARD • *Contribution of plasma membrane lipid domains to red blood cell (re)shaping* • Promoter: M.-P. Mingeot

Marc HENNEQUART • *Deciphering the pathways that lead to constitutive IDO1 expression in human cancer cells* • Promoter: E. De Plaen

Lucie EVENEPOEL • *Genetic, histologic, and molecular characterisation of pheochromocytomas and paragangliomas: an integrated approach* • Promoter: A. Persu

Aurélie DIMAN • *New molecular insights into human telomere transcription and the ALTernative telomere maintenance mechanism* • Promoter: A. Decottignies

Camille GOEMANS • *Unraveling the functions of unusual thioredoxins: the stories of Cnox and CcTrx1* • Promoter: J.-F. Collet

Michael PEETERS • *The Leader protein of Cardioviruses hijacks cellular protein kinases via an evolutionary convergent mechanism to trigger host protein shut-off and to escape innate immune responses* • Promoter: T. Michiels

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Emeline BOLLAERT • *Regulation of HBP1 via the AKT/FOXO pathway and impact on cancer cell proliferation* • Promoter: J.-B. Demoulin

Elsa GHURBURRUN • *Mechanisms of pancreatic cancer initiation: what is the role of the ductal cells?* • Promoter: P. Jacquemin

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Stéphanie LIENART • *Blocking immunosuppression by human Tregs with antibodies against GARP/latent TGF-β1 complexes* • Promoter: S. Lucas

Marie-Sophie DHEUR • *Unexpected expression profile of MAGEA9 gene in diffuse large B-cell lymphoma and in normal germinal center cells* • Promoter: P. Coulie

Sophie JACOBS • *Crossing frontiers: impact of interferon-lambda (IFN-λ) on virus transmission* • Promoter: T. Michiels

Charlotte SIX • *Gasdermin D-independent IL-1β secretion by living human monocytic cells* • Promoter: P. Coulie

Elodie FASTRE • *Targeted next generation sequencing unravels loss-of-function mutations in two lymphangiogenic factors in primary lymphedema patients* • Promoter: M. Vikkula

Nahla A. HUSSEIN • *Molecular and functional dissection of IgaA, the negative regulator of the E. coli Rcs system* • Promoter: J.-F. Collet

Lectures & Scientific Events - August 2017 to December 2018

3rd de Duve Memorial Lecture

David SABATINI • *Whitehead Institute for Biomedical Research & MIT, Boston, MA, USA*
mTOR and lysosomes in growth control

22nd Heremans Memorial Lecture

Stefan H.E. KAUFMANN • *Max Planck Institute for Infection Biology, Berlin, Germany*
How to deal with the most successful pathogen on earth: Rational design of immunologic intervention strategies

Heremans lectures and de Duve lectures are given every other year by a prominent international scientist (for podcasts and a complete list of speakers: http://www.deduveinstitute.be/seminars).

Dietmar ZEHN • *School of Life Sciences Weihenstephan, Technical University of Munich, Germany*
Differentiation and maintenance of 'exhausted' T cell populations in chronic infections

Man-Wah TAN • *Genentech, San Francisco, USA*
Discovering and engineering antibodies to treat viral and bacterial infections

Marc KOCKX • *HistoGeneX, Antwerp, Belgium*
The tumor micro-environment as a predictive biomarker for immunotherapy

Maike SANDER • *Institute of Engineering in Medicine, University of California San Diego, La Jolla, CA, USA*
Deconstructing pancreatic development and disease with human pluripotent stem cells

Mojgan RASTEGAR • *Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada*
Epigenetic mechanisms and their role in neurodevelopmental disorders

Malini RAGHAVAN • *University of Michigan Medical School, Ann Arbor, MI, USA*
Protein folding, antigen presentation and immunity

Matthias VERSELE • *Centre for Drug Design & Discovery, Leuven, Belgium*
Centre for Drug Design and Discovery (CD3): translating innovative academic science into drug candidates

Claudia MASINI d'AVILA-LEVY • *Oswaldo Cruz Foundation, Rio de Janeiro, Brazil*
Operational taxonomic units and binominal nomenclature – How would Linneus deal with protist biodiversity?

Mika WATANABE • *Hokkaido University Graduate School of Medicine, Sapporo, Japan*
The role of basement membrane proteins in regulating epidermal homeostasis

Oreste ACUTO • *Sir William Dunn School of Pathology, University of Oxford, UK*
How T cell activation begins

Tom LENAERTS • *Interuniversity Institute of Bioinformatics in Brussels, Université Libre de Bruxelles, Belgium*
Understanding digenic diseases: from data to first predictor

Ron WEVERS • *Radboud University Medical Centre, Nijmegen, The Netherlands*
Unraveling the metabolome – An untargeted metabolomics approach

Frédéric SORGELOOS • *Addenbrooke's Hospital, University of Cambridge, UK*
Combined transcriptomics and proteomics identifies unknown genes involved in chicken antiviral innate immunity

Alan B. FREY • *Perlmutter Cancer Center & New York University School of Medicine, New York, NY, USA*
Protocadherin-18: a differentiation marker, an activation antigen, and an inhibitory signaling receptor in tumor- infiltrating T cells

Robert KRALOVICS • *Research Center for Molecular Medicine & Medical University of Vienna, Austria*
Genetics of myeloproliferative neoplasms: impact on clinical management and therapy

Silvia BOTTINI • *Centre Méditerranéen de Médecine Moléculaire, University of Nice Sophia-Antipolis, France*
Breaking the combinatorial code of RNA regulators to decipher the biological complexity in gene expression regulation and the impact on cellular pathways in physio-pathological contexts

Jan TAVERNIER • *Cancer Research Institute Ghent, Ghent University, Belgium*
AcTakines: a novel class of immunotherapeutics – Old monkeys, new tricks

Jürgen CLAESEN • *Interuniversity Institute for Biostatistics & Statistical Bioinformatics, Hasselt University, Belgium*
A hierarchical model for paired and clustered RNAseq experiments

Alexander G. FLETCHER • *School of Mathematics & Statistics, University of Sheffield, UK*
Quantitative approaches to studying epithelial morphogenesis

Catharina OLSEN • *Interuniversity Institute of Bioinformatics in Brussels , Université Libre de Bruxelles, Belgium*
Gene regulatory networks in complex diseases

Laurent GATTO • *Cambridge Centre for Proteomics, University of Cambridge, UK*
Mapping the sub-cellular proteome

Jurgi CAMBLONG • *Sophia Genetics, Saint-Sulpice, Switzerland*
Enabling data-driven medicine

Ursula JAKOB • *University of Michigan Medical School, Ann Arbor, MI, USA*
Role of polyphosphates in amyloidogenic processes

Ian HENDERSON • *Institute for Microbiology & Infection, College of Medical & Dental Sciences, University of Birmingham, UK*
Insights into microbial physiology using transposon-directed insertion site sequencing

Inaugural Plenary Lecture - Princess Lilian Foundation Visiting Professorship 2017-2018
Valérie CORMIER-DAIRE • *Imagine Institute, Necker Enfants Malades Hospital, Paris, France*
Skeletal dysplasias and heart development: from causative gene mutation to cellular intimate changes

Sandy S. CHANG • *Yale University School of Medicine, New Haven, CT, USA*
How telomeres repress DNA damage and repair responses at chromosome ends

Samira BENHAMOUCHE • *Centre Hépato-Biliaire, Paul Brousse Hospital, University Paris South, Villejuif, France*
AAA+ ATPase Reptin, a novel player regulating mTOR signalling and glucido-lipidic metabolism in liver physiology and pathology

M. Reza J. FOROOSHANI • *Faculty of Medicine, Southampton General Hospital, University of Southampton, UK*
Gene essentiality: a paradigm shift in disease gene discovery!

Mark TRAVIS • *Manchester Academic Health Science Centre, University of Manchester, UK*
Regulation of mucosal immune responses by integrins and TGF-β

Suneel APTE • *Cleveland Clinic Lerner Research Institute, Cleveland, OH, USA*
Metalloprotease regulation of cell signaling in the context of birth defects

Neil BULLEID • *Institute of Molecular, Cell & Systems Biology, University of Glasgow, UK*
Protein folding in the endoplasmic reticulum

Sarah WETTSTADT • *MRC Centre for Molecular Microbiology & Infection, Imperial College London, UK*
Manipulating the Type VI secretion system tip in *P. aeruginosa* to achieve effector delivery

Nadim MAJDALANI • *Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA*
Signaling pathways in the Rcs phosphorelay in *E. coli*

Oliver HANTSCHEL • *Swiss Institute for Experimental Cancer Research, École polytechnique fédérale de Lausanne, Switzerland*
Targeting protein-protein interactions in cytoplasmic oncoproteins with monobody inhibitors

Terrens SAAKI • *Swammerdam Institute for Life Sciences, University of Amsterdam, The Netherlands*
Construction of a minimal divisome reveals robustness of cell division

Franck DEQUIEDT • *GIGA-Molecular Biology of Diseases, University of Liège, Belgium*
Beyond transcription: roles of transcription factors in downstream gene expression processes

Peter STÄHELI • *Medical Center University of Freiburg, Germany*
Boosting mucosal immunity with interferon-λ

Paul MICHELS • *School of Biological Sciences, University of Edinburgh, UK*
Structure-guided development of noncompetitive inhibitors of *Trypanosoma brucei* phosphofructokinase capable of curing infections in mice upon oral administation

Arndt BORKHARDT • *University Children's Hospital, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany*
Family sequencing in pediatric oncology – Experiences from Children's Cancer Center Düsseldorf

Cecilia LÄSSER • *Krefting Research Centre, Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Sweden*
Extracellular vesicles – Message in a bottle

Thomas ARNESEN • *Haukeland University Hospital & University of Bergen, Norway*
Protein N-terminal acetylation: machinery and biological impact

Sander GOVERS • *Microbial Sciences Institute, Yale University, West Haven, CT, USA*
Maintenance of the nucleocytoplasmic ratio is linked to ribosome mobility and spatial organization of translation in bacteria

Paul PIEHOWSKI • *Pacific Northwest National Laboratory, Richland, WA, USA*
NanoPOTS: adding single cell sensitivity and high spatial resolution to the proteomics toolbox

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Princess Lilian Foundation Visiting Professorship 2017-2018: awarded to Prof. Valérie CORMIER-DAIRE from Necker Enfants Malades Hospital (Paris), and co-hosted by M. Vikkula
Program: inaugural lecture, international mini-symposium, meetings with researchers from Belgian universities working in the field of genetics

> *The Princess Lilian Foundation has established a high profile visiting professorship awarded every year and aimed at fostering interaction between researchers in Belgium and established experts.*

PhD Day

> *All graduate students of the de Duve Institute present their work either as a talk or as a poster.*

de Duve Institute

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The appeal for sponsoring postdoctoral fellowships was also widely followed. Since August 2017, the Institute has been able to allocate the following fellowships, entirely supported by our donors:

the 'Haas-Teichen' fellowship was attributed to Angela Queisser (Germany),

the 'Maurange' fellowship to Sven Potelle (France),

and an ICP fellowship has been awarded to Mohamad Assi (Lebanon), followed by Annika Bruger (Germany).

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Luc Bertrand
President of the Development and Expansion Council

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