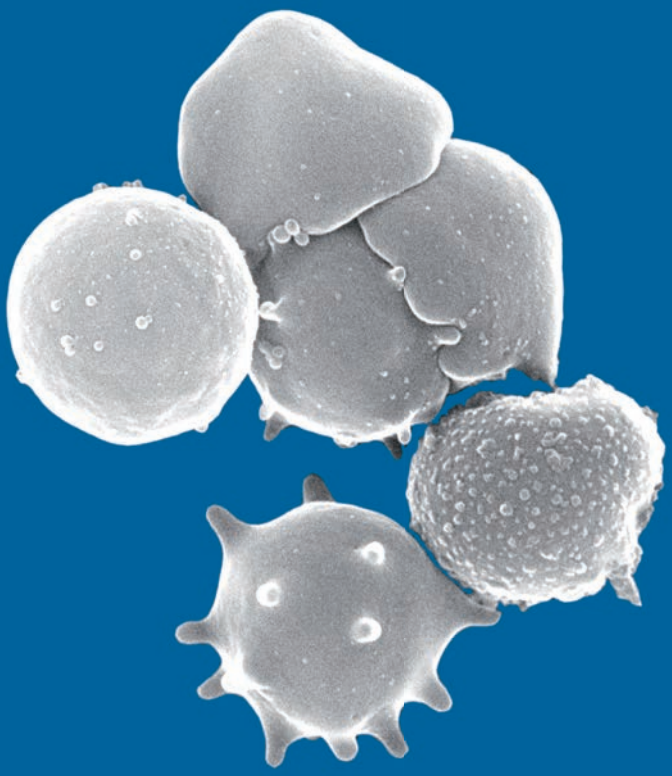
de Duve INSTITUTE

SCIENTIFIC REPORT 2019

de Duve Institute
&
Ludwig Cancer Research - Brussels

UCLouvain



de Duve INSTITUTE

Avenue Hippocrate 75
B-1200 Brussels, BELGIUM

[T] + 32-2-764 75 50
[F] + 32-2-764 75 73
[E] deduve_institute@uclouvain.be
[W] www.deduveinstitute.be

Directors	Prof. Benoît Van den Eynde Prof. Jean-François Collet Prof. Sophie Lucas Prof. Miikka Vikkula
Finance Manager	Serge Thibaut
External Relations	Isabelle de Duve
Photographs	Jacky Delorme & Hugues Depasse
Research Highlights	Francisca Voermans

For a copy of this report, please contact: nathalie.krack@uclouvain.be

Picture: Scanning electron microscopy picture of red blood cells (imaging platform, Tyteca's group)

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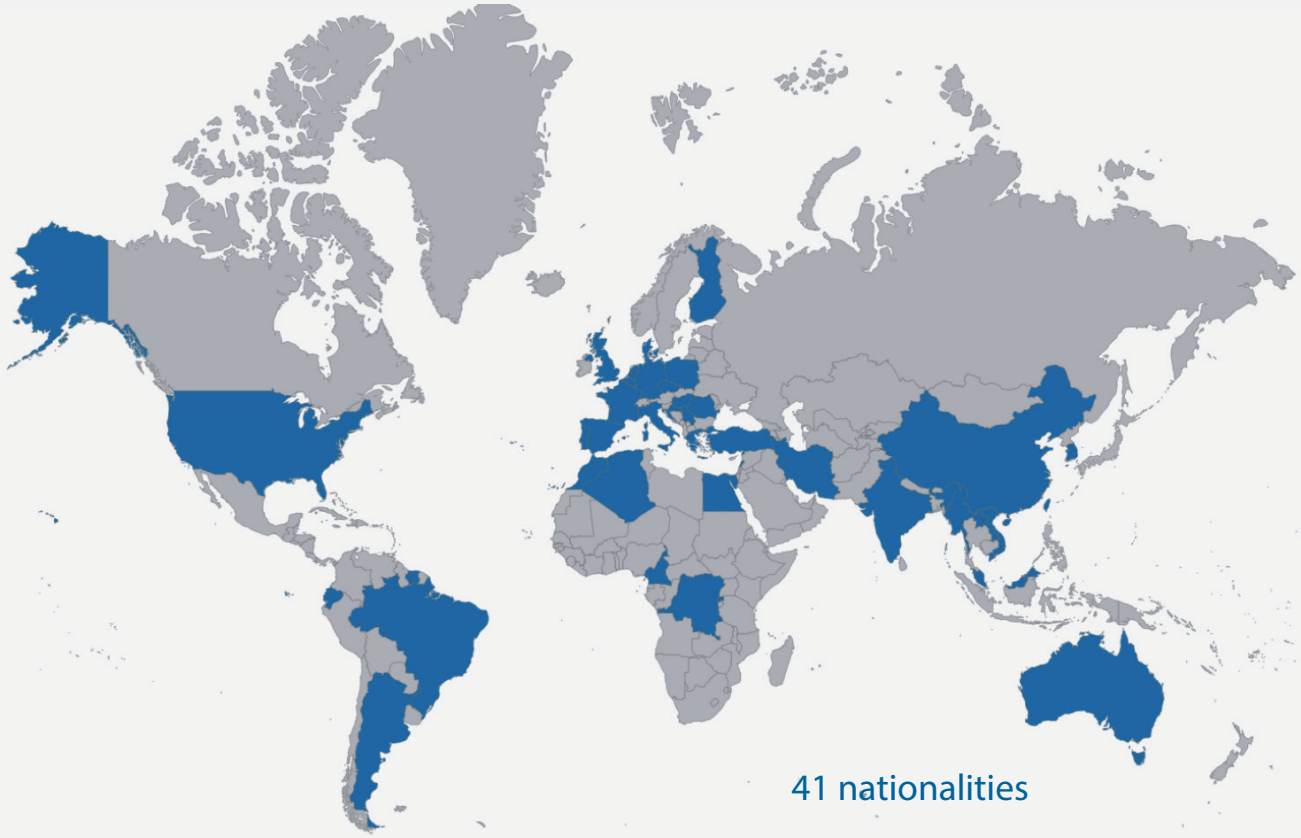


41 nationalities

297 members

45% 55%

94 PhD students

37 postdoctoral students

95 publications

36 international lectures

6 technology platforms

8000 m^2

From the Director

The year 2019 was marked with important changes in the management of our Institute. The Directorate was renewed following the retirement of Professor Emile Van Schaftingen after 15 years at the head of the Directorate. In its meeting held in May 2019, the Board of Directors of the de Duve Institute appointed a new Directorate, composed of Professors Jean-François Collet, Benoît Van den Eynde and Miikka Vikkula. As a new addition, Jean-François Collet will bring fresh blood in the management team, while Van den Eynde and Vikkula will ensure strategic continuity as they have already been part of the Directorate during the last 15 years. The new Directorate is presided by Benoît Van den Eynde. This trio is a balanced representation of the different research areas explored at the Institute, with expertise in bacteriology and biochemistry (Collet), in immunology and cancer (Van den Eynde) and in genetics of human diseases (Vikkula). The mission of the Directorate is to organize, coordinate and support scientific activities and collaborations within the Institute in a manner that will best promote excellence and achieve the goal expressed in our motto: 'Deeper knowledge for better cures'.

De Duve Institute has close links with university UCLouvain. University matters pertaining to our activities are managed by DDUV, a university structure (also called an 'Institute') that has replaced the previous departments. DDUV is headed by a President: the mandate of Professor Frédéric Lemaigre, who held this position in the last six years, came to an end in September 2019. He was replaced by Professor Sophie Lucas. To ensure optimal efficiency, these two structures work in close collaboration, and all management meetings are held jointly with the Directorate and the DDUV President.

We express our deepest gratitude to Emile Van Schaftingen and Frédéric Lemaigre for their dedicated involvement in the management of the Institute(s) in recent years.

The year 2019 was filled with a number of important discoveries, ranging from a new mechanism of telomere maintenance, which may represent a therapeutic target in pediatric cancers (see page 27), to the understanding of the pathogenesis of an orphan neutrophilic disease, which led to the identification of a drug acting on this pathogenic process to treat the disease (see pages 6-7 and page 38). These are only two examples, and there are many other biomedical discoveries that you will find detailed in this report.

Our research activities are supported in large part by research grants, but also, increasingly, through donations from our sponsors coming in largely on the occasion of our annual gala dinner. In terms of grants, 2019 was a successful year as our scientists performed remarkably well in the last call for WELBIO grants, which are the most prestigious public research grants available in the French-speaking part of Belgium. In this highly competitive call, our Institute obtained five new grants and three renewals.

One of the challenges of the Institute is the renewal of the research teams, as a number of professors will retire in the coming years. To this end, a young promising scientist named Nick van Gastel was invited to settle in the Institute and create a new group focusing on leukemia research. Of Belgian origin, Nick was trained at KULeuven and at Harvard University. He will join us in the early summer 2020.

Benoît Van den Eynde

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

Uncovering the secrets of metabolism

Maria Veiga-da-Cunha elucidated, in collaboration with Emile Van Schaftingen, how a deficiency of two proteins leads to neutropenia. It has led to a new treatment for patients. The motto of the Institute "Deeper knowledge for better cures" could not be illustrated better.

Lisbon-born Maria Veiga-da-Cunha is a longtime collaborator of Emile Van Schaftingen. Their partnership started in 1991 when she joined his team as a postdoctoral researcher. They form a perfect team: she is the experimental wizard, he has a tremendous biochemical knowledge. Together, they have elucidated various metabolic puzzles and the last one is a beautiful story that explains the origin of the very handicapping neutropenia in two rare metabolic diseases. In the more common disease, patients are deficient in a transporter called G6PT, which allows specific sugar-phosphates to get in a compartment in the cell called the endoplasmic reticulum. In the rarer one, patients are deficient in the phosphatase G6PC3, which is inside the endoplasmic reticulum. Patients with these diseases have very low levels of the most abundant white blood cells (the neutrophils) in the bloodstream, a condition called neutropenia. Since the function of neutrophils is to kill invading bacteria, they suffer from frequent infections: they develop chronic inflammation that resembles Crohn's disease, have aphthous lesions in the mouth and various mucosal and skin abscesses.

Twenty years ago, the team had identified the genetic cause of the deficiency in G6PT. The missing link required to understand the neutropenia in these two rare genetic disorders had stayed in their minds ever since. "We knew the genetic causes of both deficiencies, we knew that it impacted neutrophil's metabolism, but we did not understand what was intoxicating and killing these neutrophils", says Maria Veiga-da-Cunha.

The research to find this missing link illustrates the strength of their collaboration. Maria Veiga-da-Cunha developed various experimental methods to be able to perform reliable experiments on the membrane-bound proteins. But when all techniques worked, she could not find the substrate that they were looking for. "We knew that the substrate must look like glucose 6-phosphate, but we could not find a compound that met all requirements. We were stuck." In the previous years, the team had done much work on the specificity of metabolic enzymes and discovered that cells need dedicated metabolite-repair enzymes to prevent diseases. This concept helped them to come up with the solution. It was Emile Van Schaftingen who remembered a paper from 1954 by Sols and Crane, who purified and carefully studied the substrate specificity of hexokinase 1. Sols showed that hexokinases have side activities that allow them to phosphorylate other substrates that look like glucose, if these are present in the cell. It was this lack of specificity of hexokinase, together with the finding that in blood we all have a molecule that looks very much like glucose (called 1,5-anhydroglucitol or 1,5-AG) that pointed them to the solution: the molecule intoxicating the neutrophils could be 1,5-AG-6-phosphate, formed by side activities of glucose-phosphorylating enzymes acting on 1,5-AG.

"When the girl started to take the antidiabetic, her situation improved after a week. She can, for the first time, live a normal life."

This hypothesis proved to be the answer they were looking for. With all the experimental tools at hand, and with the help of Guido Bommer, the team was able to demonstrate that cells defective in G6PT or G6PC3 accumulated 1,5-AG-6-phosphate when 1,5-AG was added to the culture media. 1,5-AG, a food derivative that resembles glucose, can be erroneously phosphorylated by enzymes present in neutrophils that normally act on glucose. As patients with deficiencies of G6PC3 or G6PT cannot undo this reaction, phosphorylated 1,5-AG accumulates in the patient's neutrophils and inhibits the first step of glycolysis, depriving these cells of energy. This is particularly detrimental for neutrophils, because glycolysis is their only source of energy and explains the neutropenia.

Though this finding was of great scientific importance, the researchers went on to answer the next question: Could they help the patients? Reducing the 1,5-AG concentration in the blood should restore the neutrophil levels. A new class of antidiabetics, which prevents the re-uptake of glucose back into the blood circulation in the kidney, might do the trick. Indeed, these antidiabetics were also shown to lower blood 1,5-AG. Tests in a mouse model of G6PC3 deficiency showed that the drug indeed reduced 1,5-AG levels in blood and, by doing so, treated the neutropenia in these mice. It then all went very quickly. Soon after they had published their results in PNAS, they were contacted by clinicians that were eager to test their hypothesis on patients that were particularly crippled by the disease. They first tested it on a 20-year-old girl, who was in a desperate condition. "She did not respond to her treatment anymore and was in terrible pain. She had many infections and severe intestinal problems. When the girl started to take the antidiabetic, her situation improved after a week. Her intestines now function almost normal again, the ulcers in her mouth and the abscesses on her skin healed. She can, for the first time, live a normal life."

The trials are now extended to more patients, to adults but also young children in Belgium and across the world. Maria Veiga-da-Cunha: "I believe it will become the standard treatment for these rare diseases. The current treatment is injection of a cytokine that accelerates the development of neutrophils in the bone marrow. This becomes very painful after a while and some patients become resistant. And it increases their risk of developing a type of a myelodysplastic syndrome, which is a group of cancers affecting the immature blood cells in the bone marrow. The antidiabetic is much cheaper, painless and can be taken at home."

Reference

Veiga-da-Cunha M, Chevalier N, Stephenne X, Dufour JP, Paczia N, Ferster A, Achouri Y, Dewulf JP, Linster CL, Bommer GT, Van Schaftingen E. Failure to eliminate a phosphorylated glucose-analog leads to neutropenia in patients with G6PT and G6PC3 deficiency. Proc Natl Acad Sci USA. 2019;116:1241-50.

Tracing the origin of cancer

Frédéric Lemaigre and Patrick Jacquemin try to understand how a normal cell turns into a cancer cell. They recently made breakthroughs on the mechanisms causing liver and pancreatic cancer.

How is the development of the liver and pancreas in an embryo controlled? Why are specific genes expressed in these cells and others not? Frédéric Lemaigre and Patrick Jacquemin try to answer these fundamental questions about the early phases of life. Their work leads to interesting new knowledge on how we are created, but also – and that is their main goal – to a better understanding of how cancer springs. "In cancer, embryonic development is in a way reversed. Cells regain numerous embryonic characteristics and start proliferating again. If we know how cells differentiate in a normal embryo, we also know how they can dedifferentiate in an adult. Our research thus helps to understand mechanisms that initiate cancer", explains Lemaigre. The groups of the two researchers work closely together. Lemaigre's group studies the liver, Jacquemin's the pancreas. Two organs that have a lot in common: they have the same embryonic origin and architecture, similar active genes and proteins, and overlapping mechanisms of development. The organs are thus studied in similar ways and the two groups share tools and know-how. And, more importantly, the two researchers habitually discuss new ideas and results. "A new proposal never leaves the group before the other has reviewed it", says Lemaigre.

The collaboration between Frédéric Lemaigre and Patrick Jacquemin goes back a long way. They got acquainted in '89 when they were both pioneering control mechanisms of tissue-specific gene expression, Lemaigre as a PhD student in Brussels, Jacquemin as a PhD student in Liège. Later, after they both switched to studying developmental biology, Lemaigre thought of Jacquemin to set up his new group at ICP (now de Duve Institute). Then a postdoc in France, Jacquemin happily agreed to return to Belgium. They have been working together ever since.

Jacquemin's group recently made a discovery on the earliest phase of pancreatic cancer, one of the deadliest cancers with a survival rate at 5 years of only 6 to 7%. The disease starts with precancerous ('neoplastic') lesions that may or may not become malignant. "We had the idea in mind that the initiation of pancreas cancer is related to perturbation in cell differentiation. The intention of our research was to identify the pancreas cell type that gives rise to precancerous lesions", says Jacquemin. Based on publications by other labs, his group was able to develop a good mouse model of the disease. "With the model we showed that ductal cells can be at the origin of the lesions. These are the cells that line the pancreatic duct and that drive the digestive secretions from the pancreatic cells to the duodenum, the first part of the intestine." They also identified the signaling pathway that drives the development of the lesions. "Mutations in one gene, of the so-called β-catenin pathway, lead to the precancerous lesions. We found that these mutations are responsible for a significant part of the development of pancreas cancer in our mouse model. Not for all cases though, another

"In cancer, embryonic development is in a way reversed."

part is independent of this pathway." There are inhibitors of this pathway available, but unfortunately they cannot be used clinically due to side effects. Jacquemin: "There are no direct clinical applications of the discovery. It is a contribution to obtain the picture of how cancer develops. Each contribution is important to find a cure one day."

The group of Frédéric Lemaigre studies hepatocellular carcinoma, the most common type of liver cancer. It results from a variety of conditions such as viral infections or cirrhosis, giving rise to a significant heterogeneity among patients and variable responses to therapeutic agents. "It is known for many years that the β-catenin pathway is involved in the development of hepatocellular carcinoma. The question was: Does the pathway influence the dedifferentiation of cells, so they lose their adult properties and start proliferating again?" The answer was not straightforward. "We found that dedifferentiation is indeed caused by mutations in the pathway. But it is not an individual gene that is responsible, instead it's a number of genes acting in concert. These genes function as a dynamic network, some activating the expression of other genes, others acting as suppressors." Using a combination of computational biology and experiments, the researchers identified a network comprising seven genes, which regulates the progression of a subset of liver cancer with poor prognosis. They made a mathematical model of how the genes interact. The model was validated with experiments on primary human cells in culture and human data from literature. "Thanks to computational biology we could study such a gene network. Using tools like transgenic mice, one can only study two or maximum three genes at a time", says Lemaigre.

The model predicts how one gene influences all other genes of the network. It helps to better understand the development of the cancer and it can be used to predict the efficacy of a drug in individual patients. The model is available to other researchers through the web, who can use it on their cancer samples to find the best target to modulate the network dynamics. Mathematical modeling of gene networks has become a regularly used tool in their research, says Jacquemin: "It's very useful to make predictions and set up a good hypothesis, which can then be tested in experiments." Though it's a great tool, one has to be careful with the results, adds Lemaigre: "Biological know-how is indispensable to interpret and validate the results. The mix of both areas of expertise is one of the strengths of our groups."

References

Collet L et al. Kras and Lkb1 mutations synergistically induce intraductal papillary mucinous neoplasm derived from pancreatic duct cells. Gut. 2019; epub Jun 1.

Gérard C et al. Dynamics and predicted drug response of a gene network linking dedifferentiation with beta-catenin dysfunction in hepatocellular carcinoma. J Hepatol. 2019;71:323-32.

The fundamentals of a bacterium's life

***Bdellovibrio bacteriovorus* predates on other bacteria and might therefore be used as a new type of antibiotic. The team of Géraldine Laloux studies how this bacterium orchestrates its eccentric life cycle.**

A small bag containing a fluid and randomly distributed molecules. That's how a bacterium was for long envisioned. But, as scientists study the unicellular organisms in detail, they discover their well-organized and diverse ways to survive. "Bacteria do not have organelles, the specialized intracellular structures that animal and plant cells have. But they are still able to localize activities within the cell. During thousands of years of evolving, each bacterium developed its own way to reproduce", says Géraldine Laloux, a microbiologist who studies the life cycles of bacteria.

Her passion for the odd little creatures was born when she worked as a postdoc at Yale University. Her subject was *Caulobacter crescentus*, a harmless organism with a conspicuous stem-like extension. "It divides into two different daughter cells: one goes swimming around, the other stays attached to the surface. It has a very fancy life cycle." Using fluorescence microscopy to study the processes on a single cell level, she could see how proteins move in the bacterium and at the same time watch its shape changing. "During these 3.5 years at Yale, I fell in love with cell biology", she says.

Géraldine Laloux is one of the young group leaders at the de Duve Institute. She studied biology in Namur, during which she did her practical work at Harvard University in the group of the Belgian genetics professor Marc Vidal. She continued with a doctoral study in the lab of Xavier De Bolle in Namur, where she first started to work on bacteria. After her postdoc at Yale, she came to the de Duve Institute to join the lab of Jean-François Collet. Here, the at Yale acquired knowledge on fluorescence microscopy proved of great value. "The lab studies the responses of bacteria to stress. They use techniques from molecular biology, genetics and biochemistry to investigate the signaling proteins in the cell envelope. When I started to study the stress responses with the microscope, I could see weird shapes of dividing cells. This led us to identify an ensemble of proteins that monitor the status of the cell wall. Before, this system was thought to have another function! A discovery by serendipity."They also discovered the function of a protein associated with this stress-sensing system: it turns on the alarm when there is something wrong with the trafficking of specific molecules of the bacterial envelope.

In 2016, Géraldine Laloux started to develop her own research path at the Institute. Which put her for the big question: What topic to choose? After careful consideration, she decided to focus her research on *Bdellovibrio bacteriovorus*, a predatory bacterium. Again an organism with a curious life cycle, she explains: "*B. bacteriovorus* attacks Gram-negative bacteria, which are characterized by a double cell membrane. It does so by invading and nesting in the periplasm, the space between the inner and

"We see the predator entering the prey cell, eating the prey content, growing, dividing and finally attacking another prey."

outer membrane. From here, it eats the contents of the host bacterium and grows to form a long spaghetti-like filament before dividing into small daughter cells. Finally, the host cell lyses and the new *B. bacteriovorus* cells go searching for a next victim."

The bacterium is a promising alternative for current antibiotics to which more and more bacteria become resistant. "Many antibiotic-resistant pathogens are Gram-negative and could thus be attacked by *B. bacteriovorus*, which itself is harmless to humans. Many labs study the bacterium for this purpose", says Géraldine Laloux. She herself is more interested in the fundamental questions about the bacterium's life cycle. "The bacterium divides into a variable number of daughter cells: from 2 up to 7 or even more provided that the prey bacterium is large enough. We want to find out how these processes are orchestrated. How is the chromosome – a bacterium has only one – copied a certain number of times? How does the segregation of these chromosomes take place?" The team uses a combination of disciplines to answer these questions. "From genome sequencing data, we know which proteins are present in the bacterium. We make interesting proteins fluorescent by modifying the genes, so we can follow them in the living cell by microscopy. We also edit genes, to see what the bacterium does without certain proteins. And we use biochemistry to investigate the interactions between proteins."

The group of Géraldine Laloux had a kick-start in 2018. After being appointed as FNRS researcher, she obtained an ERC Starting grant and an FNRS-MIS grant. To make the year even more hectic, she also gave birth to her second child. Thanks to the ERC grant she could buy an advanced microscope that is crucial to the research. With a high resolution, it is able to detect the faint signals within living cells of one micrometer (1000 times smaller than a millimeter). "We can visualize the full predator cycle. We see the predator entering the prey cell, eating the prey content, growing, dividing and finally attacking another prey", she says.

Her team now consists of one postdoc, two PhD students and a technician. "They are working very well together and are really motivated to give our young lab a good start", she says proudly. Though the research is not directly aimed at clinical application, the results will be important for the development of *B. bacteriovorus* as a new antibiotic, says Géraldine Laloux: "If you want to use the bacterium in a clinical context, you have to know how it behaves, how it can be engineered. We must be able to control what we put in a patient."

From millions of data to a new therapy

The genetic research of Miikka Vikkula led to the first molecular therapy for several types of vascular anomalies. He was awarded the prestigious Generet Prize for his work.

In 1993, young MD Miikka Vikkula left Helsinki for Boston as a postdoc, to study the role that collagens play in vascular biology. His intention was to return to Finland after a few years to become a cardiologist. It all went differently. In Boston, he was introduced to Dr Laurence Boon, a plastic surgeon in training, who had just arrived from Brussels for a fellowship at the Children's hospital. Her chief had recognized a big Italian family with multiple cases of vascular anomalies. The two fellows were asked to identify the genetic cause. A challenge that Vikkula eagerly accepted. "I was interested in the cardiovascular system and in genetics. In this research, it all came together."

That first meeting in Boston changed both the career and life of Miikka Vikkula. Together with Laurence Boon, he threw himself into the laborious work of collecting and analyzing samples of the patients. "At that time, we used big gels to run genetic tests, and after they were labelled radioactively, we developed films and scored bands on them. We could do one genetic marker per gel. Today we run 50,000 markers at a time", the Finnish researcher says. The two fellows succeeded to find the genetic mutation responsible for the disease of the Italian family. It would be the first of many discoveries on vascular anomalies by Vikkula. In these years in Boston, something beautiful grew between the two fellows and four years later they got married.

The couple had found their mission in helping patients with vascular anomalies. Laurence Boon went to work as a plastic surgeon in the University Hospital Saint-Luc in Brussels, where she coordinates the Center for Vascular Anomalies. Miikka Vikkula also searched a position in Belgium, which he found at the de Duve Institute, then called ICP. Here he set up his own research group and continued his work on vascular anomalies. "Vascular anomalies are a group of over forty disorders, most of which are relatively rare, and in which the blood or lymph vessels develop in an uncontrolled way", explains Vikkula. "Patients have dark red to purple sponge- or cyst-like lesions on their bodies. People with severe forms have chronic pain. Some have headaches, others have trouble with breathing, eating or moving their limbs."

Building on the successful approach in Boston, the couple started the collection of samples of vascular anomaly patients. That biobank, today containing thousands of samples, became the basis for Miikka Vikkula's research. His group performs genetic analyses on the samples to find the mutations that cause the disease. In a next step, they characterize the changes induced by these mutations within the cells. Once they know what goes wrong in the cell, they try to find a way to interfere. "The beauty is that we do not have any idea of the molecular dysfunction a priori. We don't need it. Because the disease is inherited, we know that behind the cause there must lie a mutated

"A treatment like this was unthinkable in 1993, when we started this research."

gene."The research group has found the genetic causes of multiple vascular anomalies. They for example identified the mutation responsible for a potentially deadly malformation of the vein of Galen in the brain. Besides increasing the understanding of the diseases, this knowledge has allowed to achieve better and faster diagnoses.

A major breakthrough came in 2006. The lab was still researching the venous malformation of the Italian family, because, though they had found the inherited mutation, they could not explain why the lesions were localized and other veins were normal. The group then discovered a second mutation in the cells of the malformations themselves, a so-called somatic mutation. Only cells with both mutations develop the disease. These mutations were thereafter found to make vascular cells to over-activate a specific signaling pathway. An existing drug, called Rapamycin, inhibits this pathway. The researchers investigated the effects of the drug in in vitro and in vivo models and showed that it indeed stopped lesion development. Because the drug was already approved for use in humans for transplantations, the group could quickly start clinical trials, in collaboration with Prof. Laurence Boon. In two small groups of patients, Rapamycin drastically relieved patients from their painful symptoms. One of them suffered from chronic headaches and is, since the treatment, able to work full-time again. A large trial is now being run with over 100 patients already involved. It is the first molecular therapy for a venous malformation, which has provoked a revolution in the field. "A treatment like this was unthinkable in 1993, when we started this research. Now everybody is talking about it", says Vikkula.

The discovery of the second mutation made the lab also look at tissular mutations as explanation for vascular lesions in patients with no family history of such. Thanks to the high-quality samples of the biobank, they were able to identify the first somatic mutations explaining non-inherited lesions with regular Sanger sequencing. This opened the doors for the whole world to look for similar explanations for other diseases. Now, roughly 70% of non-inherited vascular malformations is explained by a somatic mutation. Armed with the newest NGS tools and Highlander, an in-house developed software tool to analyze the enormous amounts of genetic data, and a large data cluster, the Vikkula lab continues its search for genetic explanations for human diseases. Next to vascular anomalies, they also investigate lymphedema and cleft lips. "We believe many more diseases are caused by genetic mutations. Finding these mutations can lead to a more effective treatment for patients and greatly improve their quality of life."That is what drives Miikka Vikkula who, though he became a researcher, also still is a doctor: "To be able to go back to the patient is the most important reward of this work."

Research Groups

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.

Cancer

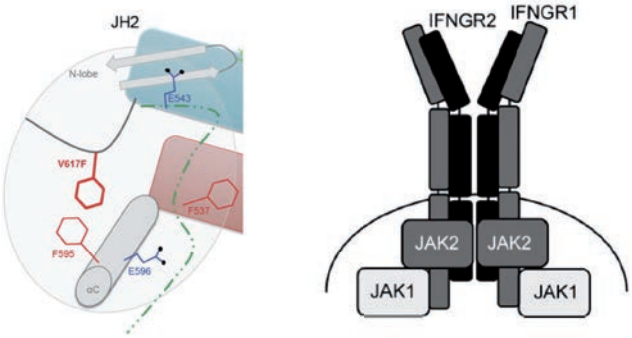
Stefan Constantinescu

LUDWIG CANCER RESEARCH
Brussels

Cell Signaling & Molecular Hematology

We study how cytokines regulate blood formation via their membrane receptors, Janus kinases, STAT proteins and other signaling pathways. We decipher how blood cancers evolve and can be targeted by treatment.

Formation of blood requires small proteins, denoted as cytokines, such as erythropoietin, thrombopoietin, interleukins or interferons. These proteins 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. 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). Our hypothesis is that a curative treatment needs a JAK2 V617F-specific inhibitor. To this end, we delineated the circuit of JAK2 kinase activation by the V617F acquired mutation in the pseudokinase domain that could be a target for specific inhibition. The same circuit is required for signaling by the tetrameric interferon (IFN)-γ receptor (Figure, left), suggesting that a common set of molecules might inhibit both IFN-γ signaling and JAK2 V617F (Figure, right). The same strategy is taken for mutants in the Tpo receptor (TpoR/MPL) that we discovered in 2006, where mutations in W515 just after the transmembrane domain activate the receptor.



Substitution of V617 to phenylalanine (V617F) in JAK2 pseudokinase (JH2) domain creates an aromatic stacking interaction (left) that is responsible for kinase domain activation; the same circuit is required for activation of wild-type JAK2 by the ligand stimulated IFN-γ receptor tetramer (right).

More recently, we discovered that mutations can endow a chaperone protein, calreticulin, the oncogenic ability to persistently activate the Tpo receptor (TpoR/MPL). This closes the circle of major driver mutations in MPNs. The next challenge is the delineation of the pathway by which MPNs evolve to leukemia. We also study myeloproliferation and myeloid leukemia in children, especially those being resistant to treatment. This work is supported by 'Les avions de Sébastien'.

In order to pursue our aims, we use molecular biology approaches like extensive mutagenesis as well as functional assays as read-outs for structural determinants, biophysical approaches, as well as 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:** Audrey de Rocca Serra, Anita Roy, Leila Varghese • **PhD Students:** Alina Alexandru, Thomas Balligand, Harsh Goyal, Gabriel Levy, Florian Perrin, Gaëlle Vertenoeil • **Undergraduate Students:** Nicolas Papadopoulos, Elisabeth Pop • **Research Assistants:** Lidvine Genet, Céline Mouton, Yacine Rahmani, Madeleine Swinarska • **Technical Assistant:** Florin Militaru

Jean-Baptiste Demoulin

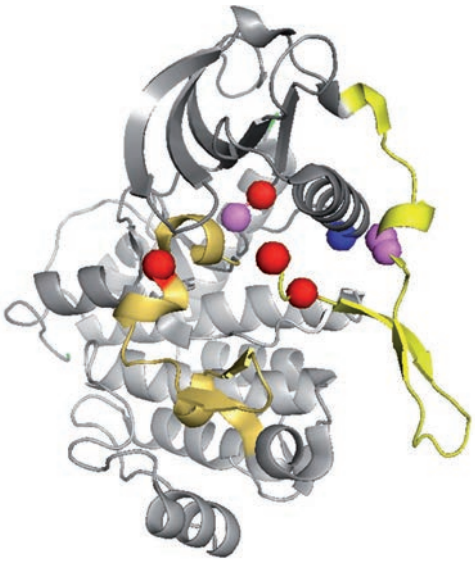
Cancer Signaling

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.

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.



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

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:** Emeline Bollaert • **PhD Students:** Guillaume Dachy, Emilie Guérit, Ariane Sablon • **Undergraduate Student:** Boutaina Boulouadnine • **Research Assistants:** Sandrine Lenglez, Virginie Vandewalle • **Administrative Support:** Geneviève Schoonheydt

Pierre Coulie

Human Tumor Immunology

Cancer immunotherapy is a breakthrough but only for a minority of 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 • **Research Assistants:** Gérald Hames, Catherine Muller, Nathalie Remy, Athina-Elena Somerhausen • **Administrative Support:** Suzanne Depelchin

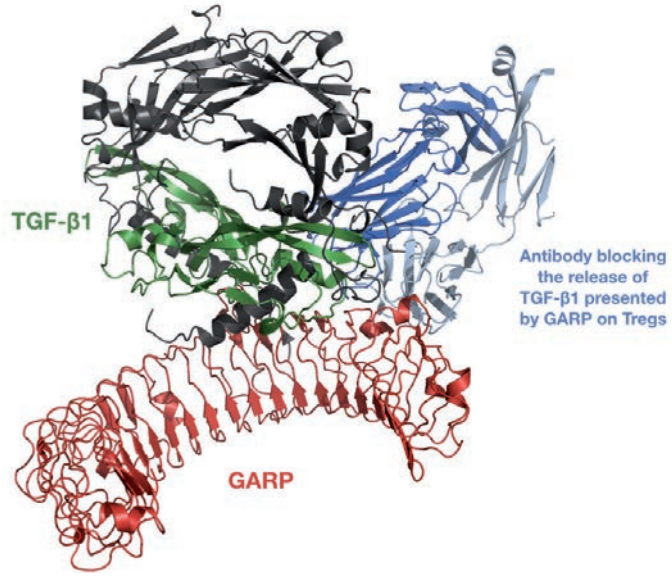
Sophie Lucas

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.

Regulatory T cells & TGF-β

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 explore in mouse models whether these tools could be used as drugs to block Treg immunosuppression in patients suffering from cancer. Recently, we obtained encouraging results indicating that anti-GARP antibodies favor the elimination of tumors when they are combined to another approach of cancer immunotherapy known as PD1/PD-L1 blockade. The latter is the best currently available immunotherapeutic approach, but it is still insufficiently efficient when used on its own. Our data indicate that anti-GARP antibodies could improve the anti-tumor efficacy of PD1/PD-L1 blockade. Our antibodies were licensed to the biotech company argenx, then to the pharmaceutical company AbbVie, for further development towards the clinic. A first clinical trial to test these antibodies in cancer patients was initiated in March 2019. 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, Stéphanie Liénart • **PhD Students:** Charlotte Bertrand, Grégoire de Streel, Julien Devreux, Fanny Lambert, Sara Lecomte, Pierre Van Meerbeeck, Xuhao Zhang • **Undergraduate Student:** Pierre Maus • **Research Assistants:** Noora Bleeckx, Nicolas Chalon • **Administrative Support:** Suzanne Depelchin

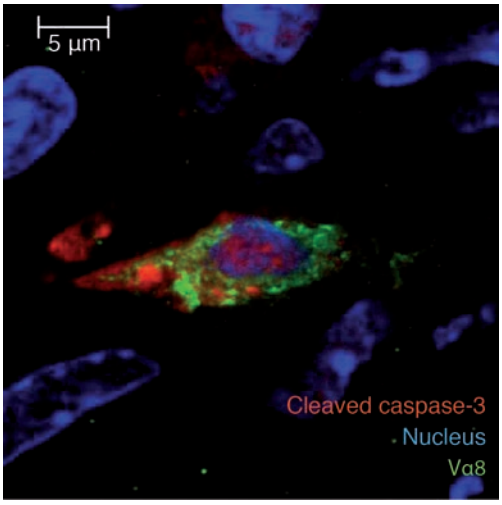
Benoît Van den Eynde

LUDWIG CANCER RESEARCH Brussels

Improving Cancer Immunotherapy

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.

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

Senior Investigators: Christophe Lurquin, Vincent Stroobant • **Postdoctoral Fellows**: Joanna Abi Habib, Veronica Finisguerra, Wenbin Ma, Stefan Naulaerts, Nathalie Vigneron, Jingjing Zhu • **PhD Students:** Raphaële Bombart, Tereza Dvorakova, Violette Ferrari, Simon Klaessens, Julie Lesenfants, Pierre-Florent Petit, Marie Solvay, Jiali Yang • **Undergraduate Students:** Célina Nielsen, Charlotte Wautelet • **Research Assistants:** Thérèse Aerts, Loubna Boudhan, Rui Cheng, Martin Doyen, 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 ask why tumor-infiltrating lymphocytes (TILs) are often unable to eliminate tumors, and aim to find strategies to overcome this challenge.

Most tumors are not ignored by the immune system of cancer patients. They contain immune cells, particularly T cells directed against tumor antigens.

In the '90s we identified the gene MAGE-1, which encodes the first known antigen that is expressed by many tumors but not by normal tissues, and that is recognized by cytolytic T lymphocytes. We subsequently identified genes with the same expression profiles (e.g. gene families MAGE, BAGE, and GAGE). Antigenic peptides encoded by these genes can be recognized by both CD4 and CD8 T cells. We designed approaches to identify the antigenic peptides and measure patients' T cell responses to vaccines.

"T cells are described as 'exhausted' in mouse tumors but this concept of T cell exhaustion remains abstract in human tumor biology."

Today, we remain dedicated to studying T cells and the different immunosuppressive mechanisms that operate in human tumors. Tumor-infiltrating T cells (TILs) are often dysfunctional, and we focus on three factors that might limit TIL function: extracellular galectins, TIL exhaustion and myeloid-derived suppressor cells (MDSCs).

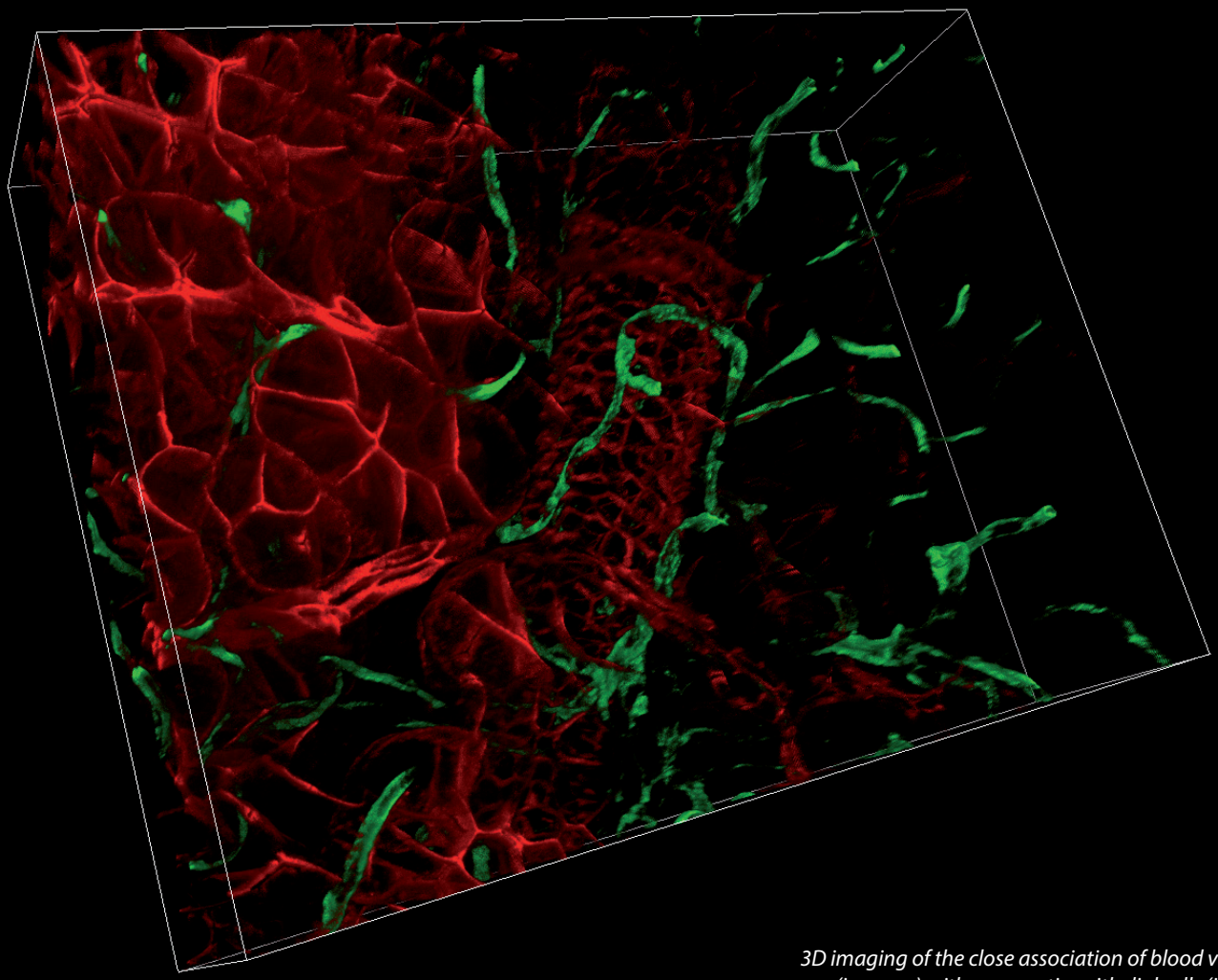
We discovered that extracellular galectin-3 secreted by tumor cells and macrophages binds glycoproteins at the T cell surface, which blocks human TIL functions. Galectin-3 binds both glycans decorating IFN-γ and the extracellular matrix. T cell recruitment towards tumors requires a chemokine gradient of IFN-γ-induced chemokines; the presence of galectin-3 reduces IFN-γ diffusion through the matrix, and prevents the establishment of a chemokine gradient by tumor cells, T cell infiltration into tumors and control of tumor growth.

TILs become less functional in tumors, a phenomenon often named exhaustion. We are characterizing in-depth CD8 T cells infiltrating human ovarian carcinomas functionally, phenotypically and molecularly. We abrogate or increase the expression of specific transcription factors to study how they contribute to or prevent TIL exhaustion. The results may help to improve adoptive transfer therapies with engineered CAR T cells.

Finally, we ask how MDSCs impede T cell functions. While rare in healthy individuals, MDSCs are found in greater numbers in patients with some chronic diseases or cancer. We assess the suppressive functions of MDSCs from blood and tumors from ovarian carcinoma patients in T cell co-cultures and by transcriptomic approaches.

Staff members

Postdoctoral Fellow: Annika Bruger • **PhD Students:** Thibault Hirsch, Mathieu Luyckx, Shufeng Nan, Damien Neyens, Christophe Vanhaver • **Undergraduate Student:** Antoine Huaux • **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)

Genetics and Development

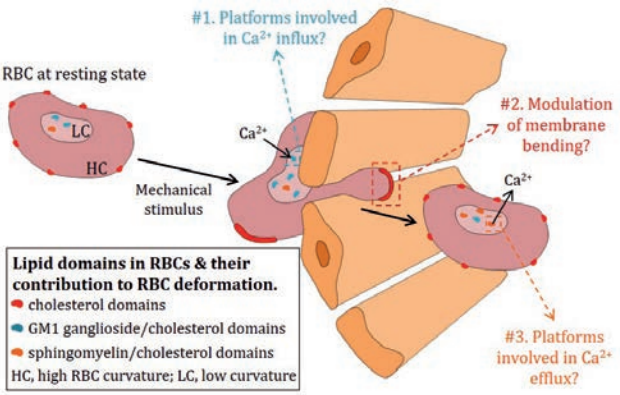
All cells of a human body originate from one cell that, directed by the genetic information, divides, grows and differentiates into a fully functional organism. How do our cells develop in the embryo? Which genetic mutations lead to diseases? How do cells maintain themselves during a lifetime and how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

Donatienne Tyteca

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.

Membrane Biology

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 diseases.



We mainly use RBCs, as the simplest and best-characterized human cell model with remarkable deformability. Using high-resolution confocal imaging and atomic force microscopy (coll. D. Alsteens, UCLouvain), we discovered the existence of stable submicrometric lipid domains at the living RBC plasma membrane. Three types of domains coexist, showing differential composition, membrane curvature association and lipid order (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. Moreover, we found that plasma membrane organization and properties are deregulated in RBCs from patients suffering from spherocytosis and elliptocytosis, two genetic RBC deformability disorders (coll. B. Brichard, C. Lambert & C. Vermylen, University Hospital Saint-Luc).

Some lipid domains are lost upon RBC storage at 4°C, suggesting they could represent sites susceptible to vesiculation, with potential implication for blood storage before transfusion. To test this hypothesis, we isolate and purify extracellular vesicles released by stored RBCs to determine their composition, biogenesis and pathophysiological implications. Similar approaches are developed to determine the biogenesis and significance of erythroid cell-derived extracellular vesicles in erythroleukemia, a rare type of acute myeloid leukemia with poor prognosis (coll. V. Havelange).

We recently started to explore the importance of plasma membrane organization and biophysical properties for (i) muscular cell migration and fusion into myotubes and Duchenne myopathy; and (ii) breast cancer cell invasion.

Staff members

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

Nisha Limaye

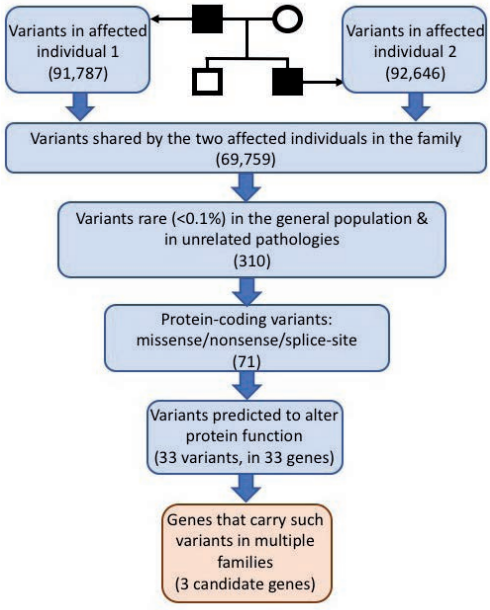
Genetics of Autoimmunity & Cancer

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 Hodgkin lymphoma, a hematological malignancy. In very rare cases, these diseases run in families. By sequencing the genomes of multiple members of such families, we identify genetic variants that are shared by the affected individuals, but not their healthy relatives. These genes may therefore contribute to disease.

This is no trivial task: we all carry tens-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 share with each other. A tremendous amount of accumulated information, knowledge-based predictions, and data-processing is therefore required to distinguish the one-to-a-few genetic variants that actually impact disease, from the thousands of others incidentally shared by family members.



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 genetic variant that we hypothesize may cause disease, we test for functional evidence of its impact: we induce cells to express the faulty version of the gene, and study how this changes their appearance, behavior and function. We also screen patients with non-inherited ('sporadic') forms of the same disease for the gene or the biological pathway it participates in, 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 Students:** Cécile Boulanger, Elsa Khoury • **Research Assistant:** Delphine Nolf

Miikka Vikkula

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.

Human Genetics

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 malformations, lymphedema, and cleft lip and palate. We also collaborate in studies on various cancers: (angio) sarcoma, breast cancer, uveal melanoma and pheochromocytomas. This research is based on blood and tissue samples collected from patients in collaboration with clinical centers worldwide, and especially with University Hospital Saint-Luc. We analyze the genome using high-throughput sequencing and we have developed and implemented specialized bioinformatics tools. We also manage the UCLouvain Genomics Platform and an important computational cluster.

"Understanding the primary causes of these diseases allows us to develop targeted molecular approaches, resulting in more specific treatments, thereby providing great hope for the patients."

Vascular anomalies are a heterogeneous group of localized disorders in which the lesions are 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 in TIE2 and PIK3CA activate the PI3K/AKT signaling pathway. We demonstrated that the mTOR inhibitor rapamycin can control expansion of lesions. We also demonstrated effectiveness in patients and a phase III European trial is coordinated by Prof. L. Boon at University Hospital Saint-Luc.

After having unraveled the second gene causing capillary malformations associated with arterio-venous malformations (CM-AVM2; EPHB4), we have identified mosaic and double-hit mutations in sporadic patients. The proteins encoded by the two discovered genes regulate the RAS/MAPK signaling pathway. To test potential therapies, we have now generated an AVM mouse model.

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 *VEGFC* and *ADAMTS3*. Altogether, 28 genes are known, explaining 30% of the cases. We are currently performing functional validations on a series of genes we have recently discovered.

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 likely pathogenic variants in 30% of non-syndromic discontinuous CL/P patients. We currently develop novel bioinformatics tools to study these complex diseases.

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, Reza Salimi • **PhD Students:** Murat Alpaslan, Mirta Basha, Simon Boutry, Martina De Bortoli, Eleonore Pairet, Peyman Ranji, Nassim Homayun Sepehr, Matthieu Schlögel, Cedric van Marcke de Lummen • **Undergraduate Students:** Anne-Bénédicte Hong, Elise Sepulchre • **Research Assistants:** Bill Brancart, Fabrice Cahay, Dominique Cottem, Audrey Debue, Séverine Gonze, Liliana Niculescu • **Technical Assistants:** Mourad El Kaddouri, Danny Plessiet • **Administrative Support:** Liliana Niculescu, Mina Todorovic

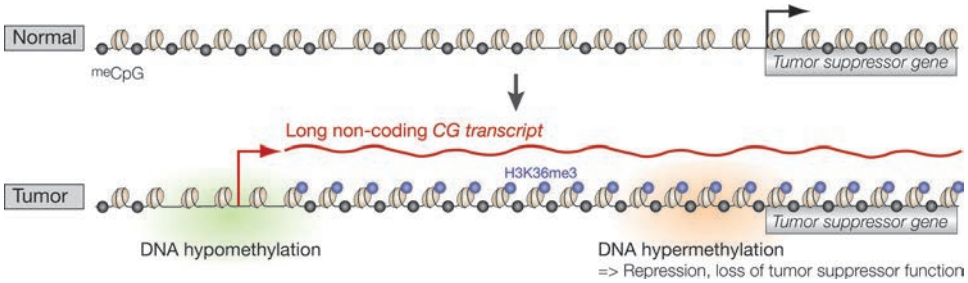
Charles De Smet

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.

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.



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.

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:** Elias Aajja Maazoubi

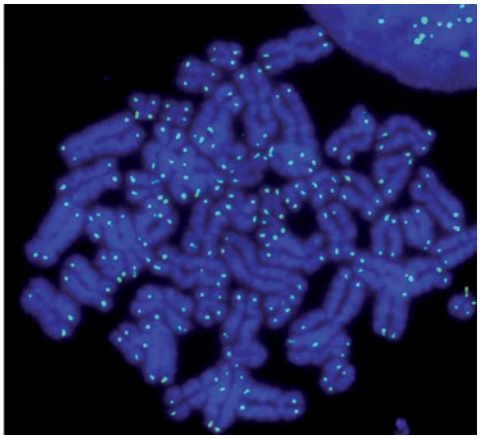
Anabelle Decottignies

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 protective protein-RNA-DNA structures at chromosome ends. In normal cells, telomeres shorten with successive cell divisions until they get too short to ensure faithful protection of chromosomes, leading to a permanent exit from cell cycle and cellular senescence.

How do cancer cells avoid telomere shortening with divisions? In 90% of tumors, telomerase expression is reactivated. Telomerase is the enzyme which, in embryonic stem cells, counteracts telomere shortening, but whose expression is lost upon cell differentiation. Sarcomas or central nervous system tumors (including pediatric tumors), however, frequently activate a telomerase-independent mechanism, called ALT (Alternative Lengthening of Telomeres), based on homologous recombinations between telomeric sequences. ALT is not active in normal cells, thus offering interesting perspectives for targeted cancer therapy. Thanks to a genetic system of cellular hybrids, we discovered new important (epi)genetic features of ALT cells. We identified TSPYL5 as a possible therapeutic target that, when inactivated in cultured cells, induces the specific death of ALT cancer cells, while not affecting normal cell viability. In collaboration with chemists, we are currently working on the identification of anti-TSPYL5 drugs.



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

We also found that some melanoma cells do not activate any telomere maintenance mechanism and yet form aggressive tumors, suggesting that indefinite replicative potential is not a general cancer cell hallmark. This is important in the context of anti-cancer therapies targeting telomere maintenance.

Another part of our research focuses on the regulation of telomere transcription into non-coding RNA species dubbed TERRA (TElomeric Repeat-containing RNA), which contribute to telomere protection. We discovered that the AMPK/PGC1-α metabolic pathway, activated by endurance exercise, promotes human telomere transcription through NRF1, suggesting a role for antioxidant defenses. We are currently investigating mouse TERRA species.

Finally, we study cellular ageing, notably in the context of premature ageing diseases linked to defective telomere maintenance (telomeropathies). We recently studied the cellular defects induced by loss of function of *PARN*, a gene mutated in some telomeropathy patients. Diagnostic of telomeropathies is possible through telomere length measurement in blood cells with a technique called Flow-FISH, which was not available in Belgium. This year, we set up the technique in collaboration with University Hospital Saint-Luc. We enrolled nearly 500 healthy volunteers to establish the standard curves for telomere length. Flow-FISH is now ready to be used by clinicians.

Staff members

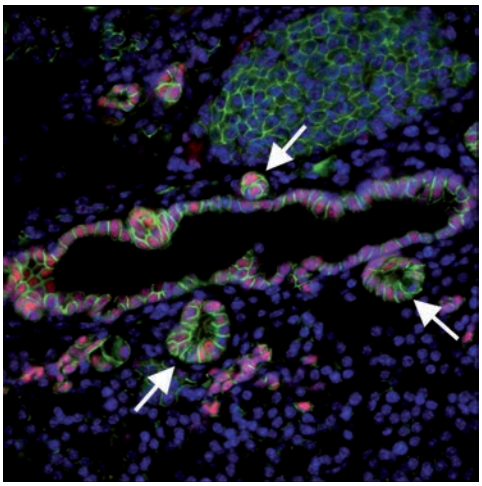
Postdoctoral Fellows: Harikleia Episkopou, Maya Raghunandan • **PhD Students:** Eloïse Claude, Dan Geelen • **Undergraduate Student:** Hélène Lefort • **Research Assistant:** Manon Mahieu

Frédéric Lemaigre &
Patrick Jacquemin

Cell Differentiation

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.

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.



Immunolabelling of the pancreas of a mutant mouse showing the presence of initiating neoplastic lesions derived from duct cells (arrows).

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 microRNA miR-337 which controls the dynamics of 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. Recently we identified the duct cells as the cell type of origin for a neoplastic lesion giving rise to PDAC. In our studies of liver cancer, we developed 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 gene networks which we investigate in pancreas and liver. This resulted in the design of a mathematical model that predicts the behavior and drug response of a gene network involved in hepatocellular cancer. This network links dedifferentiation of the hepatocytes during tumorigenesis with dysfunction of β-catenin, a protein that controls differentiation in embryonic and adult liver.

Staff members

Senior Investigator: Younes Achouri (Platform Manager) • **Guest Investigator:** Paul Van Liedekerke • **Postdoctoral Fellows:** Mohamad Assi, Mickaël Di-Luoffo, Claude Gérard, Malak Haidar • **PhD Students:** Catalina De Schrevel, Angeline Fages, Lila Gannoun, Maxime Libert, Nora Meyers, Marie-Albane Minati, Sophie Pirenne • **Undergraduate Student:** Corentin Timmermans • **Research Assistants:** Sabine Cordi, Hajar Dahou, Jean-Nicolas Lodewykx • **Technical Assistants:** Freddy Abrassart, Mourad El Kaddouri • **Administrative Support:** Marjorie Decroly, Julie Klein

Wen-Hui Lien

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.

Signaling Crosstalk

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.

"An integrative view of signaling regulation for regenerative medicine and treatment of cancers."

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.

Staff members

Postdoctoral Fellow: Chim Kei Chan • **PhD Students:** Gaia Cangiotti, Christopher Lang • **Research Assistant:** Bahar Zafarani • **Administrative Support:** Aimée-Lys Rusesabagina

Christophe Pierreux

Epithelial Differentiation

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.

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.

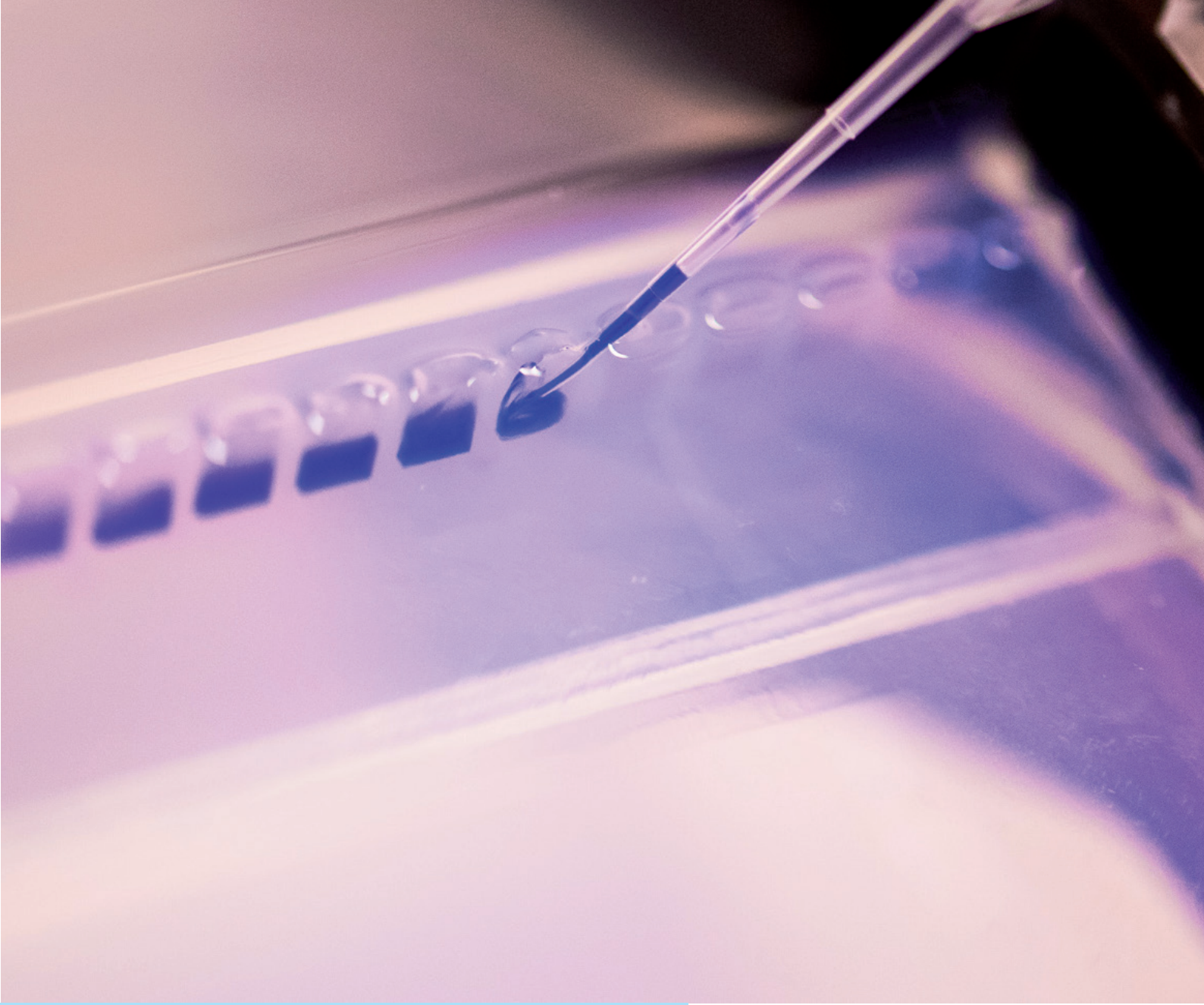
"In-depth characterization of tissular, cellular and molecular mechanisms during embryonic development and disease paves the way towards organ bioprinting and therapeutic testing."

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 the role of these intercellular communications in developing and diseased thyroid and pancreas..

We are also investigating epithelial homeostasis in adult organs. On the one hand, we studied 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, as well as hypothyroidism. On the other hand, we also addressed the pathophysiology of cystinosis, a multisystemic lysosomal disease due to defective lysosomal membrane cystine/H+ antiporter, cystinosin. We found that the disease first manifests by a kidney Fanconi syndrome, largely caused by megalin-dependent cystine accumulation in kidney lysosomes. We are now investigating the possibility to translate our basic discoveries into a simple diet-based therapy for cystinosis.

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 Students:** Julie Degrève, Ludovic Lepers • **Research Assistants:** Pascale Lemoine, Siam Mahibullah • **Technical Assistant:** Abdelkader El Kaddouri • **Administrative Support:** Aimée-Lys Rusesabagina



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.

Infections and Inflammation

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

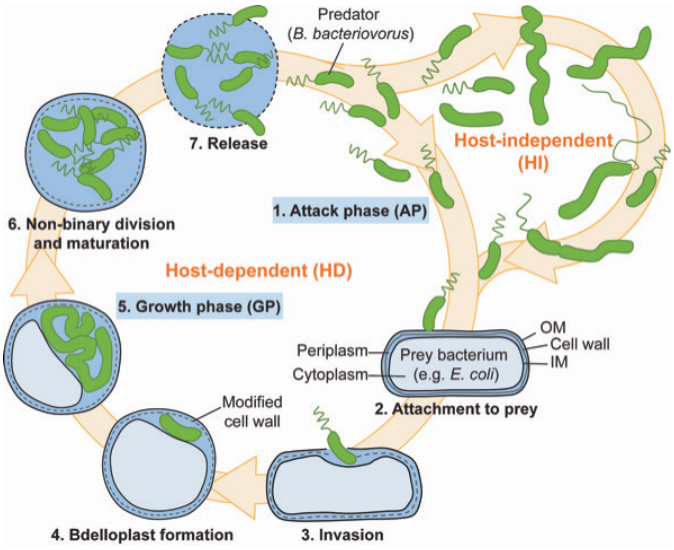
Senior Investigators: Seung Hyun Cho, Pauline Leverrier • **Postdoctoral Fellows:** Abir Asmar, Michaël Deghelt, Antoine Delhaye, Alexandra Gennaris, Chi Nguyen • **PhD Students:** Naemi Csoma, Kilian Dekoninck, Emile Dupuy, Jessica El Rayes, Elisa Pierre, Raquel Rodriguez Alonso • **Undergraduate Student:** Emmanuelle Latour • **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 the biology of these microbes to understand how they proliferate inside their prey.

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. In our group, we study how bacteria organize their cellular content in space and time to achieve complex lifestyles, using a combination of bacterial genetics, molecular biology, live fluorescence microscopy and quantitative image analysis at the single-cell level. Over the past decades, tremendous advances in microscopy and genetic engineering – including the labeling of proteins of interest with fluorescent molecules – revealed that bacterial cells organize their intracellular content in the most exquisite manner. For instance, proteins or chromosomal regions occupy specific and dynamic positions inside the cell. This spatio-temporal organization of the cell is in fact essential for bacterial life.



During its predatory cell cycle, *B. bacteriovorus* (in green) 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.

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 or complement to classical 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. How cellular processes are orchestrated to govern the non-canonical biology of *B. bacteriovorus* is largely unknown. Yet, discovering the molecular determinants underlying the cell cycle of the micro-predator is a prerequisite to understand how it thrives inside its prey and to envision its use as a therapeutic agent.

In 2019, we made the first important steps towards understanding how the chromosome of this bacterium is arranged within the cell and throughout its lifecycle. Our data reveal a novel spatial organization of key elements of the chromosome, and the intriguing dynamics of DNA replication and segregation. We are now investigating the molecular factors underlying these observations, in order to unravel the mechanism by which *B. bacteriovorus* copies and segregates its genome multiple times before cell division. In parallel, we examine the function of proteins that may act as molecular organizers that keep the content of the bacterial cell in order.

Staff members

Guest Investigator: Sander Govers • **Postdoctoral Fellow:** Terrens Saaki • **PhD Students:** Jovana Kaljevic, Ophélie Remy • **Undergraduate Student:** Antoine Gérard • **Research Assistant:** Charles de Pierpont

Jean-Paul Coutelier

Infections & Immunity

Our project is to analyze the relationships between infectious agents and the immune microenvironment, and their consequences on unrelated diseases that develop concomitantly in the infected host, with a special focus on developing countries.

The possibility for evoluted organisms to survive infections depends on the ability of their immune system to eliminate the pathogenic agent without induction of immunopathology. Therefore, both quantitative and qualitative parameters of the immune responses will determine the outcome of infections. For instance, infection with *Plasmodium* parasites may result in asymptomatic carriage, mild or severe malaria. Our main project is to determine in patients from Rwanda some of the causative environmental events that modulate anti-parasite responses and thus lead to severe forms of malaria or to asymptomatic persistence of the parasite.

> ***"Modulation of the host immune microenvironment by infections enhances susceptibility to some diseases (blood autoimmune diseases, septic shock), but prevents the development of others (autoimmune encephalitis, some cancers such as myeloma)."***

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. 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.

In mice, LDV- and *Plasmodium*-modulated immune microenvironment resulted in an enhanced susceptibility to diseases concomitant to the infection, but of unrelated cause, such as septic shock, through macrophage activation leading to enhanced TNF production. These infectious agents triggered an increased production of soluble receptors for bacterial lipopolysaccharide, which might serve as early indicators of this enhanced susceptibility to develop shock. Similarly, autoantibody-mediated hemolytic anemia and thrombocytopenia were aggravated by viral infection because of enhanced phagocytosis of opsonized erythrocytes and platelets by activated macrophages. 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 and experimental autoimmune encephalitis. Similarly, mouse 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. In contrast, *Schistosoma* antigen decreased both IFN-γ production and plasmacytoma prevention. Similarly, a study of Egyptian myeloma patients suggested a preventive effect of viral infections, but an enhanced risk to develop cancer after *Schistosoma* infection.

Staff members

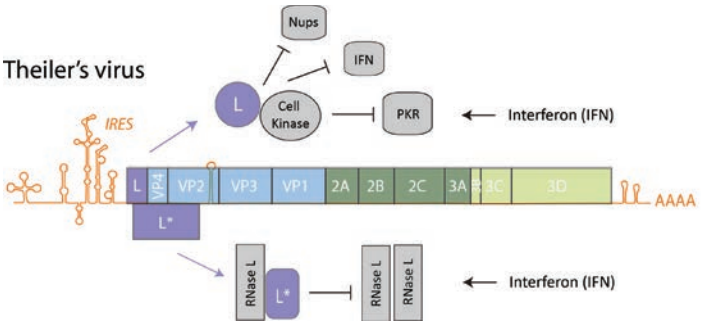
PhD Students: Mohamed Mandour, Jean d'Amour Mutoni, Ella Larissa Ndoricyimpaye, Pyone-Pyone Soe

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.

Owing to their rapid multiplication, viruses constantly evolve to adapt to their host. They thereby developed many strategies to counteract immune defenses. Among antiviral immune defenses, the interferon (IFN) system is likely the most potent one. IFNs are a family of substances secreted by infected cells. They act on neighboring cells and make them resistant to viral infection. Dysfunction of the IFN system can lead to dramatic viral infections in humans. Excessive IFN production is also detrimental and results in skeletal growth anomalies and mental retardation, as observed in patients presenting with Aicardi-Goutières syndrome.



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

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

• Theiler's virus "leader" (L) protein: Theiler's virus is a mouse picornavirus that has a striking ability to persist in the central nervous system in the presence of a strong and specific immune response. We study how the L protein of this virus and related cardioviruses interfere with innate immunity. 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. We currently analyze how the recruitment of these kinases by L relates to the different L protein activities.

• Interferon (IFN) response: One key molecule that can trigger IFN production by infected cells is double-stranded RNA (dsRNA). dsRNA is produced in infected cells, as a byproduct of viral replication. Cellular dsRNA sensing pathways participate in IFN production but also in the activation of antiviral effector proteins such as protein kinase R (PKR). PKR activation is observed in pathological conditions such as Aicardi-Goutières syndrome and systemic lupus erythematosus. We analyze the mechanisms that regulate dsRNA recognition in the cell, by proteins such as PKR.

Understanding the mechanisms leading to (aberrant) PKR activation is important to set up future therapeutic strategies that balance antiviral activities and risks of autoimmune effects.

Our group is also studying the specificities of the IFN-λ family of interferons in the antiviral defense. We showed previously that IFN-λ acts mostly on epithelial cells, thus acting to protect mucosal surfaces.

Staff members

Postdoctoral Fellows: Melissa Drappier, Frédéric Sorgeloos • **PhD Students:** Teresa Cesaro, Belén Lizcano-Perret • **Research Assistants:** Stéphane Messe, Fanny Wavreil • **Technical Assistant:** Danny Plessiet


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 work towards improving our understanding of the role of cytokines (small signaling proteins) in inflammation. More specifically, our research is focused on two cytokines, IL-9 and IL-22, crucial players in the inflammatory process, both of which were discovered by our lab.

IL-9 is a double-edged sword depending on disease. For instance, it 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, pointing to both IL-9 and the IL-9 receptor genes as major candidates for human asthma. We collaborate with pharmaceutical companies to produce molecules that can 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 and IL-22-related cytokines in skin inflammatory disorders including psoriasis, allergic contact dermatitis and urticaria. In collaboration with the dermatology department of University Hospital Saint-Luc, we have shown that IL-22-related cytokines are highly expressed in the skin of patients with these three inflammatory diseases. These results strongly suggest that these cytokines are involved in skin inflammatory processes. Indeed, we have been able to show that in animal models of psoriasis, administration of an antibody blocking IL-22 activity is able to decrease some features such as scaly lesions and redness, demonstrating the deleterious role of this cytokine in the disease.

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 can 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 aim to develop a therapy that blocks only the deleterious arm of IL-22 activity, leaving intact its beneficial functions in Crohn's disease.

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

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.

Metabolism and Hormones

Emile Van Schaftingen &
Maria Veiga-da-Cunha

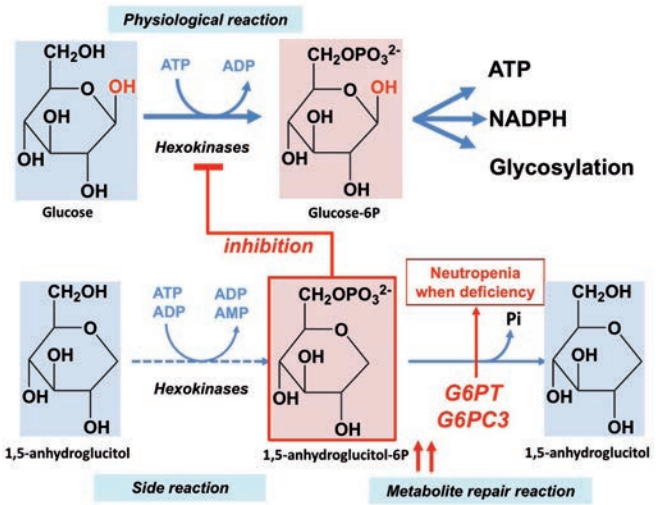
Metabolite Repair

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.

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 enzymes 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. Others serve to eliminate toxic phosphate esters produced by glycolytic enzymes, an abnormal intermediate in lipid synthesis and an abnormal form of NADH.



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. Inhibitors of the sodium-dependent glucose transporter SGLT2, which cause a depletion of 1,5-anhydroglucitol in serum, are presently tested to treat these two forms of neutropenia.

Staff members

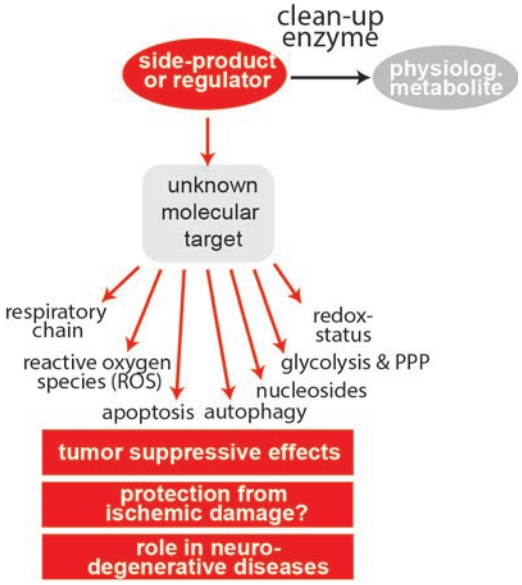
Senior Investigator: Elsa Wiame • **Postdoctoral Fellows:** Joseph Dewulf, Takfarinas Kentache • **Undergraduate Student:** Hernan Tirado • **Research Assistant:** Nathalie Chevalier • **Technical Assistant:** Karim Acherki • **Administrative Support:** Pauline Leverrier, Marie-Victoire Uwimana

Guido Bommer

Metabolism in Cancer & Other Diseases

Cells need to adjust their metabolism to fulfill changing needs for building blocks, energy and protection from stress. We search for vulnerabilities in known or newly discovered metabolic pathways that might be targeted in 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 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 bio-mass, 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.



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.

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.

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 ribitol-phosphorylation. Furthermore, we are following-up on observations that suggest that so far unknown biochemical changes may contribute to the development of Parkinson's disease.

Staff members

Senior Investigator: Isabelle Gerin • **Postdoctoral Fellows:** Marina Bury, Sven Potelle • **PhD Students:** Francesco Caligiore, Mathias Halbout, Isaac Heremans, Stéphanie Paquay, Benoît Ury • **Undergraduate Student:** Louison Descampe • **Research Assistant:** Julie Graff

Mark Rider

Protein Phosphorylation

We study control by protein phosphorylation in relation to diseases such as type 2 diabetes. AMP-activated protein kinase is our main interest. We also run the mass spectrometry protein analysis facility.

Metformin is the most prescribed drug used for the treatment of type 2 diabetes (T2D) 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 hypoxia or 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 is a well recognized 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. We found that genetic deletion of cytosolic 5'-nucleotidase-II (NT5C2) had beneficial effects in insulin-resistant mice on a high-fat diet (HFD) by lowering glycaemia and reducing body weight gain, although these effects seemed not to be AMPK-dependent. However, NT5C2 could be a viable drug target for the treatment of T2D. We recently isolated two isoprenylated flavonoids from the roots of a plant, *Dorstenia psilurus* (common dorstenia) used in African traditional medecine, that activated AMPK. The compounds increased the intracellular AMP:ATP ratio by inhibiting the mitochondrial respiratory chain, increased skeletal muscle glucose uptake and inhibited hepatocyte glucose production. Moreover, the compounds lowered blood gluose in vivo when administered to insulin-resistant mice on a HFD.

"Drug targeting AMPK and soluble NT5C2 could be a viable strategy for the treatment of type 2 diabetes."

In addition to our work on AMPK, we run the protein mass spectrometry (MS) protein analysis facility (MASSPROT) on the Brussels campus of UCLouvain. We developed a MS-based phosphoproteomics strategy, validated by identifying key metabolic enzymes whose phosphorylation increased in brown adipose tissue during ground squirrel hibernation. The use of MS for our research and collaborations has led to well over 110 publications. The acquisition by the de Duve Institute of the High Resolution/Accurate Mass Orbitrap Lumos has enabled us to perform quantitative proteomics and increases our capabilities to study other protein modifications. We released the first draft of the human ovarian proteome and identified a new class of holdases called 'chaperedoxins' that prevent the irreversible oxidation of proteins. We also participated in the identification of two enzymes involved in the post-translational modification of human actin that could be relevant to health and disease.

Staff members

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

Etienne Marbaix &
Patrick Henriet

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.

Endometrium Physiopathology

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
PhD Students: Charlotte Thieffry, Marie Van Wynendaele • **Undergraduate Student:** Katarzyna Glowacka • **Administrative Support:** Aimée-Lys Rusesabagina

Computational Biology

Modern high throughput biology produces huge amounts of data that can be analyzed, and the challenges of modern biology are statistical interpretation and integration of these data. Research and developments in computational biology and bioinformatics aim to provide the methods and tools to comprehend these high dimensional data and understand their underlying biological processes.

Laurent Gatto

Computational Biology & Bioinformatics

Our group uses statistical learning, computational techniques and visualization to analyze and understand high throughput and multivariate biological data and comprehend complex biological processes.

For the last decades, biology and biomedical sciences have seen an impressive increase in the size of the data that are collected as part of routine research projects. The increase in amount and complexity of these data lead some to call it a data deluge. Indeed, we have reached a situation where the sheer volume of data that is produced is overwhelming the capacity of individ-ual researchers and research groups to manage, analyze and extract meaningful information from them. This revolution is shifting biomedical research towards a quantitative, data-driven discipline. This evolution has been driven by technological breakthroughs that, today, allow us to sequence whole genomes, quantify the near complete set of transcripts or proteins, measure epigenetic modifications across whole genomes, assay proteins for post-translational modifications, interactions and localization. But the question remains: what to do with all that data?

"This revolution is shifting biomedical research towards a quantitative, data-driven discipline."

Our group works on diverse projects and benefits from computational and biological expertise. We work on transcriptomics and proteomics gene expression projects in collaboration with other research groups at the de Duve Institute, to identify differen-tially expressed genes and processes related to cancer development, cell signaling, or metabolomic disorders. We are also in-volved in single cell-level assays, at the RNA and protein level, to contribute to the identification of cell types and cell states in organ development or the immune response.

The lab is also heavily invested in the development of novel, open source research software, with a long-standing interest in mass spectrometry-based proteomics data. These include quantitative data processing and analysis, sub-cellular spatial prote-omics methods, or the identification of protein-protein interactions.

Finally, the lab is also involved in integrative omics, i.e the development of methods to integrate different types of omics data or experimental and publicly available resources. Indeed, it becomes essential to integrate different biological modalities or com-plementary resources to gain further insights into the complexity of biological processes and their regulation.

Clarity and traceability of the data and the analysis methodology enable us to better understand what we do, how and why we do it and consequently exploit complex data and comprehend the underlying biology. The collaborative and interdisciplinary nature of high throughput biology calls for open approaches, from communication between stake holders, open research and development and open dissemination of all research outputs, which our lab fully adheres to.

Staff members

Senior Investigator: Axelle Loriot • **PhD Students:** Chong Tang, Christophe Vanderaa • **Undergraduate Student:** Philippe Hauchamps • **Research Assistant:** Theo Killian • **Administrative Support:** Marjorie Decroly

Selected Publications

Stefan Constantinescu

1. Balligand T, Achouri Y, Pecquet C, Gaudray G, Colau D, Hug E, Rahmani Y, Stroobant V, Plo I, Vainchenker W, Kralovics R, Van den Eynde B, Defour J-P, Constantinescu SN. Knock-in of murine Calr del52 induces essential thrombocythemia with slow-rising dominance in mice and reveals key role of Calr exon 9 in cardiac development. Leukemia. 2020;34:510-21.

2. Pecquet C, Chachoua I, Roy A, Balligand T, Vertenoeil G, Leroy E, Albu RI, Defour J-P, Nivarthi H, Hug E, Xu E, Ould-Amer Y, Mouton C, Colau D, Vertommen D, Marlar SM, Marty C, Plo I, Vainchenker W, Kralovics R, Constantinescu SN. Calreticulin mutants as oncogenic rogue chaperones for TpoR and traffic-defective pathogenic TpoR mutants. Blood. 2019;133:2669-81.

3. Labuhn M, Perkins K, Papaemmanuil E, Matzk S, Varghese L, Metzner M, Kennedy A, Amstislavskiy V, Risch T, Bhayadia R, Samulowski D, Garnett C, Cruz Hernandez D, Stoilova B, Iotchkova V, Scheer C, Yoshida K, Schwarzer A, Taub J, Crispino JD, Weiss MJ, Hayashi A, Taga T, Ito E, Ogawa S, Reinhardt D, Yaspo ML, Campbell PJ, Roberts I, Constantinescu SN, Vyas P, Heckl D, Klusmann JH. Mechanisms of progression of myeloid preleukemia to transformed myeloid leukemia in children with Down syndrome. Cancer Cell. 2019;36:123-38.e10.

4. Leroy E, Balligand T, Pecquet C. Mouton C, Colau D, Shiau AK, Dusa A, Constantinescu SN. Differential effect of inhibitory strategies of the V617 mutant of JAK2 on cytokine receptor signaling. J Allergy Clin Immunol. 2019;144:224-35.

5. Chachoua I, Pecquet C, El-Khoury M, Nivarthi H, Albu RI, Marty C, Gryshkova V, Defour J-P, Vertenoeil G, Ngo A, Raslova H, Courtoy PJ, Choong ML, Plo I, Vainchenker W, Kralovics R, Constantinescu SN. Thrombopoietin receptor activation by myeloproliferative neoplasm associated calreticulin mutants. Blood. 2016;127:1325-35.

6. Defour J-P, Itaya M, Gryshkova V, Brett IC, Pecquet C, Sato T, Smith SO, Constantinescu SN. A tryptophan at the transmembrane-cytosolic junction modulates thrombopoietin receptor dimerization and activation. Proc Natl Acad Sci USA. 2013;110:2540-5.

7. Staerk J, Defour J-P, Pecquet C, Leroy E, Poirel HA, Brett I, Itaya M, Smith SS, Vainchenker W, Constantinescu SN. Orientation-specific signalling by thrombopoietin receptor dimers. EMBO J. 2011;30:4398-413.

8. Staerk J, Lacout C, Sato T, Smith SO, Vainchenker W, Constantinescu SN. An amphipathic motif at the transmembrane-cytoplasmic junction prevents autonomous activation of the thrombopoietin receptor. Blood. 2006;107:1864-71.

9. Staerk J, Kallin A, Demoulin J-B, Vainchenker W, Constantinescu SN. JAK1 and Tyk2 activation by the homologous polycythemia vera JAK2 V617F mutation: cross talk with IGF1 receptor. J Biol Chem. 2005;280:41893-9.

10. James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, Garcon L, Raslova H, Berger R, Bennaceur-Griscelli A, Villeval JL, Constantinescu SN, Casadevall N, Vainchenker W. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature. 2005;434:1144-8.

Jean-Baptiste Demoulin

1. Dachy G, de Krijger RR, Fraitag S, Théate I, Brichard B, Hoffman SB, Libbrecht L, Arts FA, Brouillard P, Vikkula M, Limaye N, Demoulin J-B. Association of PDGFRB mutations with pediatric myofibroma and myofibromatosis. JAMA Dermatol. 2019;155:946-50.

2. Bollaert E, de Rocca Serra A, Demoulin J-B. The HMG box transcription factor HBP1: a cell cycle inhibitor at the crossroads of cancer signaling pathways. Cell Mol Life Sci. 2019;76:1529-39.

3. Pond D*, Arts FA*, Mendelsohn NJ, Demoulin J-B, Scharer G, Messinger Y. A patient with germ-line gain-of-function PDGFRB p.N666H mutation and marked clinical response to imatinib. Genet Med. 2018;20:142-50. (*equal contribution)

4. Arts FA, Sciot R, Brichard B, Renard M, de Rocca Serra A, Dachy G, Noël LA, Velghe AI, Galant C, Debiec-Rychter M, Van Damme A, Vikkula M, Helaers R, Limaye N, Poirel HA, Demoulin J-B. PDGFRB gain-of-function mutations in sporadic infantile myofibromatosis. Hum Mol Genet. 2017; 26:1801-10.

5. Coomans de Brachène A, Demoulin J-B. FOXO transcription factors in cancer development and therapy. Cell Mol Life Sci. 2016;73:1159-72.

6. Arts FA, Chand D, Pecquet C, Velghe AI, Constantinescu S, Hallberg B, Demoulin J-B. PDGFRB mutants found in patients with familial infantile myofibromatosis or overgrowth syndrome are oncogenic and sensitive to imatinib. Oncogene. 2016; 35:3239-48.

7. Demoulin J-B, Essaghir A. PDGF receptor signaling networks in normal and cancer cells. Cytokine Growth Factor Rev. 2014; 25:273-83.

8. Velghe AI, Van Cauwenberghe S, Polyansky AA, Chand D, Montano-Almendras CP, Charni S, Hallberg B, Essaghir A, Demoulin J-B. PDGFRA alterations in cancer: characterization of a gain-of-function V536E transmembrane mutant as well as loss-of-function and passenger mutations. Oncogene. 2014;33:2568-76.

9. Toffalini F, Demoulin J-B. New insights into the mechanisms of hematopoietic cell transformation by activated receptor tyrosine kinases. Blood. 2010;116:2429-37.

10. Medves S, Duhoux FP, Ferrant A, Toffalini F, Ameye G, Libouton JM, Poirel HA, Demoulin J-B. KANK1, a candidate tumor suppressor gene, is fused to PDGFRB in an imatinib-responsive myeloid neoplasm with severe thrombocythemia. Leukemia. 2010; 24:1052-5.

Pierre Coulie

1. Narasimhaiah D, Legrand C, Damotte D, Remark R, Munda M, De Potter P, Coulie PG, Vikkula M, Godfraind C. DNA alteration-based classification of uveal melanoma gives better prognostic stratification than immune infiltration, which has a neutral effect in high-risk group. Cancer Med. 2019;8:3036-46.

2. Dheur M-S, Poirel HA, Ameye G, Tilman G, Saussoy P, Defour J-P, Camboni A, Van Den Neste E, Coulie PG, van Baren N. Characterization of two new high-grade B-cell lymphoma cell lines with MYC and BCL2 rearrangements that are suitable for in vitro drug sensitivity studies. Leuk Lymphoma. 2019;60:1043-52.

3. 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.

4. Gross S, Erdmann M, Haendle I, Voland S, Berger T, Schultz E, Strasser E, Dankerl P, Janka R, Schliep S, Heinzerling L, Sotlar K, Coulie P, Schuler

G, Schuler-Thurner B. Twelve-year survival and immune correlates in dendritic cell-vaccinated melanoma patients. JCI Insight. 2017;2:e91438.

5. Lethé B, Snauwaert S, Bricard O, Schroder D, Gomard T, Hames G, Muller C, Lurquin C, Gauthy E, Essaghir A, Vandekerckhove B, Coulie PG. A new transcript in the TCRB locus unveils the human ortholog of the mouse pre-Dss1 promoter. Immun Inflamm Dis. 2017;5:346-54.

6. Kunert A, van Brakel M, van Steenbergen-Langeveld S, da Silva M, Coulie PG, Lamers C, Sleijfer S, Debets R. MAGE-C2-Specific TCRs combined with epigenetic drug-enhanced antigenicity yield robust and tumor-selective T cell responses. J Immunol. 2016;197:2541-52.

7. Cochez PM, Michiels C, Hendrickx E, Van Belle AB, Lemaire MM, Dauguet N, Warnier G, de Heusch M, Togbe D, Ryffel B, Coulie PG, Renauld J-C, Dumoutier L. AhR modulates the IL-22-producing cell proliferation/recruitment in imiquimod-induced psoriasis mouse model. Eur J Immunol. 2016;46:1449-59.

8. Coulie PG, Van den Eynde BJ, van der Bruggen P, Boon T. Tumour antigens recognized by T lymphocytes: at the core of cancer immunotherapy. Nat Rev Cancer. 2014;14:135-46.

9. Cipponi A, Mercier M, Seremet T, Baurain JF, Theate I, van den Oord J, Stas M, Boon T, Coulie PG, van Baren N. Neogenesis of lymphoid structures and antibody responses occur in human melanoma metastases. Cancer Res. 2012;72:3997-4007.

10. Corbière V, Chapiro J, Stroobant V, Ma W, Lurquin C, Lethé B, van Baren N, Van den Eynde BJ, Boon T, Coulie PG. Antigen spreading contributes to MAGE Vaccination-induced regression of melanoma metastases. Cancer Res. 2011;71:1253-62.

Sophie Lucas

1. 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.

2. Stockis J, Liénart S, Colau D, Collignon A, Nishimura SL, Sheppard D, Coulie PG, Lucas S. Blocking immunosuppression by human Tregs in vivo with antibodies targeting integrin αVβ8. Proc Natl Acad Sci USA. 2017;114:E10161-8.

3. Li Y, Strick-Marchand H, Lim AI, Ren J, Masse-Ranson G, Li D, Jouvion G, Rogge L, Lucas S, Li B, Di Santo JP. Modeling IL-2 therapy in human immune system mice reveals the critical role of regulatory T cells to control toxicity. Nat Commun. 2017;8:1762.

4. Dedobbeleer O, Stockis J, van der Woning B, Coulie PG, Lucas S. Cutting Edge: Active TGF-beta1 Released from GARP/TGF-beta1 complexes on the surface of stimulated human B lymphocytes increases class-switch recombination and production of IgA. J Immunol. 2017;199:391-6.

5. Wilgenhof S, Corthals J, Heirman C, van Baren N, Lucas S, Kvistborg P, Thielemans K, Neyns B. Phase II study of autologous monocyte-derived mRNA electroporated dendritic cells (TriMixDC-MEL) plus Ipilimumab in patients with pretreated advanced melanoma. J Clin Oncol. 2016;34:1330-8.

6. Cuende J, Liénart S, Dedobbeleer O, van der Woning B, De Boeck G, Stockis J, Huygens C, Colau D, Somja J, Delvenne P, Hannon M, Baron F, Dumoutier L, Renauld J-C, De Haard H, Saunders M, Coulie PG, Lucas S. Monoclonal antibodies against GARP/TGF-beta1 complexes inhibit the immunosuppressive activity of human regulatory T cells in vivo. Sci Transl Med. 2015;7:284ra56.

7. Huygens C, Liénart S, Dedobbeleer O, Stockis J, Gauthy E, Coulie PG, Lucas S. Lysosomal-associated transmembrane protein 4B (LAPTM4B) decreases transforming growth factor beta1 (TGF-beta1) production in human regulatory T cells. J Biol Chem. 2015;290:20105-16.

8. Gauthy E, Cuende J, Stockis J, Huygens C, Lethe B, Collet J-F, Bommer G, Coulie PG, Lucas S. GARP is regulated by miRNAs and controls latent TGF-beta1 production by human regulatory T cells. PLoS One. 2013;8:e76186.

9. Lucas S, van Baren N, De Smet C, Coulie PG. Demethylation of the FOXP3 gene in human melanoma cells precludes the use of this epigenetic mark for quantification of Tregs in unseparated melanoma samples. Int J Cancer. 2012;130:1960-6.

10. Stockis J, Colau D, Coulie PG, Lucas S. Membrane protein GARP is a receptor for latent TGF-β on the surface of activated human Treg. Eur J Immunol. 2009;39:3296-300.

Benoît Van den Eynde

1. Hoffmann D, Dvorakova T, Stroobant V, Bouzin C, Daumerie A, Solvay M, Klaessens S, Letellier M-C, Renauld J-C, van Baren N, Lelotte J, Marbaix E, Van den Eynde BJ. Tryptophan 2,3-dioxygenase expression identified in human hepatocellular carcinoma cells and in intratumoral pericytes of most cancers. Cancer Immunol Res. 2020;8:19-31.

2. Schramme F, Crosignani S, Frederix K, Hoffmann D, Pilotte L, Stroobant V, Preillon J, Driessens G, Van den Eynde BJ. Inhibition of tryptophan-dioxygenase activity increases the antitumor efficacy of immune checkpoint inhibitors. Cancer Immunol Res. 2020;8:32-45.

3. Ma W, Stroobant V, Heirman C, Thielemans K, Mulder A, van der Bruggen P, Van den Eynde BJ. The vacuolar pathway of long peptide cross-presentation can be TAP-dependent. J Immunol. 2019;202:451-9.

4. Zhu J, Powis de Tenbossche CG, Cane S, Colau D, van Baren N, Lurquin C, Schmitt-Verhulst A-M, Liljeström P, Uyttenhove C, Van den Eynde BJ. Resistance to cancer immunotherapy mediated by apoptosis of tumor-infiltrating lymphocytes. Nat Commun. 2017; 8:1404.

5. Hennequart M, Pilotte L, Cane S, Hoffmann D, Stroobant V, De Plaen E, Van den Eynde BJ. Constitutive IDO1 expression in human tumors is driven by cyclooxygenase-2 and mediates intrinsic immune resistance. Cancer Immunol Res. 2017;5:695–709.

6. Pilotte L, Larrieu P, Stroobant V, Colau D, Dolušić E, Frédérick R, De Plaen E, Uyttenhove C, Wouters J, Masereel B, Van den Eynde BJ. Reversal of tumoral immune resistance by inhibition of tryptophan 2,3-dioxygenase. Proc Natl Acad Sci USA. 2012;109:2497-502.

7. Guillaume B, Chapiro J, Stroobant V, Colau D, Van Holle B, Parvizi G, Bousquet-Dubouch M-P, Théate I, Parmentier N, Van den Eynde BJ. Two abundant proteasome subtypes that uniquely process some antigens presented by HLA class I molecules. Proc Natl Acad Sci USA. 2010;107:18599-604.

8. Parmentier N, Stroobant V, Colau D, de Diesbach P, Morel S, Chapiro J, van Endert P, Van den Eynde BJ. Production of an antigenic peptide by insulin-degrading enzyme. Nat Immunol. 2010;11:449-54.

9. Warren EH, Vigneron NM, Coulie PG, Gavin MA, Stroobant V, Chapiro J, Dalet A, Tykodi SS, Xuereb SM, Mito JK, Riddell SR, Van den Eynde BJ. An antigen produced by splicing of noncontiguous peptides in the reverse order. Science. 2006;313:1444-7.

10. Vigneron N, Stroobant V, Chapiro J, Ooms A, Degiovanni G, Morel S, van der Bruggen P, Boon T, Van den Eynde BJ. An antigenic peptide produced by peptide splicing in the proteasome. Science. 2004;304:587-90.

Pierre van der Bruggen

1. Ma W, Stroobant V, Heirman C, Sun Z, Thielemans K, Mulder A, van der Bruggen P, Van den Eynde BJ. The vacuolar pathway of long peptide cross-presentation can be TAP dependent. J Immunol. 2019;202:451-9.

2. Boon L, Ugarte-Berzal E, Martens E, Vandooren J, Rybakin V, Colau D, Gordon-Alonso M, van der Bruggen P, Stöcker W, Becker-Pauly C, Witters P, Morava-Kozics E, Jaeken J, Proost P, Opdenakker G. Propeptide glycosylation and galectin-3 binding decrease proteolytic activation of human proMMP-9/progelatinase B. FEBS J. 2019;286:930-45.

3. Gordon-Alonso M, Bruger AM, van der Bruggen P. Extracellular galectins as controllers of cytokines in hematological cancer. Blood. 2018;132:484-91.

4. Bruger AM, Dorhoi A, Esendagli G, Barczyk-Kahlert K, van der Bruggen P, Lipoldova M, Perecko T, Santibanez J, Saraiva M, Van Ginderachter JA, Brandau S. How to measure the immunosuppressive activity of MDSC: assays, problems and potential solutions. Cancer Immunol Immunother. 2019;68:631-44.

5. Gordon-Alonso M, Hirsch T, Wildmann C, van der Bruggen P. Galectin-3 captures interferon-gamma in the tumor matrix reducing chemokine gradient production and T-cell tumor infiltration. Nat Commun. 2017;8:793.

6. Lu YC, Parker LL, Lu T, Zheng Z, Toomey MA, White DE, Yao X, Li YF, Robbins PF, Feldman SA, van der Bruggen P, Klebanoff CA, Goff SL, Sherry RM, Kammula US, Yang JC, Rosenberg SA. Treatment of patients with metastatic cancer using a major histocompatibility complex class II-restricted T-cell receptor targeting the cancer germline antigen MAGE-A3. J Clin Oncol. 2017;35:3322-9.

7. Petit AE, Demotte N, Scheid B, Wildmann C, Bigirimana R, Gordon-Alonso M, Carrasco J, Valitutti S, Godelaine D, van der Bruggen P. A major secretory defect of tumour infiltrating T lymphocytes due to galectin impairing LFA-1-mediated synapse completion. Nat Commun. 2016; 7:12242.

8. Demotte N, Stroobant V, Courtoy PJ, Van Der Smissen P, Colau D, Luescher IF, Hivroz C, Nicaise J, Squifflet J-L, Mourad M, Godelaine D, Boon T, van der Bruggen P. Restoring the association of the T cell receptor with CD8 reverses anergy in human tumor infiltrating lymphocytes. Immunity. 2008;28: 414-24.

9. Boël P, Wildmann C, Sensi M-L, Brasseur R, Renauld J-C, Coulie P, Boon T, van der Bruggen P. BAGE, a new gene encoding an antigen recognized on human melanomas by cytolytic T lymphocytes. Immunity. 1995;2:167-75.

10. van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, Boon T. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science.1991;254:1643-7.

Donatienne Tyteca

1. Conrard L, Tyteca D. Regulation of membrane calcium transport proteins by the surrounding lipid environment. Biomolecules. 2019;9(10).

2. Verstraeten SL, Deleu M, Janikowska-Sagan M, Claereboudt EJS, Lins L, Tyteca D, Mingeot-Leclercq M-P. The activity of the saponin ginsenoside Rh2 is enhanced by the interaction with membrane sphingomyelin but depressed by cholesterol. Sci Rep. 2019;9:7285.

3. Conrard L, Stommen A, Cloos A-S, Steinkühler J, Dimova R, Pollet H, Tyteca D. Spatial relationship and functional relevance of three lipid domain populations at the erythrocyte surface. Cell Physiol Biochem. 2018;51:1544–65.

4. Pollet H, Conrard C, Cloos A-S, Tyteca D. Plasma membrane lipid domains as platforms for vesicle biogenesis and shedding? Biomolecules. 2018;8:94.

5. Léonard C, Pollet H, Vermylen C, Gov N, Tyteca D*, Mingeot-Leclercq M-P*. Tuning of differential lipid order between submicrometric domains and surrounding membrane upon erythrocyte reshaping. Cell Physiol Biochem. 2018;48:2563–82. (*equal contribution)

6. Dumitru AC, Conrard L, Lo Giudice C, Henriet P, Veiga-da-Cunha M, Derclaye S, Tyteca D, Alsteens D. High-resolution mapping and recognition of lipid domains using AFM with toxin-derivatized probes. Chem Commun (Camb). 2018;54:6903-6.

7. Gournas C, Gkionis S, Carquin M, Twyffels L, Tyteca D, André B. Conformation-dependent partitioning of yeast nutrient transporters into starvation-protective membrane domains. Proc Natl Acad Sci USA. 2018;115:E3145-54.

8. Léonard C, Alsteens D, Dumitru AC, Mingeot-Leclercq M-P, Tyteca D. Lipid domains and membrane (re)shaping: from biophysics to biology. In: Epand RM and Ruysschaert J-M, eds. The biophysics of cell membranes (Springer Series in Biophysics 19), Chapter 5. Springer Nature (Singapore). 2017 pp.121-75.

9. Léonard C, Conrard L, Guthmann M, Pollet H, Carquin M, Vermylen C, Gailly P, Van Der Smissen P, Mingeot-Leclercq M-P, Tyteca D. Contribution of plasma membrane lipid domains to red blood cell (re)shaping. Sci Rep. 2017;7:4264.

10. Carquin M, D'Auria L, Pollet H, Bongarzone ER, Tyteca D. Recent progress on lipid lateral heterogeneity in plasma membranes: From rafts to submicrometric domains. Progr Lipid Res. 2016;62:1-24.

Nisha Limaye

1. Dachy G, de Krijger RR, Fraitag S, Théate I, Brichard B, Hoffman SB, Libbrecht L, Arts FA, Brouillard P, Vikkula M, Limaye N, Demoulin J-B. Association of PDGFRB mutations with pediatric myofibroma and myofibromatosis. JAMA Dermatol. 2019;155:946-50.

2. Arts FA, Sciot R, Brichard B, Renard M, de Rocca Serra A, Dachy G, Noël LA, Velghe AI, Galant C, Debiec-Rychter M, Van Damme A, Vikkula M, Helaers R, Limaye N, Antoine-Poirel H, Demoulin J-B. PDGFRB gain-of-function mutations in sporadic infantile myofibromatosis. Hum Mol Genet. 2017;26:1801-10.

3. Wong EB, Soni C, Chan AY, Domeier PP, Shwetank, Abraham T, Limaye N, Khan TN, Elias MJ, Chodisetti SB, Wakeland EK, Rahman ZS. B Cell-

intrinsic CD84 and Ly108 maintain germinal center B cell tolerance. J Immunol. 2015;194:4130-43.

4. Nätynki M, Kangas J, Miinalainen I, Sormunen R, Pietilä R, Soblet J, Boon LM, Vikkula M, Limaye N, Eklund L. Common and specific effects of TIE2 mutations causing venous malformations. Hum Mol Genet. 2015;24:6374-89.

5. Limaye N, Kangas J, Mendola A, Godfraind C, Schlögel MJ, Helaers R, Eklund L, Boon LM, Vikkula M. (2015) Somatic activating PIK3CA mutations cause venous malformation. Am J Hum Genet. 2015;97: 914-21.

6. Boscolo E, Limaye N, Huang L, Kang KT, Soblet J, Uebelhoer M, Mendola A, Natynki M, Seront E, Dupont S, Hammer J, Legrand C, Brugnara C, Eklund L, Vikkula M, Bischoff J, Boon LM. Rapamycin improves TIE2-mutated venous malformation in murine model and human subjects. J Clin Invest. 2015;125:3491-504.

7. Uebelhoer M, Nätynki M, Kangas J, Mendola A, Nguyen H, Soblet J, Godfraind C, Boon LM, Eklund L, Limaye N*, Vikkula M*. Venous malformation-causative TIE2 mutations mediate an AKT-dependent decrease in PDGFB. Hum Mol Genet. 2013;22:3438-48. (*equal contribution)

8. Limaye N*, Wouters V*, Uebelhoer M, Tuominen M, Wirkkala R, Mulliken JB, Eklund L, Boon LM, Vikkula M. (2009) Somatic mutations in the angiopoietin receptor gene TIE2 cause solitary and multiple sporadic venous malformations. Nat Genet. 2009;41:118-24. (*equal contribution)

9. Limaye N, Belobrajdic K, Wandstrat AE, Bonhomme F, Edwards SV, Wakeland EK. Prevalence and evolutionary origins of autoimmune susceptibility alleles in natural mouse populations. Genes Immun. 2008;9:61-8.

10. Wandstrat AE*, Nguyen C*, Limaye N*, Chan AY, Subramanian S, Tian X-H, Yim Y-S, Pertsemlidis A, Gardner, HR Jr, Morel L, Wakeland EK. Association of extensive polymorphisms in the SLAM/CD2 gene cluster with murine lupus. Immunity. 2004;21:769-80. (*equal contribution)

Miikka Vikkula

1. Seront E, Van Damme A, Boon LM, Vikkula M. Rapamycine and treatment of venous malformations. Curr Opin Hematol. 2019;26:185-92.

2. Demeer B, Revencu N, Helaers R, Gbaguidi C, Dakpe S, François G, Devauchelle B, Bayet B, Vikkula M. Likely pathogenic variants in one third of non-syndromic discontinuous cleft lip and palate patients. Genes (Basel). 2019;10:833.

3. Hammer J, Seront E, Duez S, Dupont S, Van Damme A, Schmitz S, Hoyoux C, Chopinet C, Clapuyt P, Hammer F, Vikkula M, Boon LM. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Orphanet J Rare Dis. 2018;13:191.

4. Quéré I, Nagot N, Vikkula M. Incidence of cellulitis among children with primary lymphedema. New Engl J Med. 2018;378:2047-8.

5. Basha M, Demeer B, Revencu N, Helaers R, Theys S, Bou Saba S, Boute O, Devauchelle B, Francois G, Bayet B, Vikkula M. Whole exome sequencing identifies mutations in 10% of patients with familial non-syndromic cleft lip and/or palate in genes mutated in well-known syndromes. J Med Genet. 2018;55:449-58.

6. Fastré E, Lanteigne LE, Helaers R, Giacalone G, Revencu N, Dionyssiou D, Demiri E, Brouillard P, Vikkula M. Splice-site mutations in VEGFC cause loss of function and Nonne-Milroy-like primary lymphedema. Clin Genet. 2018;94:179-81.

7. Brouillard P, Dupont L, Helaers R, Coulie R, Tiller GE, Peeden J, Colige A, Vikkula M. Loss of ADAMTS3 activity causes Hennekam lymphangiectasia-lymphedema syndrome 3. Hum Mol Genet. 2017;26:4095-104.

8. Amyere M, Revencu N, Helaers R, Pairet E, Baselga E, Cordisco M, Chung W, Dubois J, Lacour JP, Martorell L, Mazereeuw-Hautier J, Pyeritz RE, Amor DJ, Bisdorff A, Blei F, Bombei H, Dompmartin A, Brooks D, Dupont J, González-Enseñat MA, Frieden I, Gérard M, Kvarnung M, Hanson-Kahn AK, Hudgins L, Léauté-Labrèze C, McCuaig C, Metry D, Parent P, Paul C, Petit F, Phan A, Quere I, Salhi A, Turner A, Vabres P, Vicente A, Wargon O, Watanabe S, Weibel L, Wilson A, Willing M, Mulliken JB, Boon LM, Vikkula M. Germline loss-of-function mutations in EPHB4 cause a second form of capillary malformation-arteriovenous malformation (CM-AVM2) deregulating RAS-MAPK signaling. Circulation. 2017;136:1037-48.

9. Boscolo E, Limaye N, Huang L, Kang KT, Soblet J, Uebelhoer M, Mendola A, Natynki M, Seront E, Dupont S, Hammer J, Legrand C, Brugnara C, Eklund L, Vikkula M*, Bischoff J*, Boon LM*. Rapamycin improves TIE2-mutated venous malformation in murine model and human subjects. J Clin Invest. 2015;125:3491-504. (*equal contribution)

10. Limaye N, Wouters V, Uebelhoer M, Tuominen M, Wirkkala R, Mulliken JB, Eklund L, Boon LM, Vikkula M. Somatic mutations in angiopoïetin-receptor gene TEK cause solitary and multiple sporadic venous malformations. Nat Genet. 2009;41:118-24.

Charles De Smet

1. Fain JS, Van Tongelen A, Loriot A, De Smet C. Epigenetic coactivation of MAGEA6 and CT-GABRA3 defines orientation of a segmental duplication in the human X chromosome. Cytogenet Genome Res. 2019;159:12-8.

2. Gérard C, Di-Luoffo M, Gonay L, Caruso S, Couchy G, Loriot A, Castven D, Tao J, Konobrocka K, Cordi S, Monga SP, Hanert E, Marquardt JU, Zucman-Rossi J, Lemaigre FP. Dynamics and predicted drug response of a gene network linking dedifferentiation with beta-catenin dysfunction in hepatocellular carcinoma. J Hepatol. 2019;71:323-32.

3. De Pauw A, Andre E, Sekkali B, Bouzin C, Esfahani H, Barbier N, Loriot A, De Smet C, Vanhoutte L, Moniotte S, Gerber B, di Mauro V, Catalucci D, Feron O, Hilfiker-Kleiner D, Balligand J-L. Dnmt3a-mediated inhibition of Wnt in cardiac progenitor cells improves differentiation and remote remodeling after infarction. JCI Insight. 2017;2:e91810.

4. Van Tongelen A, Loriot A, De Smet C. Oncogenic role of DNA hypomethylation through the activation of cancer-germline genes. Cancer Lett. 2017;396:130-7.

5. Cannuyer J, Van Tongelen A, Loriot A, De Smet C. A gene expression signature identifying transient DNMT1 depletion as a causal factor of cancer-germline gene activation in melanoma. Clin Epigenetics. 2015;7:114.

6. Loriot A*, Van Tongelen A*, Blanco J, Klaessens S, Cannuyer J, van Baren N, Decottignies A, De Smet C. A novel cancer-germline gene

carrying pro-metastatic miR-105 and TET-targeting miR-767 induced by DNA hypomethylation in tumors. Epigenetics. 2014;9:1163-71. (*equal contribution)

7. De Smet C and Loriot A. DNA hypomethylation and activation of germline-specific genes in cancer. In: Karpf AR, ed. Epigenetic alterations in oncogenesis (Adv Exp Med Biol 754), Chapter 7. Springer (NY). 2013 pp.149-66.

8. De Smet C and Loriot A. DNA hypomethylation in cancer: epigenetic scars of a neoplastic journey. Epigenetics. 2010;5:206-13.

9. Loriot A, De Plaen E, Boon T, De Smet C. Transient down-regulation of DNMT1 methyltransferase leads to activation and stable hypomethylation of MAGEA1 in melanoma cells. J Biol Chem. 2006;281:10118-26.

10. De Smet C, Loriot A, Boon T. Promoter-dependent mechanism leading to selective hypomethylation within the 5′ region of gene MAGE-A1 in tumors cells. Mol Cell Biol. 2004;24:4781-90.

Anabelle Decottignies

1. Claude E, Episkopou H, Decottignies A. Specific death of ALT cells through TSPYL5 depletion. Mol Cell Oncol. 2019;6:e1651603.

2. Bevernaegie R, Doix B, Bastien E, Diman A, Decottignies A, Feron O, Elias B. J Am Chem Soc. 2019;141:18486-91.

3. Episkopou H*, Diman A*, Claude E, Viceconte N, Decottignies A. TSPYL5 depletion induces specific death of ALT cells through USP7-dependent proteasomal degradation of POT1. Mol Cell. 2019;75:469-82. (*equal contribution)

4. Benyelles M, Episkopou H, O'Donohue MF, Kermasson L, Frange P, Poulain F, Burcu Belen F, Polat M, Bole-Feysot C, Langa-Vives F, Gleizes PE, de Villartay JP, Callebaut I, Decottignies A*, Revy P*. Impaired telomere integrity and rRNA biogenesis in PARN-deficient patients and knock-out models. EMBO Mol Med. 2019;11:e10201. (*equal contribution)

5. Diman A, Decottignies A. Genomic origin and nuclear localization of TERRA telomeric repeat-containing RNA: from darkness to dawn. FEBS J. 2018;285:1389-98.

6. Viceconte N, Dheur M-S, Majerova E, Pierreux CE, Baurain J-F, van Baren N, Decottignies A. Highly aggressive metastatic melanoma cells unable to maintain telomere length. Cell Rep. 2017;19:2529-43.

7. Diman A*, Boros J*, Poulain F, Rodriguez J, Purnelle M, Episkopou H, Bertrand L, Francaux M, Deldicque L, Decottignies A. Nuclear respiratory factor 1 and endurance exercise promote human telomere transcription. Sci Adv. 2016;2:e1600031. (*equal contribution)

8. Episkopou H*, Draskovic I*, Van Beneden A*, Tilman G, Mattiussi M, Gobin M, Arnoult N, Londoño-Vallejo A, Decottignies A. Alternative lengthening of telomeres is characterized by reduced compaction of telomeric chromatin. Nucleic Acids Res. 2014;42:4391-405. (*equal contribution)

9. Boros J*, Arnoult N*, Stroobant V, Collet J-F, Decottignies A. Polycomb repressive complex 2 and H3K27me3 cooperate with H3K9 methylation to maintain heterochromatin protein 1alpha at chromatin. Mol Cell Biol. 2014;34:3662-74. (*equal contribution)

10. Arnoult N*, Van Beneden A*, Decottignies A. Telomere length regulates TERRA levels through increased trimethylation of telomeric H3K9 and HP1alpha. Nat Struct Mol Biol. 2012;19:948-56. (*equal contribution)

Frédéric Lemaigre & Patrick Jaquemin

1. Collet L, Ghurburrun E, Meyers N, Assi M, Pirlot B, Leclercq IA, Couvelard A, Komuta M, Cros J, Demetter P, Lemaigre FP, Borbath I, Jacquemin P. Kras and Lkb1 mutations synergistically induce intraductal papillary mucinous neoplasm derived from pancreatic duct cells. Gut. 2019; epub Jun 1.

2. Gérard C, Di-Luoffo M, Gonay L, Caruso S, Couchy G, Loriot A, Castven D, Tao J, Konobrocka K, Cordi S, Monga SP, Hanert E, Marquardt JU, Zucman-Rossi J, Lemaigre FP. Dynamics and predicted drug response of a gene network linking dedifferentiation with beta-catenin dysfunction in hepatocellular carcinoma. J Hepatol. 2019;71:323-32.

3. Lesaffer B, Verboven E, Van Huffel L, Moya I, van Grunsven L, Leclercq I, Lemaigre F, Halder G. Comparison of the Opn-CreER and Ck19-CreER drivers in bile ducts of normal and injured mouse livers. Cells. 2019;8:380.

4. Gérard C, Lemaigre F, Gonze D. Modeling the dynamics of Let-7-coupled gene regulatory networks linking cell proliferation to malignant transformation. Front Physiol. 2019;10:848.

5. Demarez C, Gérard C, Cordi S, Poncy A, Achouri Y, Dauguet N, Rosa DA, Gunning PT, Manfroid I, Lemaigre FP. MiR-337-3p controls hepatobiliary gene expression and transcriptional dynamics during hepatic cell differentiation. Hepatology. 2018;67:313-27.

6. Ober EA, Lemaigre FP. Development of the liver: Insights into organ and tissue morphogenesis. J Hepatol. 2018;68:1049-62.

7. Augereau C, Collet L, Vargiu P, Guerra C, Ortega S, Lemaigre FP, Jacquemin P. Chronic pancreatitis and lipomatosis are associated with defective function of ciliary genes in pancreatic ductal cells. Hum Mol Gen. 2016;25:5017-22.

8. Prévot PP, Augereau C, Simion A, Van den Steen G, Dauget N, Lemaigre FP, Jacquemin P. Let-7b and miR-495 stimulate differentiation and prevent metaplasia of pancreatic acinar cells by repressing HNF6. Gastroenterology. 2013;145:668-78.

9. Prévot PP, Simion A, Grimont A, Colletti M, Khalaileh A, Van den Steen G, Sempoux C, Xu X, Roelants V, Hald J, Bertrand L, Heimberg H, Konieczny SF, Dor Y, Lemaigre FP, Jacquemin P. Role of the ductal transcription factors HNF6 and Sox9 in pancreatic acinar-to-ductal metaplasia. Gut. 2012;61:1723-32.

10. Carpentier R, Español Suñer R, Van Hul N, Kopp JL, Beaudry JB, Cordi S, Antoniou A, Raynaud P, Lepreux S, Jacquemin P, Leclercq IA, Sander M, Lemaigre FP. Embryonic ductal plate cells give rise to cholangiocytes, periportal hepatocytes and adult liver progenitor cells. Gastroenterology. 2011;141:1432-8.

Wen-Hui Lien

1. Lang CMR, Chan CK, Veltri A, Lien WH. Wnt signaling pathways in keratinocyte carcinomas. Cancers. 2019;11:1216.

2. Veltri A, Lang C, Lien WH. Concise Review: Wnt signaling pathways in skin development and epidermal stem cells. Stem Cells. 2018;36:22-35.

3. Jossin Y, Lee M, Klezovitch O, Kon E, Alexia C, Lien WH, Fernandez TE, Cooper JA, Vasioukhin V. Llgl1 connects cell polarity with cell-cell adhesion in embryonic neural stem cells. Dev Cell. 2017;41:481-95.

4. Li P, Silvis MR, Honaker Y, Lien WH, Arron ST, Vasioukhin V. αE-Catenin inhibits a Src-YAP1 oncogenic module that couples tyrosine kinases and the effector of Hippo signaling pathway. Genes Dev. 2016;30:798-811.

5. Lien WH, Fuchs E. Wnt some lose some: transcriptional governance of stem cells by Wnt/β-catenin signaling. Genes Dev. 2014;28:1517-32.

6. Lien WH, Polak L, Lin M, Lay K, Zheng D, Fuchs E. In vivo transcriptional governance of hair follicle stem cells by canonical Wnt regulators. Nat Cell Biol. 2014;16:179-90.

7. Beronja S, Janki P, Heller E, Lien WH, Keyes BE, Oshimori N, Fuchs E. RNAi screens in mice identify physiological regulators of oncogenic growth. Nature. 2013;501:185-90.

8. Lien WH, Guo X, Polak L, Lawton LN, Young RA, Zheng D, Fuchs E. Genome-wide maps of histone modifications unwind in vivo chromatin states of the hair follicle lineage. Cell Stem Cell. 2011;9:219-32.

9. Ezhkova E, Lien WH, Stokes N, Pasolli HA, Silva JM, Fuchs E. EZH1 and EZH2 cogovern histone H3K27 trimethylation and are essential for hair follicle homeostasis and wound repair. Genes Dev. 2011;25:485-98.

10. Lien WH, Klezovitch O, Fernandez TE, Delrow J, Vasioukhin V. αE-Catenin controls cerebral cortical size by regulating the hedgehog signaling pathway. Science. 2006;311:1609-12.

Christophe Pierreux

1. Grieco G*, Wang T*, Delcorte O*, Spourquet C*, Janssens V, Strickaert A, Gaide Chevronnay HP, Liao XH, Bilanges B, Refetoff S, Vanhasebroeck B, Maenhaut C, Courtoy PJ*, Pierreux CE*. Class III PI3k Vps34 controls thyroid hormone production by regulating thyroglobulin iodination, lysosomal proteolysis, and tissue homeostasis. Thyroid. 2020;30:133-46. (*equal contribution)

2. Janssens V, Gaide-Chevronnay HP, Marie S, Vincent M-F, Nevo N, Vaino S, Nielsen R, Christensen EI, Jouret F, Antignac C, Pierreux CE*, Courtoy PJ*. Protection of cystinotic mice kidney by Wnt4 CRE-driven megalin ablation supports an endocytosis-based disease mechanism. J Am Soc Nephrol. 2019;30:2177-90. (*equal contribution)

3. Heymans C, Degosserie J, Spourquet C, Pierreux CE. Pancreatic acinar differentiation is guided by differential laminin deposition. Sci Rep. 2019;9:2711.

4. Degosserie J, Heymans C, Spourquet C, Halbout M, D'Auria L, Van Der Smissen P, Vertommen D, Courtoy PJ, Tyteca D, Pierreux CE. Extracellular vesicles produced by endothelial progenitor cells promote thyroid follicle formation. J Extracell Vesicles. 2018;7:1487250.

5. Bulanova EA, Koudan EV, Degosserie J, Heymans C, Pereira FD, Parfenov VA, Sun Y, Wang Q, Akhmedova SA, Sviridova IK, Sergeeva NS, Frank GA, Khesuani YD, Pierreux CE, Mironov VA. Bioprinting of functional vascularized mouse thyroid gland construct. Biomaterials. 2017;9:034105.

6. Villacorte M*, Delmarcelle AS*, Lernoux M, Bouquet M, Lemoine P, Bolsée J, Umans L, de Sousa Lopes SC, Van Der Smissen P, Sasaki T, Bommer G, Henriet P, Refetoff S, Lemaigre FP, Zwijsen A, Courtoy PJ, Pierreux CE. Thyroid follicle development requires Smad1/Smad5- and endothelial-dependent basement membrane assembly. Development. 2016;143:1958-70. (*equal contribution)

7. Gaide Chevronnay HP, Janssens V, Van Der Smissen P, Liao XH, Abid Y, Nevo N, Antignac C, Refetoff S, Cherqui S, Pierreux CE*, Courtoy PJ*. A mouse model suggests two mechanisms for thyroid alterations in infantile cystinosis: decreased thyroglobulin synthesis due to endoplasmic reticulum stress/unfolded protein response and impaired lysosomal processing. Endocrinology. 2015;156:2349-64. (*equal contribution)

8. Gaide Chevronnay HP, Janssens V, Van Der Smissen P, N'Kuli F, Nevo N, Guiot Y, Levtchenko E, Marbaix E, Pierreux CE, Cherqui S, Antignac C, Courtoy PJ. Time-course of pathogenic and adaptative mechanisms in cystinotic mice kidneys. J Am Soc Nephrol. 2014;25:1256-69.

9. Hick AC, Delmarcelle AS, Bouquet M, Klotz S, Copetti T, Forez C, Van Der Smissen P, Sonveaux P, Feron O, Courtoy PJ, Pierreux CE. Reciprocal epithelial: endothelial paracrine interactions during thyroid development govern follicular organization and C-cells differentiation. Dev Biol. 2013;381:227-40.

10. Pierreux CE, Cordi S, Hick AC, Achouri Y, Ruiz de Almodovar C, Prévot PP, Courtoy PJ, Carmeliet P, Lemaigre FP. Epithelial: Endothelial cross-talk regulates exocrine differentiation in developing pancreas. Dev Biol. 2010;347:216-27.

Jean-François Collet

1. Delhaye A, Laloux G, Collet J-F. The lipoprotein NlpE is a Cpx sensor that serves as a sentinel for protein sorting and folding defects in the Escherichia coli envelope. J Bacteriol. 2019;201:e00611-18.

2. 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.

3. Goemans CV, Beaufay F, Arts I, Agrebi R, Vertommen D, Collet J-F. The chaperone and redox properties of CnoX chaperedoxins are tailored to the proteostatic needs of bacterial species. mBio. 2018;9:e01541-18.

4. Goemans CV, Beaufay F, Wahni K, Van Molle I, Messens J, Collet J-F. An essential thioredoxin is involved in the control of the cell cycle in the bacterium Caulobacter crescentus. J Biol Chem. 2018;293:3839-48.

5. Hussein NA, Cho SH, Laloux G, Siam R, Collet J-F. Distinct domains of Escherichia coli IgaA connect envelope stress sensing and down-regulation of the Rcs phosphorelay across subcellular compartments. PLoS Genet. 2018;14:e1007398.

6. Asmar AT, Collet J-F. Lpp, the Braun lipoprotein, turns 50-major achievements and remaining issues. FEMS Microbiol Lett. 2018;365:fny199.

7. Cao Z, Mitchell L, Hsia O, Scarpa M, Caldwell ST, Alfred AD, Gennaris A, Collet J-F, Hartley RC, Bulleid NJ. Methionine sulfoxide reductase B3 requires resolving cysteine residues for full activity and can act as a stereospecific methionine oxidase. Biochem J. 2018;475:827-38.

8. Asmar AT, Ferreira JL, Cohen EJ, Cho SH, Beeby M, Hughes KT, Collet J-F. Communication across the bacterial cell envelope depends on the size of the periplasm. PLoS Biol. 2017;15:e2004303.

9. Gennaris A, Ezraty B, Henry C, Agrebi R, Vergnes A, Oheix E, Bos J, Leverrier P, Espinosa L, Szewczyk J, Vertommen D, Iranzo O, Collet J-F,

Barras F. Repairing oxidized proteins in the bacterial envelope using respiratory chain electrons. Nature. 2015;528:409-12.

10. Cho SH, Szewczyk J, Pesavento C, Zietek M, Banzhaf M, Roszczenko P, Asmar A, Laloux G, Hov AK, Leverrier P, Van der Henst C, Vertommen D, Typas A, Collet J-F. Detecting envelope stress by monitoring beta-barrel assembly. Cell. 2014;159:1652-64.

Géraldine Laloux

1. Delhaye A, Collet J-F, Laloux G. A fly on the wall: How stress response systems can sense and respond to damages to peptidoglycan. Front Cell Infect Microbiol. 2019;9:380.

2. Delhaye A, Laloux G, Collet J-F. The lipoprotein NlpE is a Cpx sensor that serves as a sentinel for protein sorting and folding defects in the Escherichia coli envelope. J Bacteriol. 2019;201:e00611-18.

3. Hussein NA, Cho SH, Laloux G, Siam R, Collet J-F. Distinct domains of Escherichia coli IgaA connect envelope stress sensing and down-regulation of the Rcs phosphorelay across subcellular compartments. PLoS Genet. 2018;14:e1007398.

4. Laloux G, Collet J-F. Major Tom to ground control: how lipoproteins communicate extracytoplasmic stress to the decision center of the cell. J Bacteriol. 2017;199:e00216-17.

5. Delhaye A, Collet J-F, Laloux G. Fine-tuning of the Cpx envelope stress response is required for cell wall homeostasis in Escherichia coli. mBio. 2016;7:e00047–16.

6. Beaufay F, Coppine J, Mayard A, Laloux G, De Bolle X, Hallez R. A NAD-dependent glutamate dehydrogenase coordinates metabolism with cell division in Caulobacter crescentus. EMBO J. 2015;34:1786-800.

7. Deghelt M, Mullier C, Sternon J-F, Francis N, Laloux G, Dotreppe D, Van der Henst C, Jacobs-Wagner C, Letesson J-J, De Bolle X. G1-arrested newborn cells are the predominant infectious form of the pathogen Brucella abortus. Nat Commun. 2014;5:4366.

8. Cho S-H, Szewczyk J, Pesavento C, Zietek M, Banzhaf M, Roszczenko P, Asmar A, Laloux G, Hov AK, Leverrier P, Van der Henst C, Vertommen D, Typas A, Collet J-F. Detecting envelope stress by monitoring β-barrel assembly. Cell. 2014;159:1652-64.

9. Laloux G, Jacobs-Wagner C. How do bacteria localize proteins to the cell pole? J Cell Sci. 2014;127:11-9.

10. Laloux G, Jacobs-Wagner C. Spatiotemporal control of PopZ localization through cell cycle-coupled multimerization. J Cell Biol. 2013;201:827-41.

Jean-Paul Coutelier

1. Gaignage M, Marillier RG, Cochez PM, Dumoutier L, Uyttenhove C, Coutelier J-P, Van Snick J. TLR7 ligand R848 prevents mouse graft-versus-host disease and cooperates with anti-IL-27 antibody for maximal protection and Treg upregulation. Haematologica. 2019;104:392-402.

2. Gaignage M, Marillier RG, Uyttenhove C, Dauguet N, Saxena A, Ryfel B, Michiels T, Coutelier J-P, Van Snick J. Mouse nidovirus LDV infection alleviates graft versus host disease and induces type I IFN-dependent inhibition of dendritic cells and allo-responsive T cells. Immun Inflamm Dis. 2017;5:200-13.

3. Legrain S, Su D, Breukel C, Detalle L, Claassens JW, van der Kaa J, Izui S, Verbeek JS, Coutelier J-P. Involvement of Fcα/μ receptor in IgM anti-platelet, but not anti-red blood cell autoantibody pathogenicity in mice. J Immunol. 2015;195:4171-5.

4. Thirion G, Saxena A, Hulhoven X, Markine-Goriaynoff D, Van Snick J, Coutelier J-P. Modulation of the host microenvironment by a common non-oncolytic mouse virus leads to inhibition of plasmacytoma development through NK cell activation. J Gen Virol. 2014;95:1504-9.

5. Su D, Musaji A, Legrain S, Detalle L, van der Kaa J, Verbeek JS, Ryffel B, Coutelier J-P. Antibody-independent thrombocytopenia in lactate dehydrogenase-elevating virus infected mice. J Virol. 2012;86:12414-6.

6. Le-Thi-Phuong T, Dumoutier L, Renauld J-C, Van Snick J, Coutelier J-P. Divergent roles of interferons in the sensitization to endotoxin shock by lactate dehydrogenase-elevating virus. Int Immunol. 2007;19:1303-11.

7. Musaji A, Cormont F, Thirion G, Cambiaso CL, Coutelier J-P. Exacerbation of autoantibody-mediated thrombocytopenic purpura by infection with mouse viruses. Blood. 2004;104:2102-6.

8. Markine-Goriaynoff D, Coutelier J-P. Increased efficacy of the immunoglobulin G2a subclass in antibody-mediated protection against lactate dehydrogenase-elevating virus-induced polioencephalomyelitis revealed with switch mutants. J Virol. 2002;76:432-35.

9. Coutelier J-P, van der Logt JTM, Heessen FWA, Vink A, Van Snick J. Virally-induced modulation of murine IgG antibody subclasses. J Exp Med. 1988;168:2373-8.

10. Coutelier J-P, van der Logt JTM, Heessen FWA, Warnier G, Van Snick J. IgG2a restriction of murine antibodies elicited by viral infections. J Exp Med. 1987;165:64-9.

Thomas Michiels

1. Borghese F, Sorgeloos F, Cesaro T, Michiels T. The leader protein of Theiler's virus prevents the activation of PKR. J Virol. 2019;93:e01010-19.

2. Jacobs S, Zeippen C, Wavreil F, Gillet L, Michiels T. IFN-λ decreases murid herpesvirus-4 infection of the olfactory epithelium but fails to prevent virus reactivation in the vaginal mucosa. Viruses. 2019;11:757.

3. Jacobs S, Wavreil F, Schepens B, Gad HH, Hartmann R, Rocha-Pereira J, Neyts J, Saelens X, Michiels T. Species specificity of type III interferon activity and development of a sensitive luciferase-based bioassay for quantitation of mouse interferon-λ. J Interferon Cytokine Res. 2018;38:469-79.

4. Freundt EC, Drappier M, Michiels T. Innate immune detection of cardioviruses and viral disruption of interferon signaling. Front Microbiol. 2018;9:2448.

5. Drappier M, Jha BK, Stone S, Elliott R, Zhang R, Vertommen D, Weiss SR, Silverman RH, Michiels T. A novel mechanism of RNase L inhibition: Theiler's virus L* protein prevents 2-5A from binding to RNase L. PLoS Pathog. 2018;14:e1006989.

6. Drappier M, Opperdoes FR, Michiels T. Nonstructural protein L* species specificity supports a mouse origin for Vilyuisk human encephalitis virus. J Virol. 2017;91:e00573-17.

7. Sayed IM, Verhoye L, Cocquerel L, Abravanel F, Foquet L, Montpellier C, Debing Y, Farhoudi A, Wychowski C, Dubuisson J, Leroux-Roels G, Neyts

J, Izopet J, Michiels T, Meuleman P. Study of hepatitis E virus infection of genotype 1 and 3 in mice with humanised liver. Gut. 2017;66: 920-9.

8. Drappier M, Michiels T. Inhibition of the OAS/RNase L pathway by viruses. Curr Opin Virol. 2015;15:19-26.

9. Sorgeloos F, Jha BK, Silverman RH, Michiels T. Evasion of antiviral innate immunity by Theiler's virus L* protein through direct inhibition of RNase L. PLoS Pathog. 2013;9:e1003474.

10. Sommereyns C, Paul S, Staeheli P, Michiels T. IFN-lambda is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. PLoS Pathog. 2008;4:e1000017.

Jean-Christophe Renauld & Laure Dumoutier

1. Van Belle AB, Cochez PM, de Heusch M, Pointner L, Opsomer R, Raynaud P, Achouri Y, Hendrickx E, Cheou P, Warnier G, Renauld J-C, Baeck M, Dumoutier L. IL-24 contributes to skin inflammation in Para-Phenylenediamine-induced contact hypersensitivity. Sci Rep. 2019;9:1852.

2. de Montjoye L, Herman A, Hendrickx E, Cheou P, Blanchetot C, Hofman E, Baeck M, Dumoutier L. Increased expression of IL-24 in chronic spontaneous urticaria. Allergy. 2019;74:1811-3.

3. Cochez P, Michiels C, Hendrickx E, Dauguet N, Warnier G, Renauld J-C, Dumoutier L. Ccr6 is dispensable for the development of skin lesions induced by imiquimod despite its effect on epidermal homing of IL-22-producing cells. J Invest Dermatol. 2017;137:1094-103.

4. Cochez P, Michiels C, Hendrickx E, Van Belle AB, Lemaire MM, Dauguet N, Warnier G, de Heusch M, Togbe D, Ryffel B, Coulie P, Renauld J-C, Dumoutier L. AhR modulates the IL-22-producing cell proliferation/recruitment in imiquimod-induced psoriasis mouse model. Eur J Immunol. 2016;46:1449-59.

5. Van Belle AB, de Heusch M, Lemaire MM, Hendrickx E, Warnier G, Dunussi-Joannopoulos K, Fouser LA, Renauld J-C, Dumoutier L. IL-22 is required for imiquimod-induced psoriasiform skin inflammation in mice. J Immunol. 2012;188:462-9.

6. Dumoutier L, de Heusch M, Orabona C, Satoh-Takayama N, Eberl G, Sirard JC, Di Santo JP, Renauld J-C. IL-22 is produced by gammaC-independent CD25+ CCR6+ innate murine spleen cells upon inflammatory stimuli and contributes to LPS-induced lethality. Eur J Immunol. 2011;41:1075-85.

7. Dumoutier L, de Meester C, Tavernier J, Renauld J-C. New activation modus of STAT3: a tyrosine-less region of the interleukin-22 receptor recruits STAT3 by interacting with its coiled-coil domain. J Biol Chem. 2009;284:26377-84.

8. Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renauld J-C, Stockinger B. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature. 2008;453:106-9.

9. Knoops L, Renauld J-C. IL-9 and its receptor: from signal transduction to tumorigenesis. Growth Factors. 2004;22:207-15.

10. Renauld JC. Class II cytokine receptors and their ligands: key antiviral and inflammatory modulators. Nat Rev Immunol. 2003;3:667-76.

Emile Van Schaftingen & Maria Veiga-da-Cunha

1. Veiga-da-Cunha M, Van Schaftingen E, Bommer GT. Inborn errors of metabolite repair. J Inherit Metab Dis. 2020;43:14-24.

2. Veiga-da-Cunha M, Chevalier N, Stephenne X, Dufour JP, Paczia N, Ferster A, Achouri Y, Dewulf JP, Linster CL, Bommer GT, Van Schaftingen E. Failure to eliminate a phosphorylated glucose-analog leads to neutropenia in patients with G6PT and G6PC3 deficiency. Proc Natl Acad Sci USA. 2019;116:1241-50.

3. Dewulf JP, Wiame E, Dorboz I, Elmaleh-Bergès M, Imbard A, Dumitriu D, Rak M, Bourillon A, Helaers R, Malla A, Renaldo F, Boespflug-Tanguy O, Vincent MF, Benoist JF, Wevers RA, Schlessinger A, Van Schaftingen E, Nassogne MC, Schiff M. SLC13A3 variants cause acute reversible leukoencephalopathy and αKG accumulation. Ann Neurol. 2019; 85:385-95.

4. Dewulf JP, Gerin I, Rider MH, Veiga-da-Cunha M, Van Schaftingen E, Bommer GT. The synthesis of branched-chain fatty acids is limited by enzymatic decarboxylation of ethyl- and methylmalonyl-CoA. Biochem J. 2019;476:2427-47.

5. Marbaix AY, Chehade G, Noël G, Morsomme P, Vertommen D, Bommer GT, Van Schaftingen E. Pyridoxamine-phosphate oxidases and pyridoxamine-phosphate oxidase-related proteins catalyze the oxidation of 6-NAD(P)H to NAD(P). Biochem J. 2019;476:3033-52.

6. Bommer GT, Van Schaftingen E, Veiga-da-Cunha M. Metabolite repair enzymes control metabolic damage in glycolysis. Trends Biochem Sci. 2019; epub Aug 28.

7. Wiame E, Tahay G, Tyteca D, Vertommen D, Stroobant V, Bommer GT, Van Schaftingen E. NAT6 acetylates the N-terminus of different forms of actin. FEBS J. 2018;285:3299-316.

8. Peracchi A, Veiga-da-Cunha M, Kuhara T, Ellens KW, Paczia N, Stroobant V, Seliga AK, Marlaire S, Jaisson S, Bommer GT, Sun J, Huebner K, Linster CL, Cooper AJL, Van Schaftingen E. Nit1 is a metabolite repair enzyme that hydrolyzes deaminated glutathione. Proc Natl Acad Sci USA. 2017;114:E3233-42.

9. Collard F, Baldin F, Gerin I, Bolsée J, Noël G, Graff J, Veiga-da-Cunha M, Stroobant V, Vertommen D, Houddane A, Rider MH, Linster CL, Van Schaftingen E, Bommer GT. A conserved phosphatase destroys toxic glycolytic side products in mammals and yeast. Nat Chem Biol. 2016;12:601-7.

10. Rzem R, Achouri Y, Marbaix E, Schakman O, Wiame E, Marie S, Gailly P, Vincent MF, Veiga-da-Cunha M, Van Schaftingen E. A mouse model of L-2-hydroxyglutaric aciduria, a disorder of metabolite repair. PLoS One. 2015;10:e0119540.

Guido Bommer

1. Bommer GT, Baldin F, Van Schaftingen E. Accumulation of metabolic side products might favor the production of ethanol in Pho13 knockout strains. Microb Cell. 2016;3:495-9.

2. Collard F, Baldin F, Gerin I, Bolsée J, Noël G, Graff J, Veiga-da-Cunha M, Stroobant V, Vertommen D, Houddane A, Rider MH, Linster CL, Van Schaftingen E, Bommer GT. A conserved phosphatase destroys toxic glycolytic side products in mammals and yeast. Nat Chem Biol. 2016;12:601-7.

3. Gerin I, Ury B, Breloy I, Bouchet-Seraphin C, Bolsée J, Halbout M, Graff J, Vertommen D, Muccioli GG, Seta N, Cuisset JM, Dabaj I, Quijano-Roy S, Grahn A, Van Schaftingen E, Bommer GT. ISPD produces CDP-ribitol used by FKTN and FKRP to transfer ribitol phosphate onto α-dystroglycan. Nat Commun. 2016;7:11534.

4. Gerin I, Noël G, Bolsée J, Haumont O, Van Schaftingen E, Bommer GT. Identification of TP53-induced glycolysis and apoptosis regulator (TIGAR) as the phosphoglycolate-independent 2,3-bisphosphoglycerate phosphatase. Biochem J. 2014;458:439-48.

5. Feng Y, Bommer GT, Zhao J, Green M, Sands E, Zhai Y, Brown K, Burberry A, Cho KR, Fearon ER. Mutant KRAS promotes hyperplasia and alters differentiation in the colon epithelium but does not expand the presumptive stem cell pool. Gastroenterology. 2011;141:1003-1013.e1-10.

6. Bommer GT, MacDougald OA. Regulation of lipid homeostasis by the bifunctional SREBF2-miR33a locus. Cell Metab. 2011;13:241-7.

7. Fearon ER, Bommer GT. Ancestries hidden in plain sight: methylation patterns for clonal analysis. Gastroenterology. 2011;140:1139-43.

8. Gerin I, Clerbaux LA, Haumont O, Lanthier N, Das AK, Burant CF, Leclercq IA, MacDougald OA, Bommer GT. Expression of miR-33 from an SREBP2 intron inhibits cholesterol export and fatty acid oxidation. J Biol Chem. 2010;285:33652-61.

9. Herbst A, Bommer GT, Kriegl L, Jung A, Behrens A, Csanadi E, Gerhard M, Bolz C, Riesenberg R, Zimmermann W, Dietmaier W, Wolf I, Brabletz T, Göke B, Kolligs FT. ITF-2 is disrupted via allelic loss of chromosome 18q21, and ITF-2B expression is lost at the adenoma-carcinoma transition. Gastroenterology. 2009;137:639-48, 648.e1-9.

10. Bommer GT, Gerin I, Feng Y, Kaczorowski AJ, Kuick R, Love RE, Zhai Y, Giordano TJ, Qin ZS, Moore BB, MacDougald OA, Cho KR, Fearon ER. p53-mediated activation of miRNA34 candidate tumor-suppressor genes. Curr Biol. 2007;17:1298-307.

Mark Rider

1. Johanns M, Kviklyte S, Chuang S-J, Corbeels K, Jacobs R, Schakman O, Duparc T, Cani PD, Bouzin C, Andersén H, Bohlooly-Y M, Van der Schueren B, Oscarsson J, Rider MH. Genetic deletion of soluble 5′-nucleotidase II reduces body weight gain and insulin resistance induced by a high-fat diet. Mol Genet Metab. 2019;126:377-87.

2. 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;71:614-27.

3. Ouni E, Vertommen D, Chiti MC, Dolmans MM, Amorim CA. A draft map of the human ovarian proteome for tissue engineering and clinical applications. Mol Cell Proteomics. 2018;44:158-70.

4. Kwiatkowski S, Seliga AK, Vertommen D, Terreri M, Ishikawa T, Grabowska I, Tiebe M, Teleman AA, Jagielski AK, Veiga-da-Cunha M, Drozak J. SETD3 protein is the actin-specific hisitidine N-methyltransferase eLife. 2018;7:e37921.

5. Wiame E, Tahay G, Tyteca D, Vertommen D, Stroobant V, Bommer GT, Van Schaftingen E. NAT6 acetylates the N-terminus of different forms of actin. FEBS J. 2018;285:3299-316.

6. Herinckx G, Hussain N, Opperdoes FR, Storey KB, Rider MH, Vertommen D. Changes in the phosphoproteome of brown adipose tissue during hibernation in the ground squirrel, *Ictomys tridecemlineatus*. Physiol Genomics. 2017;49:462-72.

7. Houddane A, Bultot L, Novellasdemunt L, Johanns M, Gueuning M-A, Vertommen D, Coulie PG, Bartrons R, Hue L, Rider MH. Role of Akt/PKB and PFKFB isoenzymes in the control of glycolysis, cell proliferation and protein synthesis in mitogen-stimulated thymocytes. Cell Signal. 2017;34:23-37.

8. Johanns M, Pyr dit Ruys S, Houddane A, Vertommen D, Herinckx G, Hue L, Proud CG, Rider MH. Direct and indirect activation of eukaryotic elongation factor 2 kinase by AMP-activated protein kinase. Cell Signal. 2017;36:212-21.

9. Kviklyte S, Vertommen D, Yerna X, Andersén H, Xu X, Gailly P, Bohlooly-Y M, Oscarsson J, Rider MH. Effects of genetic deletion of soluble 5′-nucleotidases NT5C1A and NT5C2 on AMPK activation and nucleotide levels in contracting mouse skeletal muscles. Am J Physiol Endocrinol Metab. 2017;313:E48-62.

10. Johanns M, Lai Y-C, Hsu M-F, Jacobs R, Vertommen D, Van Sande J, Dumont JE, Woods A, Carling D, Hue L, Viollet B, Foretz M, Rider MH. AMPK antagonizes hepatic glucagon-stimulated cyclic AMP signalling via phosphorylation-induced activation of cyclic nucleotide phosphodiesterase 4B. Nat Commun. 2016;7:10856.

Etienne Marbaix & Patrick Henriet

1. Johanns M, Lemoine P, Janssens V, Grieco G, Moestrup SK, Nielsen R, Christensen EI, Courtoy PJ, Emonard H, Marbaix E, Henriet P. Cellular uptake of proMMP-2:TIMP-2 complexes by the endocytic receptor megalin/LRP-2. Sci Rep. 2017;7:4328.

2. Henriet P, Mon KS, Marbaix E. Are matrix metalloproteinases and their inhibitors reliable diagnosis biomarkers and attractive therapeutic targets in endometriosis?. Metalloproteinases Med. 2016;3:81-92.

3. Coudyzer P, Lemoine P, Po C, Jordan BF, Van Der Smissen P, Courtoy PJ, Henriet P, Marbaix E. Induction of post-menstrual regeneration by ovarian steroid withdrawal in the functionalis of xenografted human endometrium. Hum Reprod. 2015;30:1156-68.

4. Coudyzer P, Lemoine P, Jordan BF, Gallez B, Galant C, Nisolle M, Courtoy PJ, Henriet P, Marbaix E. Hypoxia is not required for human endometrial breakdown or repair in a xenograft model of menstruation. FASEB J. 2013;27:3711-9.

5. Gaide Chevronnay HP, Selvais C, Emonard H, Galant C, Marbaix E, Henriet P. Regulation of matrix metalloproteinases activity studied in human endometrium as a paradigm of cyclic tissue breakdown and regeneration. Biochim Biophys Acta. 2012;1824:146-56.

6. Selvais C, D'Auria L, Tyteca D, Perrot G, Lemoine P, Troeberg L, Dedieu S, Noël A, Nagase H, Henriet P, Courtoy PJ, Marbaix E, Emonard H. Cell cholesterol modulates metalloproteinase-dependent shedding of LRP-1 (low-density lipoprotein receptor-related protein-1) and clearance function. FASEB J. 2011;25:2770-81.

7. Selvais C, Gaide Chevronnay HP, Lemoine P, Dedieu S, Henriet P, Courtoy PJ, Marbaix E, Emonard H. Metalloproteinase-dependent shedding of LRP-1 ectodomain decreases endocytic clearance of endometrial matrix metalloproteinases-2 and -9 at menstruation. Endocrinology. 2009;150:3792-9.

8. Gaide Chevronnay HP, Galant C, Lemoine P, Courtoy PJ, Marbaix E, Henriet P. Spatio-temporal coupling of focal extracellular matrix degradation and reconstruction in the menstrual human endometrium. Endocrinology. 2009;150:5094-105.

9. Galant C, Berlière M, Dubois D, Verougstraete J-C, Charles A, Lemoine P, Kokorine I, Eeckhout Y, Courtoy PJ, Marbaix E. Focal expression and final activity of matrix metalloproteinases may explain irregular dysfunctional endometrial bleeding. Am J Pathol. 2004;165:83-94.

10. Marbaix E, Kokorine I, Moulin P, Donnez J, Eeckhout Y, Courtoy PJ. Menstrual breakdown of human endometrium can be mimicked in vitro and is selectively and reversibly blocked by inhibitors of matrix metalloproteinases. Proc Natl Acad Sci USA .1996;93:9120-5.

Laurent Gatto

1. Crook OM, Gatto L, Kirk PDW. Fast approximate inference for variable selection in Dirichlet process mixtures, with an application to pan-cancer proteomics. Stat Appl Genet Mol Biol. 2019;18(6).

2. Petyuk VA, Gatto L, Payne SH. Reproducibility and transparency by design. Mol Cell Proteomics. 2019;18:S202-4.

3. Gatto L, Breckels LM, Lilley KS. Assessing sub-cellular resolution in spatial proteomics experiments. Curr Opin Chem Biol. 2019;48:123–49.

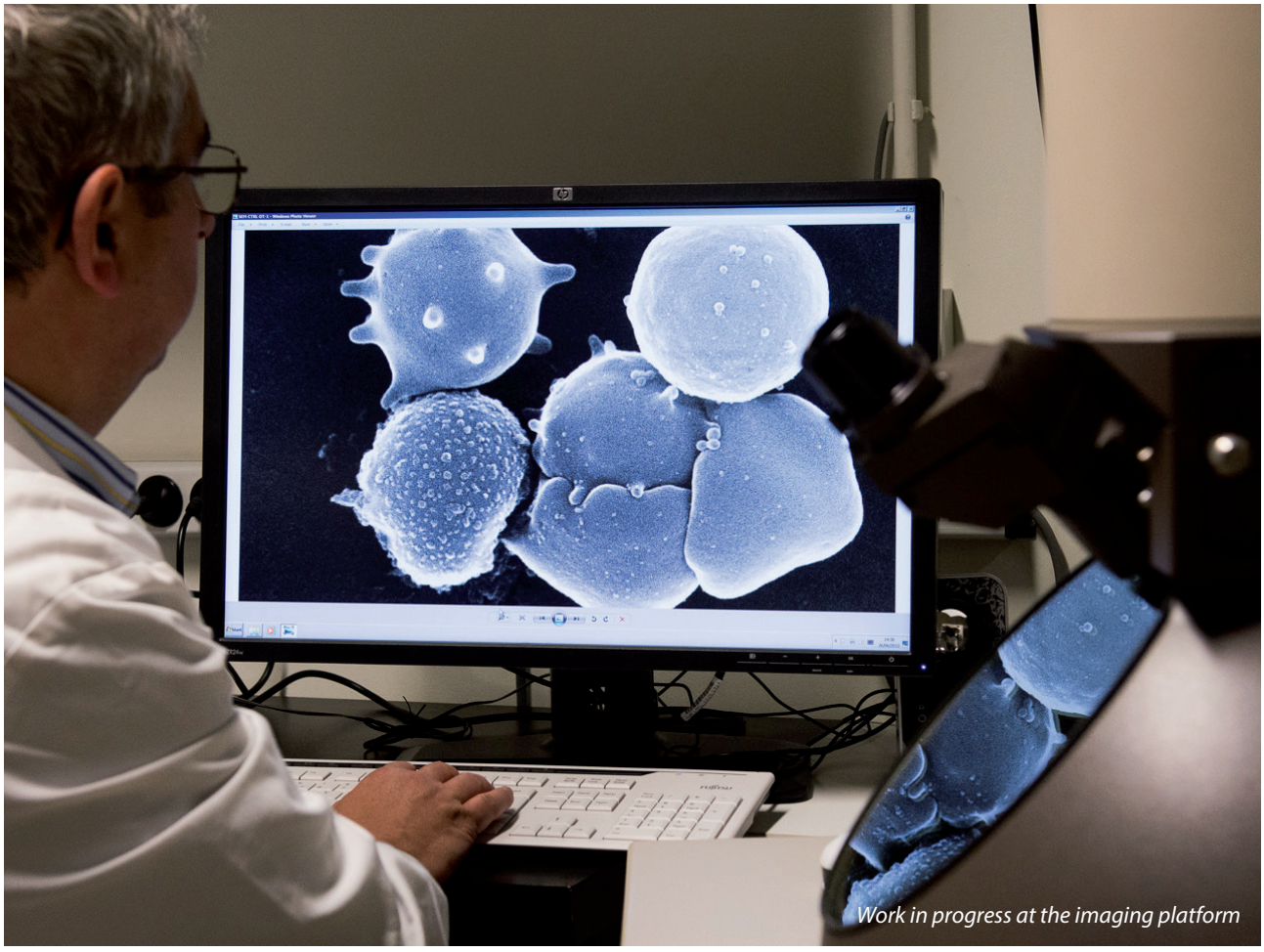
4. Rainer J, Gatto L, Weichenberger CX. ensembldb: an R package to create and use Ensembl-based annotation resources. Bioinformatics. 2019;35:3151-3.

5. Geladaki A, Kočevar Britovšek N, Breckels LM, Smith TS, Vennard OL, Mulvey CM, Crook OM, Gatto L, Lilley KS. Combining LOPIT with differential ultracentrifugation for high-resolution spatial proteomics. Nat Commun. 2019;10:331.

6. Baers LL, Breckels LM, Mills LA, Gatto L, Deery M, Stevens TJ, Howe CJ, Lilley KS, Lea-Smith DJ. Proteome mapping of a cyanobacterium reveals distinct compartment organisation and cell-dispersed metabolism. Plant Physiol. 2019;181:1721-38.

7. Eglen SJ, Mounce R, Gatto L, Currie AM, Nobis Y. Recent developments in scholarly publishing to improve research practices in the life sciences. Emerg Top Life Sci. 2018;2:775–8.

8. Crook OM, Mulvey CM, Kirk PDW, Lilley KS, Gatto L. A Bayesian mixture modelling approach for spatial proteomics. PLoS Comput Biol. 2018;14:e1006516.



Work in progress at the imaging platform

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

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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

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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

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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 Pascale Bougard, Lionel Crikeler, 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 Drs. Didier Vertommen and Sébastien Pyr dit Ruys, together with Prof. Pierre Morsomme and Dr. Hervé Degand at the Louvain Institute of Biomolecular Science and Technology.
[W] https://www.deduveinstitute.be/massprot-platform-mass-spectrometry

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Pierre COULIE • President of the Académie royale de Médecine de Belgique for 2019

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Nisha LIMAYE • Secretary of the Belgian Society of Human Genetics for 2018-2020

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Samanta KVIKLYTE • *Targeting soluble 5'-nucleotidases NT5C1A and NT5C2 as a strategy for AMPK activation* • Promoter: M. Rider

Florence SCHRAMME • *Role of tryptophan 2,3-dioxygenase in tumoral immune resistance: a preclinical study involving knock-out mice and a new inhibitor* • Promoter: B. Van den Eynde

Delia HOFFMANN • *Expression and potential immunosuppressive role of tryptophan 2,3-dioxygenase in tumours and placental tissues* • Promoter: B. Van den Eynde

François DUFRASNE • *Multilayered and versatile functions of the HIV-2 envelope glycoprotein in the viral replication cycle* • Promoter: P. Goubau, co-promoter: T. Michiels

Laurence DE MONTJOYE • *Immunological aspects of chronic spontaneous urticaria* • Promoter: M. Baeck, co-promoter: L. Dumoutier

Joanna ABI HABIB • *Degradation of oxidized proteins: role of the different 20S proteasome subtypes and effect on the production of antigenic peptides* • Promoter: B. Van den Eynde, co-promoter: N. Vigneron

Hélène POLLET • *How cytoskeletal impairment in hereditary elliptocytosis and spherocytosis affects erythrocyte membrane composition, organization and deformation* • Promoter: D. Tyteca

Orian BRICARD • *Development of a sensitive workflow to analyse T cell phenotype and specificity in patients with cancer or autoimmune diseases* • Promoter: P. Coulie

Florian PERRIN • *Molecular determinants regulating dimerization, processing and signaling of the amyloid precursor protein* • Promoter: P. Kienlen-Campard, co-promoter: S. Constantinescu

Thomas BALLIGAND • *Mouse models of myeloproliferative neoplasms identifying oncogenic and hematopoiesis dominance functions of mutated calreticulins* • Promoter: S. Constantinescu

Joseph DEWULF • *Ethylmalonyl-CoA decarboxylase (ECHDC1) prevents the synthesis of methyl- and ethyl-branched fatty acids* • Promoter: E. Van Schaftingen, co-promoter: M. Veiga-da-Cunha

Anthony VELTRI • *Understanding the role of Ror2-dependent pathway(s) in adult hair follicle stem cells* • Promoter: W.-H. Lien

Antoine DELHAYE • *Old dog, new tricks: how the Cpx stress response monitors multiple essential envelope biogenesis processes in E. Coli* • Promoter: J.-F. Collet, co-promoter: G. Laloux

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mRNA Therapeutics: ex-vivo and in-vivo modification of (antigen presenting) cells

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Gabriela OPREA • *Centogene AG, Rostock, Germany*
Rationality of precision medicine: the rare disease lesson

Stefanie KREUTMAIR • *Medical Center, Albert-Ludwigs-University of Freiburg, Germany*
Loss of the F-box protein NIPA causes bone marrow failure

Nick VAN GASTEL • *Harvard University, Cambridge, MA, USA*
Metabolic crosstalk in the bone marrow niche: implications for chemotherapy resistance in AML

Francesco REAL • *Spanish National Cancer Research Centre, Madrid, Spain*
Core and ancillary transcriptional programs contribute to pancreatic differentiation and cancer

Louise SERPELL • *School of Life Sciences, University of Sussex, Falmer, UK*
Proteins at the centre of neurodegeneration in Alzheimer's disease

Patrick REVY • *Imagine Institute for Genetic Diseases, Paris, France*
Human telomere biology disorders – New insights into NHP2 and Apollo deficiencies

Renske VAN RAAPHORST • *Faculty of Biology and Medicine, University of Lausanne, Switzerland*
Investigations into the condensation and segregation dynamics of the pneumococcal nucleoid

Natacha RUIZ • *Ohio State University, Columbus, OH, USA*
Powering transport of lipopolysaccharides across the bacterial cell envelope with ABCs

Nicolas CAPELLI • *Center for Pathophysiology of Toulouse Purpan, France*
Vectorial release of Hepatitis E virus in polarized human hepatocytes

Purnima GUPTA • *International Agency for Research on Cancer, Lyon, France*
Modulation of cellular signaling and immunological responses on disease outcomes-visceral leishmaniasis to skin carcinogenesis

Yoann SANTIN • *Institut de Microbiologie de la Méditerranée, University of Aix-Marseille, France*
In vivo proximity labeling unveils the molecular mechanism of Type 6 secretion system (T6SS) tail length control

Léonce KOUAKANOU • *University Hospital Schleswig-Holstein & Christian-Albrechts-University Kiel, Germany*
Influence of vitamin C on human γδ T cell differentiation and function

David ALSTEENS • *Louvain Institute of Biomolecular Science and Technology, UCLouvain, Belgium*
Probing ligand binding to native membrane receptors in physiologically relevant conditions using AFM

Niels H. GEHRING • *Institute for Genetics, Center of Molecular Biosciences, University of Cologne, Germany*
Guardians of the transcriptome: how RNA-binding proteins protect mRNA integrity

Ghislain OPDENAKKER • *Rega Institute for Medical Research, University of Leuven, Belgium*
Meandering in the search for a disease to target gelatinase B, alias matrix metalloproteinase-9 (MMP-9): from autoimmune diseases via inflammatory bowel diseases to chronic skin wounds

Murali C. KRISHNA • *Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*
Molecular imaging of the tumor microenvironment – Imaging biomarkers to guide treatment and monitor response

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International Summer School in Bioinformatics: organized by Laurent Gatto and Jean-Baptiste Demoulin

Instructors: Martin MORGAN *(Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA)*, Laurent GATTO *(de Duve Institute, UCLouvain, Belgium)*, Janick MATHYS *(Centre of Microbial and Plant Genetics, KU Leuven, Belgium)*, Lieven CLEMENT *(Bioinformatics Institute Ghent, UGent, Belgium)*, Charlotte SONESON *(Friedrich Miescher Institute for Biomedical Research & SIB Swiss Institute of Bioinformatics, Basel, Switzerland)*, Koen VAN DEN BERGE *(Bioinformatics Institute Ghent, UGent, Belgium)* & Oliver CROOK *(Cambridge Centre for Proteomics, University of Cambridge, UK)*

> *One-week intensive summer school on data analysis and high-throughput biology, with a special focus on R/Bioconductor and its application to a wide range of topics across bioinformatics and computational biology.*

European *Bioconductor* Meeting 2019: organized by Laurent Gatto

Speakers: Levi WALDRON *(CUNY Graduate School of Public Health and Health Policy, New York, NY, USA)*, Vince CAREY *(Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA)*, Martin MORGAN *(Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA)*, Andreas MOOR *(Institute of Molecular Cancer Research, University of Zurich, Switzerland)*, Elisabetta MEREU *(CNAG Center for Genomic Regulation, Barcelona, Spain)*, Ewa SZCZUREK *(Institute of Informatics, University of Warsaw, Poland)*, Davide RISSO *(Statistical Sciences, University of Padova, Italy)*, Lieven CLEMENT *(Bioinformatics Institute*

Ghent, UGent, Belgium), Christine CHOIRAT *(Swiss Data Science Center, Lausanne, Switzerland)* & Andrea RAU *(Animal Genetics, Institut National de la Recherche Agronomique, Jouy-en-Josas, France)*.

> *Three-day meeting aimed at biologists, bioinformaticians, statisticians, and users of the Bioconductor software, a widely used project for the analysis and comprehension of high-throughput genomic data.*

6th Annual Meeting of the Belgian Society for Stem Cell Research : organized by Frédéric Lemaigre and Wen-Hui Lien

Speakers: Cédric BLANPAIN *(Université Libre de Bruxelles, Belgium)*, Henrik SEMB *(University of Copenhagen, Denmark)*, Matthias LUTOLF *(Ecole Polytechnique Fédérale de Lausanne, Switzerland)*, Michelle PERCHARDE *(MRC London Institute of Medical Sciences & Imperial College London, UK)*, Peter COFFEY *(University College of London, UK)* & Pierre VANDERHAEGHEN *(KU Leuven and Université Libre de Bruxelles, Belgium)*.

> *One-day meeting focusing on tissue-specific stem cells, from fundamental research to translational medicine. The BeSSCR connects stem cell researchers at the national and international level, to promote scientific research on and with stem cells.*

Princess Lilian Foundation Visiting Professorship 2018-2019: awarded to Prof. Alain FISCHER from Necker Children's Hospital (Paris) and co-hosted at the de Duve Institute by Pierre Coulie

Program: lecture and master classes

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

PhD Day, poster session

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Brussels

B1.74.03
Avenue Hippocrate 74
B-1200 Brussels, Belgium
[T] +32 (2) 764 74 59
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Acknowledgements

In 2019, the de Duve Institute has attracted major gifts from several foundations, companies and individuals who have been very generous. These sponsors are providing the resources that enable our scientists to better understand and treat diseases that afflict people around the world. Gifts are the lifeblood of new research initiatives and private resources are crucial in underwriting the costs of new laboratories. On an annual basis, fund-raising from private sources has increased during the past decade over levels achieved previously and now supports about 10% of the Institute's budget.

The appeal for sponsoring postdoctoral fellowships was also widely followed. In 2019, the Institute has been able to allocate the following fellowships, entirely supported by our donors:

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

the 'Maurange' fellowship to Reza Salimi (Iran),

a de Duve fellowship to Malak Haidar (Lebanon),

and a second de Duve fellowship to Annika Bruger (Germany), followed by Maya Raghunandan (India).

In addition to their support for a postdoctoral fellow, the Maurange Fund also enabled the acquisition of cutting-edge equipment for Géraldine Laloux's laboratory.

We express our gratitude to them and to all who contributed to the financing of postdoctoral fellows and state-of-the art research laboratories at the de Duve Institute, ensuring that this institute will remain at the top in the field of biomedical research.

Luc Bertrand
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