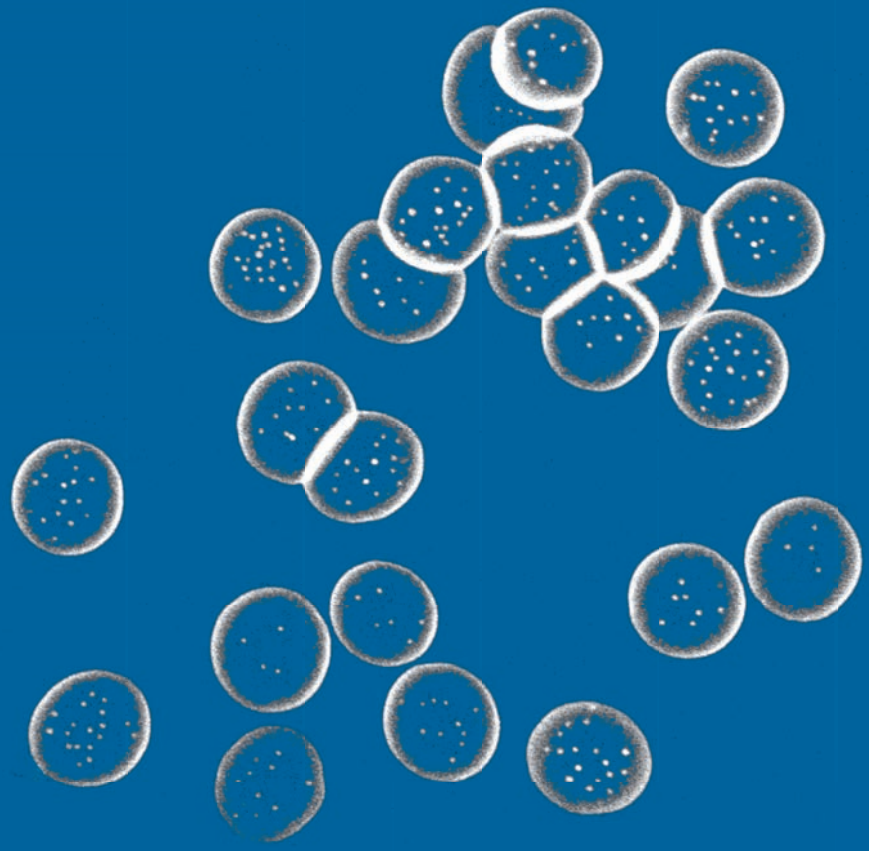
Scientific Report 2017

de Duve Institute & Ludwig Cancer Research

Brussels Branch

UCL Université catholique de Louvain



de Duve INSTITUTE

Avenue Hippocrate 75
B-1200 Brussels, BELGIUM

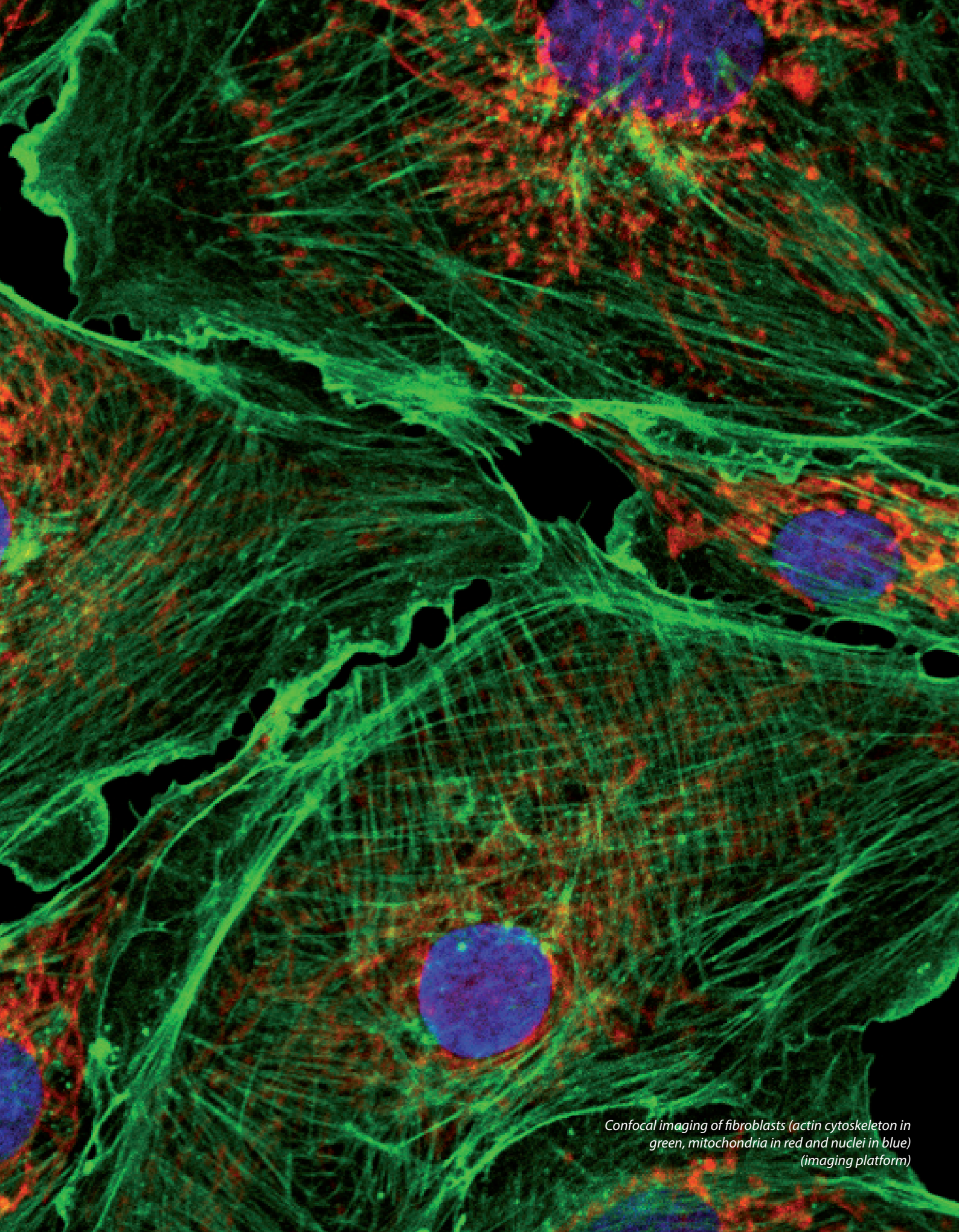
[T] + 32-2-764 75 50
[F] + 32-2-764 75 73
[E] deduve_institute@uclouvain.be
[W] www.deduveinstitute.be

Directors	Prof. Emile Van Schaftingen Prof. Frédéric Lemaigre Prof. Benoît Van den Eynde Prof. Miikka Vikkula
Finance Manager	Serge Thibaut
External Relations	Yolande de Crayencour & Isabelle de Duve
Photographs	Jacky Delorme, Hugues Depasse & Jean-Claude Verhelst

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

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

Contents



Confocal imaging of fibroblasts (actin cytoskeleton in green, mitochondria in red and nuclei in blue) (imaging platform)

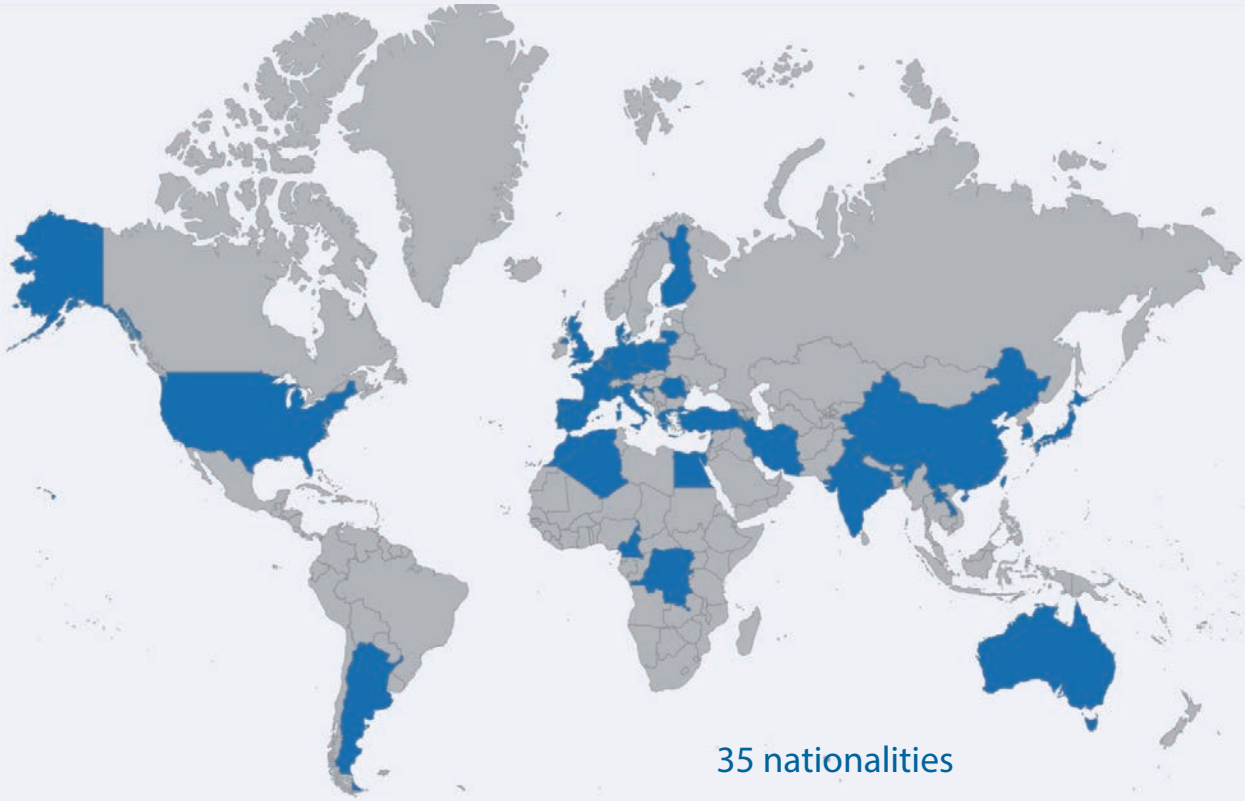
From the Director

This is a special year for us as the founder of our Institute, Professor Christian de Duve, would have been 100 years old. Trained as an MD, he started working in the laboratory of Professor J.P. Bouckaert in Leuven while in second year of medical school. This prompted him to become a researcher and after obtaining his PhD degree, he undertook postdoctoral stays in the laboratories of Hugo Theorell in Stockholm and of Carl and Gerty Cori in St. Louis. There he worked with Earl Sutherland, who was to discover cyclic AMP a few years later. Back in Leuven, de Duve set up his own laboratory with the goal of understanding the mechanism of insulin action. He discovered the glucose-producing enzyme, glucose-6-phosphatase, and found that this enzyme was associated with membranes (of the endoplasmic reticulum as we now know). The use of cell fractionation techniques for this study led him to discover serendipitously that acid phosphatase and other hydrolases with an acidic pH optimum were located in a new type of organelle that he named lysosomes, and that several enzymes producing or consuming H_2O_2 were in another 'new' organelle, for which the name peroxisome was coined. For these findings, he was awarded the Nobel Prize in 1974, the very year in which, with colleagues of the University of Louvain (UCL), he founded the 'International Institute of Cellular and Molecular Pathology', now renamed 'de Duve Institute'. The guiding principles of the Institute he created were inspired by his own experience in basic research: excellence, the freedom of researchers to choose their own research themes, the importance of using cutting-edge techniques, the importance of interdisciplinary collaborations, and the importance of keeping a strong interest in the potential medical applications of discoveries. These principles still guide research performed in our Institute.

This year we decided to change the format of our annual Scientific Report. We start with a few research highlights followed by a short presentation of the different groups working in the Institute. Representative publications are presented together on page 44 and following. Those interested to know more about the Institute and its research groups are invited to consult our website.

The use of mass spectrometry has been an important asset for research carried out in our Institute and university. Our Institute took the initiative to invest in a new machine, the latest generation Thermo Orbitrap Fusion Lumos mass spectrometer. This will allow our researchers to use state-of-the-art technology to quantify differential protein expression, differential protein phosphorylation and identify protein-protein interactions after chemical cross-linking in cells by high-resolution accurate mass spectrometry. The new machine will help our researchers to better understand diseases and improve antibiotic treatment.

Emile Van Schaftingen



35 nationalities

286 people

43% 57%

89 PhD students

34 postdoctoral students

102 publications in 2016

41 international lectures

5 technology platforms

8000 m^2

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 (UCL) 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

© CUSL / Hugues Depasse

Digging into the molecular mechanisms of the human body

Guido Bommer's team found out how three enzymes work together in modifying α-dystroglycan, a protein that is needed for muscular strength. Based on their results, a simple diet will be tested as therapy for people lacking one of these enzymes, who suffer from severe muscular disorders.

One might think that today's science knows almost everything about the human body. But sometimes researchers find things that surprise themselves. It happened to Guido Bommer when his group discovered how the modification of a protein in muscle cells works. 'We found a mechanism that occurs in bacteria, but has never been observed in mammalians before. As we first posed our theory, we didn't actually believe it was true. So we tried to prove it wrong in various ways. When we couldn't do that, we got convinced that it was right.'

Guido Bommer always wanted to be a researcher. 'I like to play with ideas, to solve problems', says the German scientist. He probably would have studied physics, if he hadn't been placed in a hospital for his social service. He then chose medicine and did his residency in gastroenterology and metabolic diseases. 'I didn't know if I was smart enough to be a researcher and one can work everywhere as a doctor', he explains. After working as a physician in Munich for three years, he followed his passion and went to do research at the University of Michigan. He there proved his doubts unfounded and in 2009 the de Duve Institute took on the talented researcher.
His research group has, at first glance, a broad scope: they study cancer, metabolic and neuromuscular diseases. These diseases come together through the underlying mechanisms, explains Bommer: 'We study the molecular mechanisms in metabolic pathways. Sometimes the same changes in a pathway lead to very diverse clinical entities.'

This is well illustrated by his recent discovery, which started with research on cancer and ended up with a breakthrough on a neuromuscular disease. 'It began with failure', recalls Bommer. 'We had a great hypothesis on an enzyme in cancer metabolism that proved completely wrong. But during this research, we found that the enzyme ISPD can make an activated form of ribitol phosphate, a structure that was not known to be present in human cells. So we started to look for human enzymes that could use these structures as substrate. This led us to two enzymes called FKTN and FKRP, which show similarity to the bacterial enzymes that use activated ribitol phosphate. FKTN and FKRP are known to be involved in neuromuscular diseases, by – when absent – causing dysfunctional α-dystroglycan. So we hypothesized: could these three enzymes work together to attach ribitols onto α-dystroglycan?'

To investigate their hypothesis, the team collaborated with several other groups. With the group of Emile Van Schaftingen they worked out the biochemistry. Methods for the complex analysis of α-dystroglycan by mass spectrometry were set up in collaboration with the University of Cologne. Various French hospitals provided cells from patients for the research.

"The difficulty was to make sure that what we saw in tubes was also happening in cells. There are so many variables."

With this joint effort, they showed that indeed ISPD first synthesizes an activated form of ribitol, called CDP-ribitol, which is then used by FKTN and FKRP to attach two sequential ribitol phosphate residues onto α-dystroglycan. 'We could demonstrate quite quickly how the enzymes perform the modification in a tube. The difficulty was to make sure that what we saw in tubes was also happening in cells. There are so many variables.'

The protein α-dystroglycan helps anchoring the cytoskeleton of a cell to other cells or to the extracellular matrix. 'If the ribitols are not attached, muscles cannot stick together. People lacking one of the three enzymes are born with normal muscular strength, but when they start moving, their strength goes down. Some people end up in a wheelchair at 40 years, others die at only one year of age. In brain cells, dysfunctional α-dystroglycan may lead to severe brain and eye disorders', says Bommer.

The researchers also made a hopeful discovery. 'In some patients with ISPD mutations, the enzyme is not completely dead, but works on a slow rate. With in vitro experiments we showed that, by adding the substrate ribitol in excess to the cells, the modification of α-dystroglycan can be restored partially or even completely. This could mean that adding ribitol to the diet of patients might help them to regain muscle strength. Tests with such a diet will be done by clinical centers.'

Bommer now tries to find out if the modification also occurs in brain cells or if the same mechanism happens in other proteins. Driven by curiosity and with his critical mind as compass, there are so many things he would like to investigate. 'When I read an explanation in literature that I don't understand or that is not supported by good data, I get suspicious. Things that don't seem right, probably aren't right. There are still a lot of things in biology that we think we understand, but in fact we don't really know what is going on.'

Reference
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. Nature Communications 2016;7:11534.

Manipulating the fate of cells

Telomeres, the caps at the end of each chromosome, play an important role in cell aging and cancer. Anabelle Decottignies' group found out that exercise helps to protect telomeres, thereby delaying the aging of cells.

The human genome is packed into 46 chromosomes in each cell's nucleus. The ends of all these chromosomes, called telomeres, are identical in every human being: they consist of a fixed 6-base-pairs long sequence, repeated several thousands of times. These apparently boring structures constitute in fact the essence of life: they determine when a cell stops dividing.

'Over a person's lifetime the telomeres get shorter and shorter due to successive cell divisions and, when they get too short, cells go into senescence. Cells that can maintain their telomeres are immortal. Embryonic stem cells have this ability, which they lose in the first steps of development. In many cancers, cells have found a way to escape telomere breakdown, giving them the ability to proliferate endlessly', explains Anabelle Decottignies, who studies telomeres since she started working at the de Duve Institute in 2004. 'It's about the immortality of cells, the genetics of cancer. When I first read about it, I was immediately fascinated.'

Decottignies started her research career in a quite different area. Both as PhD student in Louvain-la-Neuve and as postdoc in London, she had been doing biochemical research on yeast. Coming back to Belgium, she was desirous to change her field of study. 'I wanted to do biomedical research, to contribute to a better understanding and new treatments of human diseases. And I was eager to work on genetics. I first worked on this in London and really fell in love with it.' That opportunity came when she got an independent position at the de Duve Institute. All by herself, as she didn't have grants to pay staff in the first two years, she plunged into the research on telomeres. 'At the time, it was a completely new field. I was the only one in the Institute and even in Belgium to study telomeres. I hadn't learned anything about it in university, as it wasn't in any textbook yet.'

By gradually gaining knowhow and expanding her group, Decottignies built up the expertise of her lab, which today is renowned in the telomere field. The group investigates the mechanisms that cells use to maintain their telomeres. One goal is to find ways to induce shortening in cancer cells, which might be a means to end their immortality. At the same time, they research how telomeres attrition can be prevented in order to hold back the aging of cells. 'We search for ways to delay aging processes in pathologies, like Alzheimer's, not to make people immortal', clarifies Decottignies.

Recently the group demonstrated that doing physical exercises helps to maintain telomere health. This works via a molecule called TERRA, a non-coding RNA molecule that is thought to protect telomeres by forming a glue-like layer on the DNA ends. Decottignies' lab showed that working out boosts the production of TERRA.

"Because the ALT mechanism is not present in normal cells, it is a promising target to touch only cancer cells."

The researchers got on track of the mechanism by in silico analyses of human telomeric sequences. They found a potential binding site for a transcription factor called NRF1, which is activated during exercise via depletion of ATP stores. In human cell lines they proved that NRF1 indeed binds to telomeric promoters.

To demonstrate the mechanism in humans, they enlisted 10 healthy volunteers to do a 45 minutes workout on a stationary bicycle. Before and after the exercise they took muscle biopsies and blood samples. The results showed a clear relation between the exercise intensity and the TERRA transcription levels. 'The responses were even better than in vitro', says Decottignies. The results prove for the first time a link between telomere transcription and metabolism in humans.

In other research, the group studies a mechanism called ALT, a pathway that lengthens the telomeres by recombination of the DNA repeats. The mechanism is active in certain kinds of brain cancer and osteosarcomas that are most common in children. 'Because ALT is not present in normal cells, it is a promising target to touch only cancer cells. In collaboration with all Belgian hospitals, we are currently starting a project to search for therapeutic targets for which we will use cell lines obtained from children', says Decottignies.

Being still the only lab in Belgium in the field, Decottignies' group is making preparations to start a spin-off company for telomeres analyses. The service will be for cellular therapy companies that want to see if cells are in good enough shape to replenish tissue. It is also intended for hospitals that have patients with genetic telomere problems, such as children that age very early or have dysfunctional bone marrow. At the moment they have to go to France or Germany for such analyses.

All this will bring the work of the group closer to the bedside, as is the ambition of Anabelle Decottignies. 'We were recently involved in the investigation of defects in babies with bone marrow problems. Being able to help such children with our research, that is a dream coming true.'

Reference:
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. Science Advances 2016;2:e1600031.

Why does our immune defense fail in tumors?

In various types of cancer, T lymphocytes fail to attack and kill tumor cells because they are covered with galectins, as discovered by Pierre van der Bruggen's team almost 20 years ago. They now found out why. 'It's like a gun that is loaded, aimed, but then not fired.'

Pierre van der Bruggen had a remarkable reason to join the de Duve Institute in 1988. Having just obtained his PhD in plant agriculture, he filed several applications for fellowships at UK and US universities. In order to avoid the daily trips to the Social Security Agency while waiting for the outcome, he asked Prof. Thierry Boon for voluntary work at the Institute. He was offered a contract, intended for six months. But when his applications were accepted, he preferred to stay at the Institute, a decision he never regretted.

He started to work in the group of Thierry Boon, an internationally renowned immunologist whose discoveries formed the basis of today's cancer immunotherapy. Though a plant biologist, Pierre van der Bruggen fitted perfectly in the team. In 1991 he identified the first gene, MAGE-1, coding for a tumor antigen on human melanoma cells. Over the years he identified several other tumor antigens, which have been used in clinical trials.

Since Pierre van der Bruggen set up his own research group, he has been studying the interactions between cancer and immune cells, especially focusing on CD8 T lymphocytes, the killer cells of our immune system. 'Cancer cells are clearly not ignored by our immune system. They are recognized, attacked and damaged by CD8 T lymphocytes. Unfortunately, at a certain point the lymphocytes stop to work efficiently, and that is when it goes wrong', says van der Bruggen. He studies the mechanisms that cause this dysfunction. Where most researchers in his field work with mouse models, he uses human cells as study material. An approach that has proved successful many times. 'Recently, we observed an effect in exhausted T lymphocytes that has never been seen in mice studies.'

In 1998, while studying such T lymphocytes in vitro, van der Bruggen found that the cells were dysfunctional for reasons he couldn't explain. 'Then Nathalie Demotte, a PhD student in my lab, found an article relating dysfunctional T lymphocytes to galectins. Examining our dysfunctional lymphocytes showed that they were indeed covered by a glue-like galectin layer.' Galectins are soluble proteins, present at low levels in every healthy individual, but produced at elevated levels by certain tumors. They readily bind to certain sugars, producing large complexes that can cover the lymphocyte surface. Van der Bruggen found the galectin layer on dysfunctional lymphocytes from several types of human tumors. 'Importantly, when we removed the galectins on the surface, the T lymphocytes regained their functionality.' Realizing the clinical potential of this discovery, the group embarked on the identification of reagents that could remove the galectin glue from T lymphocytes in patients.

Meanwhile, the mechanism by which galectins block the lymphocytes' activity was still unknown. 'For this we would need to look into the precise physical interactions between

"In contrast to what was assumed before, dysfunctional lymphocytes do produce cytokines and lytic enzymes, but are unable to secrete them."

the T lymphocyte and its target, which was outside our field of competence. But then Anne-Elisabeth Petit came to me, asking for a PhD project. She was trained for two years in the lab of Salvatore Valitutti at the University of Toulouse in studying the molecular dynamics of lymphocyte interactions. Our research question was perfect for her.'

The immunological synapse is a specifically structured communication area in T lymphocytes, which forms during activation of the lymphocytes upon contact with their target. In CD8 T lymphocytes, the synapse contains a secretory domain, where lytic enzymes and cytokines are released to deliver lethal hits to target cells. Anne-Elisabeth Petit set up a method to examine in detail the formation of the immunological synapse, using confocal microscopy of the Institute's imaging platform. Studying human tumor-infiltrating T lymphocytes with and without galectin, she observed that the activation of galectin-covered T lymphocytes occurs normally, except for the last step of the immunological synapse formation. The results indicate that, in contrast to what was assumed before, dysfunctional lymphocytes do produce cytokines and lytic enzymes, but are unable to secrete them. In collaboration with Prof. Benoît Scheid, a specialist in microfluidics at ULB who happens to be Pierre van der Bruggen's nephew, the researchers developed a method to measure the adhesion force of the lymphocytes to their targets. With this technique they learned that dysfunctional galectin-covered T lymphocytes bind their target less tightly than their galectin-free functional brothers. All defects are relieved by releasing the surface galectin.

The results might be beneficial to current cancer immunotherapy treatments, which work by releasing the brakes on T lymphocyte proliferation. These treatments have shown impressive results, even curing melanoma patients with no other treatment options left, but work only on a minority of patients. The response percentage can become significantly higher, believes van der Bruggen, by countering the other mechanisms of T lymphocyte dysfunction. Like with galectin antagonists. 'The recent results have enforced our feeling that this problem should be targeted in the clinic.'

Reference

Petit A-E, 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. Nature Communications 2016;7:12242.

Unraveling mechanisms of metabolic control

Individuals with type 2 diabetes often have high circulating levels of the hormone glucagon, which contributes towards hyperglycemia. Activation of the enzyme AMP-activated protein kinase (AMPK) in the liver might counteract this effect of glucagon, a recent finding by Mark Rider's group.

Each cell contains millions of proteins that are indispensable for it to live. The protein population of a cell is very dynamic. New proteins are constantly synthesized, old ones broken down, while others are modified. This allows the cell to respond to a changing environment, or to grow or differentiate.

An important modification of proteins is phosphorylation, the attachment of phosphate groups to serine, threonine or tyrosine residues. This can change enzyme activity, allow protein-protein interactions, affect protein subcellular localization and stability or even affect other post-translational modifications. As the phosphate may be removed again, the change is reversible. 'Protein phosphorylation is arguably the most important post-translational modification of proteins', says Mark Rider, who studies the role of protein phosphorylation in the control of cell function, especially metabolism.

Mark Rider learned about protein phosphorylation as an undergraduate student at Bristol University. He did his final year laboratory project under the supervision of Paul England labeling cardiac contractile proteins in vitro with cyclic AMP-dependent protein kinase (PKA) and P-32, a radioactive isotope of phosphorus. He then studied for his PhD at University College London in the laboratory of David Saggerson working on the hormonal control of triglyceride synthesis in white adipose tissue and the role of PKA. He came to Brussels to work at the ICP, as the de Duve Institute was called then, in 1983. It might well have been different, he tells: 'I wanted to go to the USA for a postdoc. At the time President Reagan had just launched his "Star Wars" defense program. There was little money for research so the group leaders I approached could not finance me.'

Mark Rider obtained a Royal Society European Fellowship, which gave him the opportunity to go anywhere in Europe. He met Louis Hue of the ICP in Prakash Datta's 'beer tent' during a meeting at University College London. Louis Hue had recently discovered fructose 2,6-bisphosphate together with Emile Van Schaftingen and he convinced Mark Rider to come to Brussels. Here he started working on fructose 2,6-bisphosphate and soon gathered interesting results on insulin action in heart. Some years later this led to the elucidation of the role of protein kinase B in the mechanism by which insulin controls heart glycolysis.

Since 2000 Mark Rider's laboratory has focused on AMPK, another protein kinase controlling heart glycolysis. AMPK is important for maintaining cellular and whole body energy homeostasis. It becomes activated when energy reserves fall and then phosphorylates targets to switch off energy consuming pathways while energy-generating pathways are switched on. Because AMPK activation in muscle during exercise stimulates glucose transport, AMPK has emerged as a drug target for the management of type 2 diabetes.

"The discovery suggests that AMPK activation in the liver could oppose the short-term action of glucagon representing a new therapeutic strategy for treating type 2 diabetes."

Recently the group discovered a mechanism by which AMPK counteracts the short-term effects of glucagon on the liver. They found that AMPK activation by a compound called '991' increased the destruction of cyclic AMP, glucagon's 'second messenger'. The decreased levels of cyclic AMP reduced PKA activation, which would lower liver glucose production by inhibiting gluconeogenesis and cause glucose levels in the blood to go down. They also found that the cyclic AMP lowering effect of AMPK was mediated by phosphorylation-induced activation of cyclic nucleotide phosphodiesterase 4B. The activation of this enzyme by AMPK might be of broad physiological relevance, since phosphodiesterase 4B and its other isoforms have a wide tissue distribution.

Glucagon levels are often elevated in type 2 diabetes, which may contribute to hyperglycemia. The discovery of Mark Rider's group suggests that AMPK activation in the liver could oppose the short-term action of glucagon representing a new therapeutic strategy for treating type 2 diabetes. The group is continuing research on compound 991 to look whether it has AMPK-independent effects on the gluconeogenic pathway.

In addition to its implication for diabetes, AMPK has become a hot research topic as a possible new target for cancer treatment. Indeed, epidemiological studies indicate that patients taking metformin, the most prescribed drug for diabetes and an AMPK activator, have reduced incidence of certain cancers. The group of Mark Rider is exploring whether AMPK activation can have an anti-cancer effect by inhibiting cell proliferation or, on the contrary, plays a pro-cancer role during metabolic stress in anoxic and nutrient-deprived tumors. Which role it takes would depend on context. AMPK exists as three subunits, each of which has various isoforms. 'Cancer cells seem to only express certain subunits, which might affect the targets of AMPK', says Mark Rider.

A final goal of Mark Rider's research is to search for new direct AMPK activators that can be used safely in humans. He believes interesting compounds can be found in nature. 'Many of today's best drugs are based on plant components, such as metformin and aspirin, both of which activate AMPK. At least a hundred phytochemicals have been shown to activate AMPK, but for many nobody knows how. The aim is to screen for compounds that act directly on AMPK.'

Reference

Johanns M, Lai YC, Hsu MF, 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. Nature Commununications 2016;7:10856.

Research Groups

Cancer

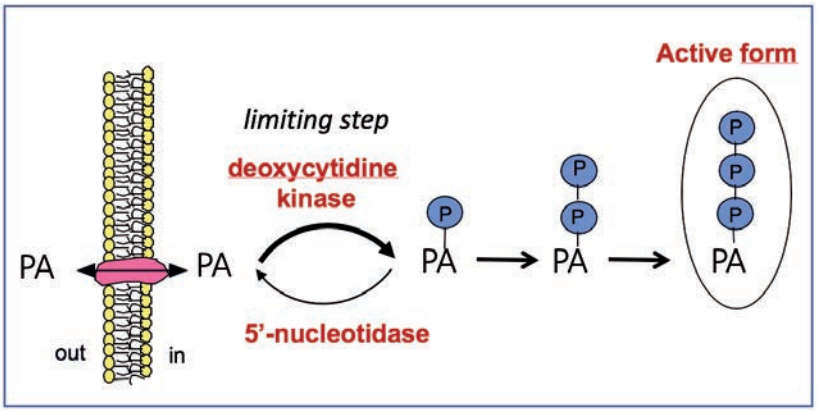
A cancer starts when cells acquire the ability to grow fast and the body's defence system cannot control them. We study how defects in signaling mechanisms cause cells to speed up their growth. Countering the mechanisms of resistance to chemotherapy for blood cancer is another goal of our research. Our institute proudly was at the basis of today's cancer immunotherapy treatments. We now investigate how the efficacy of these treatments can be enhanced.

Françoise Bontemps &
Eric Van Den Neste

The purine analogs fludarabine and cladribine are effective drugs in the treatment of chronic lymphocytic leukemia (CLL), but chemoresistance limits their clinical use. The main objective of our research was to find novel strategies to enhance their clinical efficacy.

Purine Analogs in Leukemia

To exert their action, purine analogs (PA) require intracellular conversion into an active triphosphate form. The first and rate-limiting step of this activation is catalyzed by deoxycytidine kinase (dCK) (Figure), which was shown to play a key role in purine analog efficacy. Therefore, we focused on the mechanisms that control dCK activity aiming to improve purine analog activation and counteract chemoresistance. We demonstrated that dCK activity is enhanced by phosphorylation of the Ser-74 residue. In addition, we established that increase in dCK activity in response to a genotoxic stress is correlated to an increase in Ser-74 phosphorylation. While ATM, a kinase primarily activated in response to DNA double strand breaks, was found to control dCK activation in response to ionizing radiation, we recently demonstrated that ATR, which is activated by single stranded DNA, is the kinase that controls basal dCK activity and activates dCK in response to replication stress. On the other hand, we identified the protein phosphatase 2A as the negative regulator of dCK activity.



The finding that dCK was activated in primary resting CLL cells in response to ATR activators (UV, aphidicolin), while ATR signaling has been reported to be suppressed in these cells, led us to reevaluate this view. We demonstrated that ATR, though expressed at low protein level, was actually activated in response to UV or purine analogs and able to phosphorylate known ATR targets, including the tumor suppressor p53 and dCK. Interestingly, activation of ATR in response to purine analogs in CLL cells promotes cell death, playing a substantial role in their mechanism of action.

In parallel with the latter studies, we investigated whether activation of dCK through Ser-74 phosphorylation might be a strategy to enhance the activation and thereby the efficacy of nucleoside analogs. We found that increase in dCK activity could enhance the clinical efficacy of pyrimidine analogs, such as gemcitabine, but not of the purine analogs fludarabine or cladribine. Nevertheless, we observed that aphidicolin, which induces increase in dCK Ser-74 phosphorylation without enhancing fludarabine or cladribine activation, was able to increase their cytotoxicity in primary CLL lymphocytes. This potentiating effect of aphidicolin was correlated to an increase in DNA damage, which was explained by disruption of NER (nucleotide excision repair), a DNA repair mechanism that involves aphidicolin-sensitive DNA polymerases.

Staff members
Emeritus: Georges Van den Berghe • **PhD Students:** Maxime Beyaert, Eliza Starczewska • **Administrative Support:** Pauline Leverrier, Marie-Victoire Uwimana

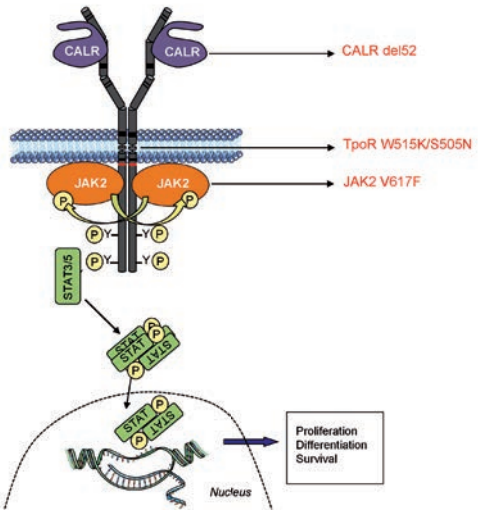
Stefan Constantinescu

LUDWIG CANCER RESEARCH Brussels

Cell Signaling & Molecular Hematology

We study how cell membrane receptors in blood precursors receive signals and transmit them to the cell nucleus. We discovered that mutations in cytokine receptors, in JAK proteins and in the chaperone calreticulin persistently activate JAK2 and induce blood cancers.

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



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

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

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

Staff members

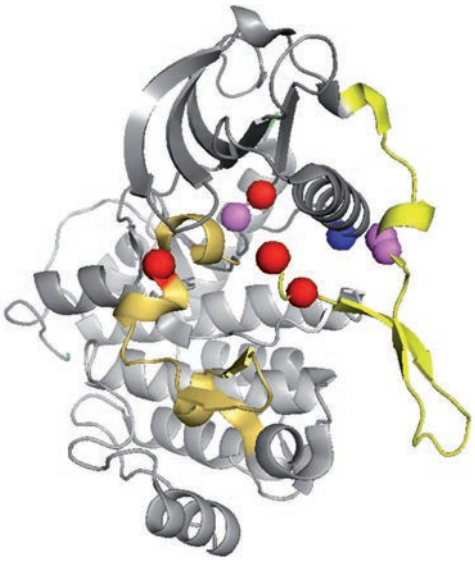
Senior Investigators: Didier Colau • **Guest Investigator:** Pierre De Meyts • **Postdoctoral Fellows:** Xavier Cahu, Jean-Philippe Defour, Christian Pecquet, Anita Roy, Leila Varghese • **PhD Students:** Thomas Balligand, Ilyas Chachoua, Emilie Leroy, Florian Perrin, Gaëlle Vertenoeil • **Research Assistants:** Lidvine Genet, Céline Mouton, Madeleine Swinarska

Jean-Baptiste Demoulin

Our team analyzes the signals that promote cell proliferation in cancer and other human diseases. We currently focus on leukemia and childhood tumors caused by mutations in membrane proteins called PDGF receptors, which are therapeutic targets.

Cancer Signaling

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 investigate how signaling cascades activated by these receptors affect transcription factors and gene expression, using techniques such as RNA sequencing, microarrays, classical molecular biology and bioinformatics. Regulation of transcription factors, such as FOXO, HBP1 and SREBP, by the phosphatidylinositol 3-kinase pathway is particularly studied in the context of cell growth. Recently, the role of microRNA (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 are found in leukemia caused 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, new fusion genes have also been characterized.

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. This drug has been successfully tested in a child harboring a germline PDGFRB mutation.

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

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

Staff members

Clinical Investigator: Violaine Havelange • **Postdoctoral Fellow:** Audrey de Rocca Serra • **PhD Students:** Florence Arts, Emeline Bollaert, Melissa Claus, Guillaume Dachy • **Research Assistants:** Sandrine Lenglez, Virginie Vandewalle, Amélie Velghe • **Administrative Support:** Geneviève Schoonheydt

Pierre Coulie

Human Tumor Immunology

Cancer immunotherapy is a breakthrough for some but not all cancers. Our group tries to understand why it is not the case for breast cancer.

The immune system protects the human body against diseases by destroying foreign substances like bacteria and viruses. T cells, a type of white blood cells, are the active components in this process as they recognize and destroy foreign cells. T cells can also recognize tumor cells. About thirty years ago, T. Boon and colleagues at the de Duve Institute and Brussels branch of the Ludwig Institute discovered specific markers on the surface of cancer cells (called tumor antigens) that can be recognized by T cells, which then destroy the tumor cells. This work paved the way for clinical applications of cancer immunotherapy, taking advantage of the tumor-specificity and memory of these T cells to propose specific and harmless cancer treatments.

In recent years, immunotherapy has emerged as a new modality of cancer treatment. Remarkable results are obtained in patients with advanced metastatic cancer, treated with immunostimulatory antibodies that enhance the activity of anti-tumor T cells. Many oncologists consider cancer immunotherapy to be at the forefront of the oncology field, as it is clear that patients with a variety of cancers are achieving clinical benefit. However, despite the indisputable clinical successes, the effectiveness of the treatments is still limited in many cases. Our research aims to better understand the mechanisms and limitations of T cell-mediated immunity to human tumors in order to improve the clinical efficacy of cancer immunotherapy.

One line of our research focuses on the specificity and functional properties of the T cells that are present within human tumors but appear to be quiescent. In breast cancer we have observed that anti-tumor T cells were often absent from the tumors, which stands in sharp contrast with what we had observed in melanomas. It probably explains why immunostimulatory antibodies do not bring a significant clinical benefit to most patients with breast cancer.

One reason for the paucity of anti-tumor T cells in breast cancer is the scarcity of tumor antigens in these tumors. In a tumor that contained many antigens we did find anti-tumor T cells, indicating that tumor-specific T cell responses do occur against breast cancer when the tumor antigenicity is high. We will explore the possibility that anti-tumor T cell responses develop at an earlier stage of breast cancer development, in the so-called in situ carcinomas. If we detect such responses, immunotherapy for very early stage breast cancers should then consist in immunization against tumor antigens, combined with immunostimulatory antibodies.

"In a tumor that contained many antigens we did find anti-tumor T cells, indicating that tumor-specific T cell responses do occur against breast cancer when the tumor antigenicity is high."

Staff members

Senior Investigators: Nicolas Dauguet (Platform Manager), Tiphanie Gomard, Nicolas van Baren • **Postdoctoral Fellows:** Abhishek Garg, Stine Larsen • **PhD Students:** Orian Bricard, Alix Devaux, Marie-Sophie Dheur, Kevin Missault, David Schröder, Charlotte Six • **Undergraduate Student:** Ophélie Remy • **Research Assistants:** Aurélie Daumerie, Gérald Hames, Catherine Muller, Nathalie Remy • **Administrative Support:** Suzanne Depelchin

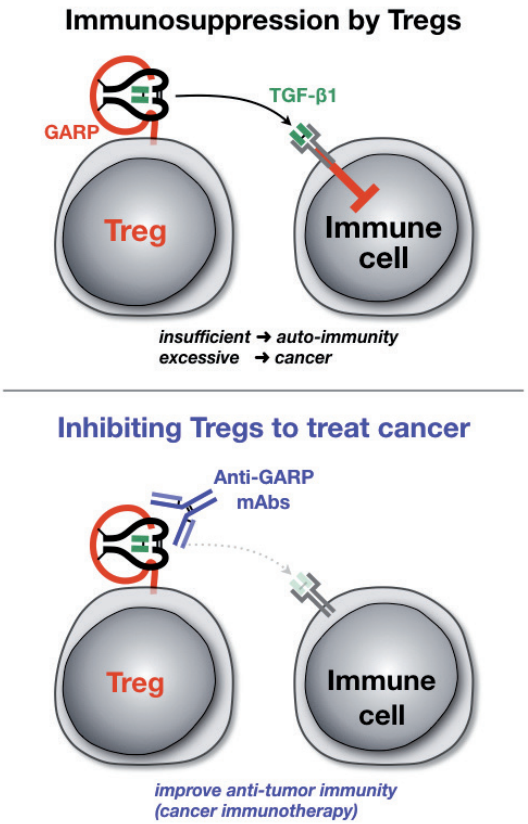
Sophie Lucas

Regulatory T cells & TGF-β

Our group studies how Regulatory T cells (aka 'Tregs') suppress immune responses. Our long-term goal is to design therapeutic approaches to modulate immunosuppression in patients suffering from diseases associated with Treg dysfunction. These include cancer, chronic infections and auto-immunity.

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

We try to identify the mechanisms by which Tregs exert their immunosuppressive activity, as these are not yet completely understood. We recently found that Tregs inhibit immune responses by producing a protein called TGF-β1, which acts as a messenger between Tregs and the immune cells they suppress (Figure). We also found that production of the immunosuppressive TGF-β1 by Tregs requires another Treg protein, called GARP. Production of TGF-β1 by any cell type is a highly regulated process, often requiring various accessory proteins. Tregs appear to be among the very few cell types of our organism producing TGF-β1 in a manner that depends on GARP. We developed tools (monoclonal antibodies) that bind to GARP and block TGF-β1 production by Tregs.



We are currently exploring whether these tools could be used as therapeutic agents to block Treg immunosuppression in individuals suffering from cancer (Figure). We are also thoroughly examining whether, and in which circumstances, cell types other than Tregs could produce TGF-β1 via GARP. This is important to predict potential adverse effects of therapeutic agents targeting GARP. Finally, we are now also trying to develop tools that would increase, rather than block, production of TGF-β1 by Tregs. These could serve as new therapeutic approaches to increase Treg immunosuppression in patients suffering from autoimmune diseases.

Staff members

Postdoctoral Fellow: Julie Stockis • **PhD Students:** Charlotte Bertrand, Olivier Dedobbeleer, Grégoire de Streel, Fanny Lambert, Sara Lecomte, Stéphanie Liénart, Xuhao Zhang • **Undergraduate Students:** Naemi Csoma, Nicolas Huyghe, Sandrine Terrisse • **Research Assistants:** Amandine Collignon, Maria Panagiotakopoulos • **Administrative Support:** Suzanne Depelchin

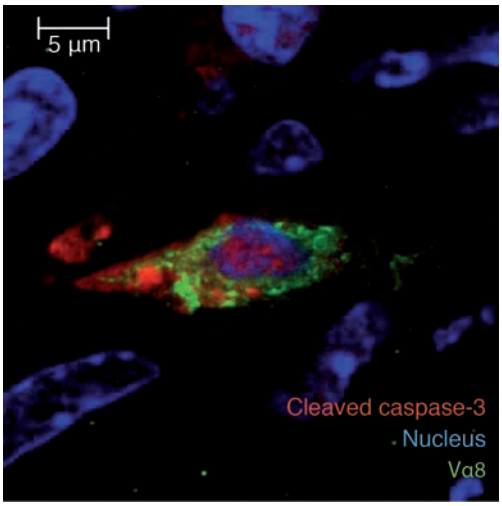
Benoît Van den Eynde

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

Emeritus: Thierry Boon • **Senior Investigators:** Etienne De Plaen, Christophe Lurquin, Vincent Stroobant • **Postdoctoral Fellows**: Veronica Finisguerra, Wenbin Ma, Nathalie Vigneron, Jingjing Zhu • **PhD Students:** Joanna Abi Habib, Violette Ferrari, Marc Hennequart, Delia Hoffmann, Simon Klaessens, Julie Lesenfants, Pierre-Florent Petit, Florence Schramme, Marie Solvay • **Research Assistants:** Thérèse Aerts, Loubna Boudhan, Rui Cheng, Dominique Donckers, Luc Pilotte, Floriane Ribeiro, Bénédicte Tollet • **Administrative Support:** Auriane Sibille

LUDWIG CANCER RESEARCH
Brussels

Pierre van der Bruggen

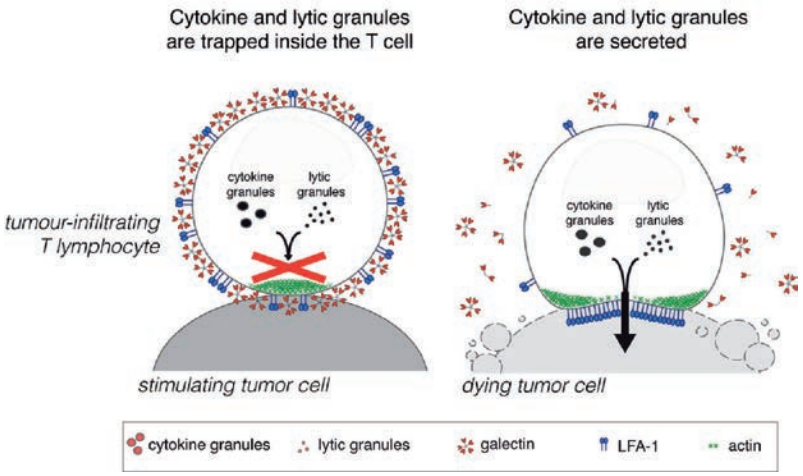
We study the interactions between cancer cells and the human immune system. We have a particular focus on understanding why tumor-infiltrating lymphocytes (TILs) are unable to kill tumor cells, and finding strategies to overcome this blockage.

T Lymphocyte Dysfunction

Most tumors are not ignored by the immune system of cancer patients. They contain immune cells and, in particular, T cells directed against tumor antigens. These tumor-infiltrating T cells are most of the time dysfunctional and this impaired function is maintained by immunosuppression. We try to better understand the different immunosuppressive mechanisms that operate in human tumors.

Galectin-3 seems to play a role in human TIL dysfunction. It belongs to a family of lectins, i.e. sugar-binding proteins, with pleiotropic functions both intracellularly and extracellularly (after secretion). Galectin-3 is mainly secreted by tumor cells and macrophages. By binding to glycoproteins at the TIL surface and forming glycoprotein-galectin lattices, galectin-3 restrains the mobility of surface molecules. We observed that extracellular galectin-3 blocks functions of human TILs, as treating TILs with an anti-galectin-3 antibody, or galectin antagonists, detached galectin-3 from the T cell surface and increased cytokine secretion and cytotoxicity of treated TILs.

We subsequently made the unexpected observation that a large fraction of TILs covered with galectin-3 failed to secrete cytokines and lytic enzymes upon stimulation, although they were activated and expressed these effector molecules in intracellular vesicles. The normal secretion process requires the formation of a secretory synapse allowing exocytosis of secretory granules. This process is blocked in TILs covered with galectin, due to impaired mobility of LFA-1, an adhesion molecule, and actin rearrangement at the secretory synapse. As a result, cytokines and lytic enzymes remain trapped inside TILs, thereby preventing their anti-tumor activity. From a practical standpoint, the new mechanism of T cell dysfunction indicates that evaluating T cell function by intracellular cytokine staining, a widely used immune-monitoring assay, can be highly misleading as it may wrongly suggest that T cells expressing intracellular cytokines are functional. According to our new mechanism of T cell dysfunction, some of these T cells may fail to secrete the cytokines.

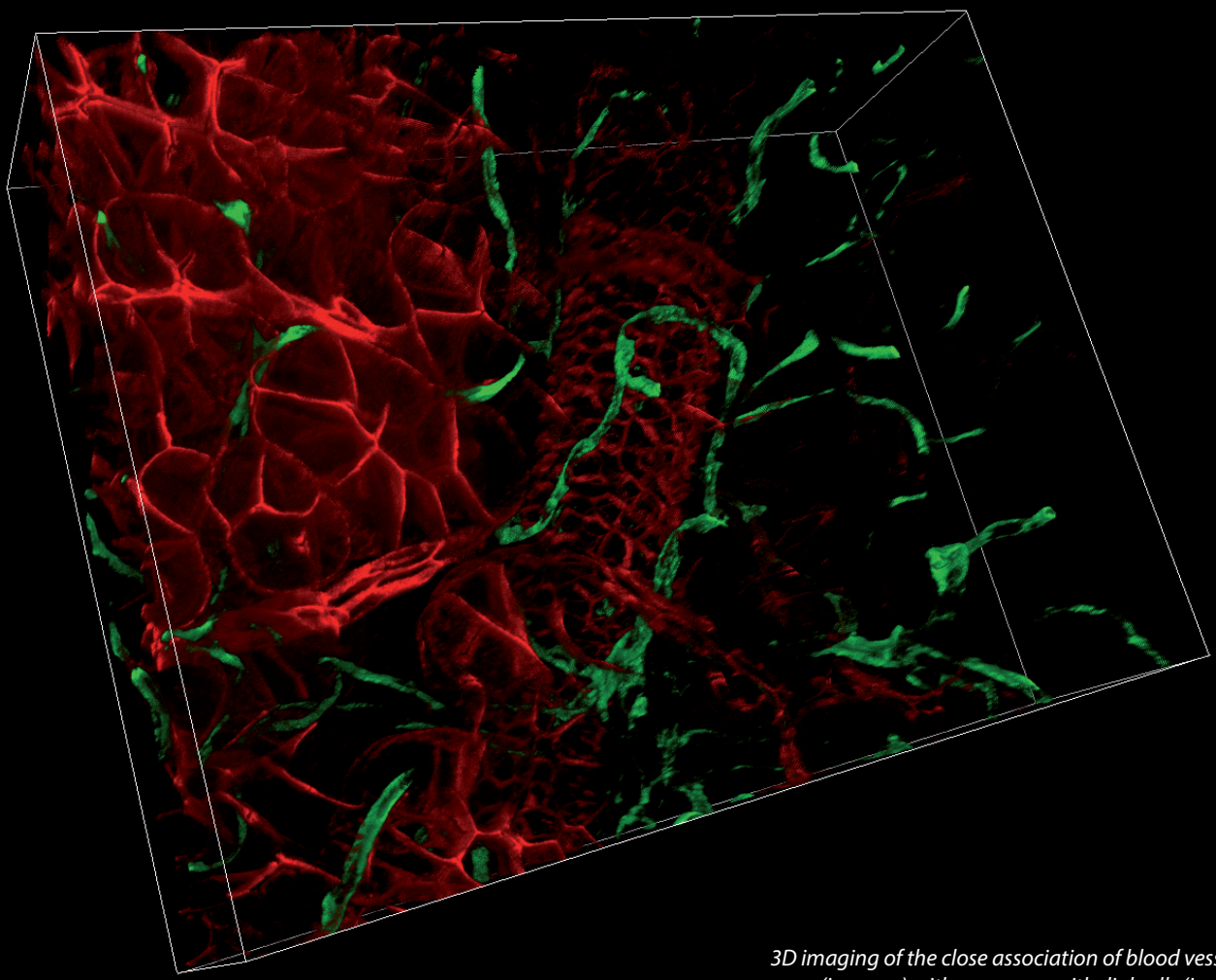


Cytokines and lytic enzymes are produced normally by human tumor-infiltrating T lymphocytes but remain trapped inside the cells.

These results also indicate that cancer immunotherapy regimens could be improved by blocking this mechanism of T cell dysfunction, and we will participate to the identification of clinical grade reagents potentially able to block galectin-3 effects in cancer patients.

Staff members

Postdoctoral Fellows: Annika Bruger, Nathalie Demotte, Monica Gordon-Alonso • **PhD Students:** René Bigirimana, Thibault Hirsch, Damien Neyens, Christophe Vanhaver • **Research Assistants:** Quentin D'Hondt, Claude Wildmann • **Administrative Support:** Julie Klein



3D imaging of the close association of blood vessels (in green) with pancreas 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.

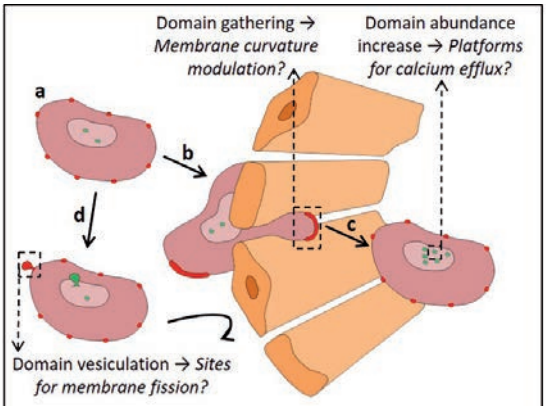
Donatienne Tyteca

Cell deformation is critical for numerous physiopathological 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.

Our group aims at bringing new insight in the importance of plasma membrane in cell deformation, as a prerequisite towards understanding membrane deformability disorders. We mainly use RBCs, as the simplest and best-characterized human cell model that exhibits remarkable deformability allowing squeezing through narrow splenic pores (more than 10,000 times in RBC lifetime). In senescence and spherocytosis, a genetic membrane deformability disorder that causes hemolytic anemia eventually requiring spleen removal, RBCs fail to deform coordinately and instead undergo local vesiculation.



Cholesterol- & sphingomyelin-enriched domains in resting RBC (**a**) & upon deformation (spleen filtration; **b,c**) & vesiculation (aging & diseases; **d**)

Using high-resolution confocal imaging, we discovered the existence of stable submicrometric lipid domains at the plasma membrane of living RBCs. At least two types of domains coexist, showing differential composition, membrane curvature association and fluidity, suggesting control by membrane biophysical properties (Figure, red & green spots at a). To explore whether membrane proteins also control lipid domains, we use the yeast S. cerevisiae, which offers a large collection of mutants and displays plasma membrane submicrometric protein domains, the eisosomes (coll. B. André, ULB).

We recently demonstrated that lipid domains contribute to RBC deformation via their gathering in highly curved areas and their increased abundance upon calcium efflux. Our findings suggest that lipid domains could stabilize/modulate membrane curvature areas and represent platforms for recruitment of proteins involved in calcium efflux (b,c). These two hypotheses are under investigation. In parallel, we examine the interplay between plasma membrane lipid domains, membrane bending proteins and the cytoskeleton for RBC deformation (coll. D. Alsteens, M.-P. Mingeot-Leclercq & P. Morsomme, UCL).

Besides implication in RBC deformation, lipid domains are lost upon RBC aging and modulated in a splenectomy-dependent manner in spherocytosis, suggesting they could represent sites susceptible to vesiculation (d). To test for this hypothesis, we isolate and purify vesicles from aged and spherocytotic RBCs and determine their lipid composition and physiopathological implications (coll. C. Vermylen, University Hospital Saint-Luc, & N. Dauguet).

We thus demonstrated that lipid domains contribute to RBC deformation. Extension to Duchenne muscular dystrophy and cancer cell migration and invasion is appealing.

Staff members

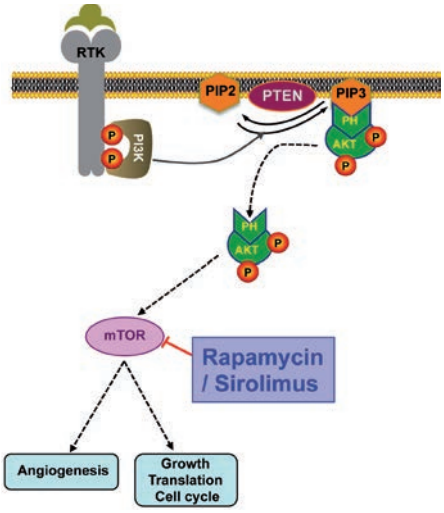
Senior Investigator: Patrick Van Der Smissen (Platform Manager) • **PhD Students:** Louise Conrard, Catherine Léonard, Hélène Pollet, Sandrine Verstraeten • **Undergraduate Student:** Anne-Sophie Cloos • **Administrative Support:** Aimée-Lys Rusesabagina

Miikka Vikkula
(with Laurence Boon, Pascal Brouillard and Nisha Limaye)

Human Genetics

The aim of our research is to understand the molecular mechanisms that underlie a variety of disorders of the cardiovascular and skeletal systems, as well as certain cancers. We specialize in evaluating the contribution of genetic variation to human disease.

The bases of many disorders remain unknown, and current treatments are often aimed at alleviating symptoms. Identification of the primary causes would allow for the development of treatments that are more specific and eventually curative. We focus on vascular anomalies (vascular tumors, such as hemangiomas) and vascular malformations, lymphedema, and cleft lip and palate. We also collaborate to study various cancers (breast cancer, hematological cancers and pheochromocytomas). As this research is based on human DNA extracted from blood and tissue samples from patients, we work closely with several clinicians and multidiciplinary centers worldwide, but especially with the Centre for Vascular Malformations, and the Cleft Lip and Palate Centre, University Hospital Saint-Luc, UCL.



Vascular anomalies are a heterogeneous group of disorders. The lesions are localized and composed of masses of malformed vessels. They can affect any organ, be painful, cause dysfunction and thus decrease quality of life.
We have been able to identify several genes that are mutated in individuals with a family history of vascular anomalies. Moreover, we have been able to demonstrate that the localized nature of the inherited lesions is due to a tissular (somatic) second-hit in the same gene that carries the inherited mutation. This led us to discover that the much more common non-hereditary, so called sporadically occurring form, of venous malformations is due to somatic mutations. These mutations have a stronger effect than the inherited mutations, and thus are able alone to induce lesion formation. Several groups have since identified similar activating somatic mutations in other genes in various forms of sporadically occurring vascular anomalies.

To understand how the activating TIE2 mutations cause venous malformations, we analyzed their cellular and molecular effects on endothelial cells. We found that the activation of the PI3K/AKT signaling pathway is the major pathogenic event (Figure). One of the downstream molecules is mTOR. We demonstrated that the mTOR inhibitor rapamycin effectively controls the expansion of lesions in a mouse model of the disease. Rapamycin also ameliorated symptoms in a preliminary trial of six patients with VMs recalcitrant to conventional therapies. This demonstrated, for the first time, the feasibility of a molecular approach to therapy in this developmental disease, and provided great hope for all patients affected with vascular anomalies.

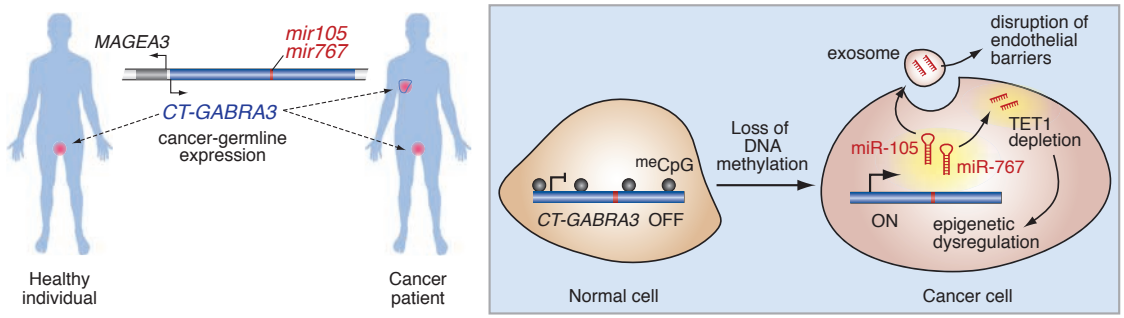
Staff members
Clinical investigators: Laurence Boon (Plastic Surgeon), Hélène Antoine-Poirel (Geneticist), Daniel Manicourt (Rheumatologist) • **Associate Member:** Nisha Limaye • **Senior Investigators:** Mustapha Amyere, Pascal Brouillard (Platform Manager), Raphaël Helaers • **Postdoctoral Fellows:** Ha-Long Nguyen, Angela Queisser • **PhD Students:** Mirta Basha (Dentist), Bénédicte Demeer (Geneticist), Lucie Evenepoel, Elodie Fastré, Nassim Homayun Sepehr, Elsa Khoury, Matthieu Schlögel, Julie Soblet • **Undergraduate Students:** Simon Boutry, Richard Coulie, Aude Ytebrouck • **Research Assistants:** Dominique Cottem, Audrey Debue, Antonella Mendola, Liliana Niculescu, Delphine Nolf • **Technical Assistants:** Mourad El Kaddouri, Christian Miserez • **Administrative Support:** Liliana Niculescu

Charles De Smet

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.

Epigenetics in Cancer

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



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

Our group discovered that DNA methylation alterations often affect a particular group of genes, which normally display specific expression in germline cells (the cells at the origin of oocytes in females and spermatozoids in males). 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).

The process leading to hypomethylation of DNA sequences in tumors remains obscure. We undertook to address this issue by using the founding member of the CG group of genes, MAGEA1, as a model. Our studies revealed that hypomethylation of this gene in tumors relies on a historical event of DNA demethylation, and on the presence of appropriate transcription factors to protect the region against subsequent remethylation. More recent work suggested that the initial process of DNA demethylation results from an episode of decreased activity of DNA methylation enzymes during the progression of the tumor.

Several CG genes were found to display oncogenic properties, and there is increasing interest for the development of drugs that target the product of these genes. It is expected indeed that therapies directed against genes expressed almost exclusively in tumor and germline cells will have only little side effects in cancer patients.

Recently, our group isolated a novel CG gene (CT-GABRA3), which 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.

Staff members

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

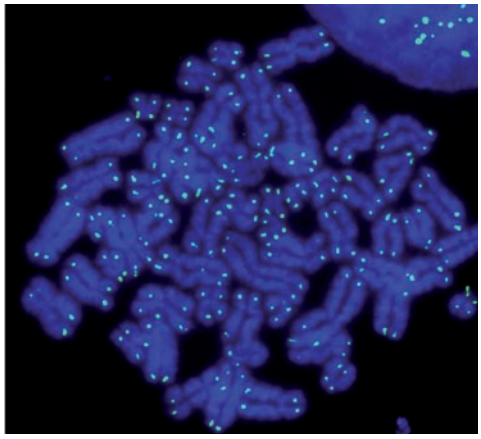
Anabelle Decottignies

Telomeres & Epigenetics

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

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

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



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

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

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

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

Staff members

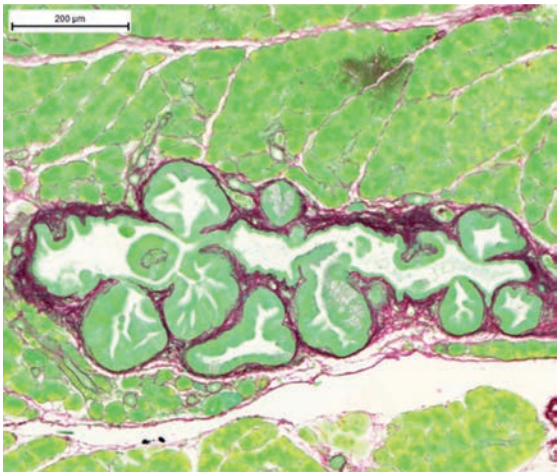
Postdoctoral Fellows: Harikleia Episkopou, Eva Majerova, Maya Raghunandan, Nikenza Viceconte • **PhD Students:** Aurélie Diman, Florian Poulain

Frédéric Lemaigre &
Patrick Jacquemin

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

Cell Differentiation

To develop into a complex organism cells in the embryo need to proliferate and differentiate, the latter consisting in the acquisition of organ-specific functions. While focusing on liver and pancreas, our group aims at identifying the molecular mechanisms that promote cell differentiation in the embryo, and those that perturb differentiation in adults and induce diseases such as liver or pancreatic cancer. We share our data on normal differentiation mechanisms 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.



Precancerous lesion in a mouse model of pancreatic cancer developed in the laboratory.

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 network that drives hepatocyte and cholangiocyte development in the embryo and identified several transcription factors required for normal liver development, e.g. HNF6, Onecut2 – both discovered in our laboratory –, and more recently SOX4. We also determine how the transcriptional network is regulated by intercellular signaling, and identified TGFβ as a key driver of bile duct development. In addition, we contributed to the understanding of the role of the Notch and Wnt-β-catenin pathways in this process. During development, tight quantitative control is exerted on gene expression by microRNAs. We identified two microRNAs (miR-122 and miR-337) which control the dynamics of the hepatic transcriptional networks. A quantitative and predictive approach is implemented using mathematical modeling of the gene networks.

Following up on earlier work in which we identified key regulators of normal pancreatic cell differentiation, we now focus on the molecular mechanisms driving development of pancreatic ductal adenocarcinoma (PDAC). We study the cell type of origin of PDAC, i.e. acinar or duct cells, and the signaling cascades promoting differentiation switches occurring during transition from normal to precancerous and eventually invasive cancer states. Our results suggest that there is a tight association between defects in primary cilia function in duct cells, and chronic pancreatitis, a risk factor for PDAC. These observations account for the increased risk to develop PDAC in patients with gene mutations affecting cilia function.

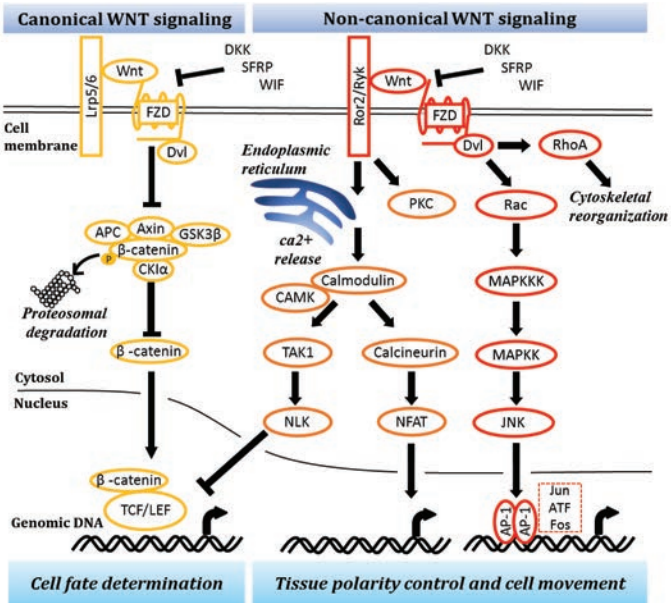
Staff members
Senior Investigator: Younes Achouri (Platform Manager) • **Postdoctoral Fellows:** Mohamad Assi, Mickaël Di-Luoffo, Claude Gérard • **PhD Students:** Louis Collet, Lila Gannoun, Elsa Ghurburrun, Nora Meyers, Janne Tys • **Research Assistants:** Sabine Cordi, Katarzyna Konobrocka • **Technical Assistants:** Freddy Abrassart, Mourad El Kaddouri • **Administrative Support:** Marjorie Decroly, Julie Klein

Wen-Hui Lien

Signaling Crosstalk

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

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



In mammals, Wnt signaling pathways, including canonical and non-canonical Wnt signaling, regulate diverse processes, such as cell proliferation, differentiation, migration and polarity (Figure). 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 tyrosine kinase-like orphan receptor 2 (Ror2) in the regulation of stem cells and tumorigenesis.

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

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

Staff members

PhD Students: Gaia Cangiotti, Christopher Lang, Anthony Veltri • **Undergraduate Student:** Maryse Schmoetten • **Research Assistant:** Marcel McCullough Figueras • **Technical Assistant:** Maria Kim • **Administrative Support:** Aimée-Lys Rusesabagina

Christophe Pierreux

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

Epithelial Differentiation

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

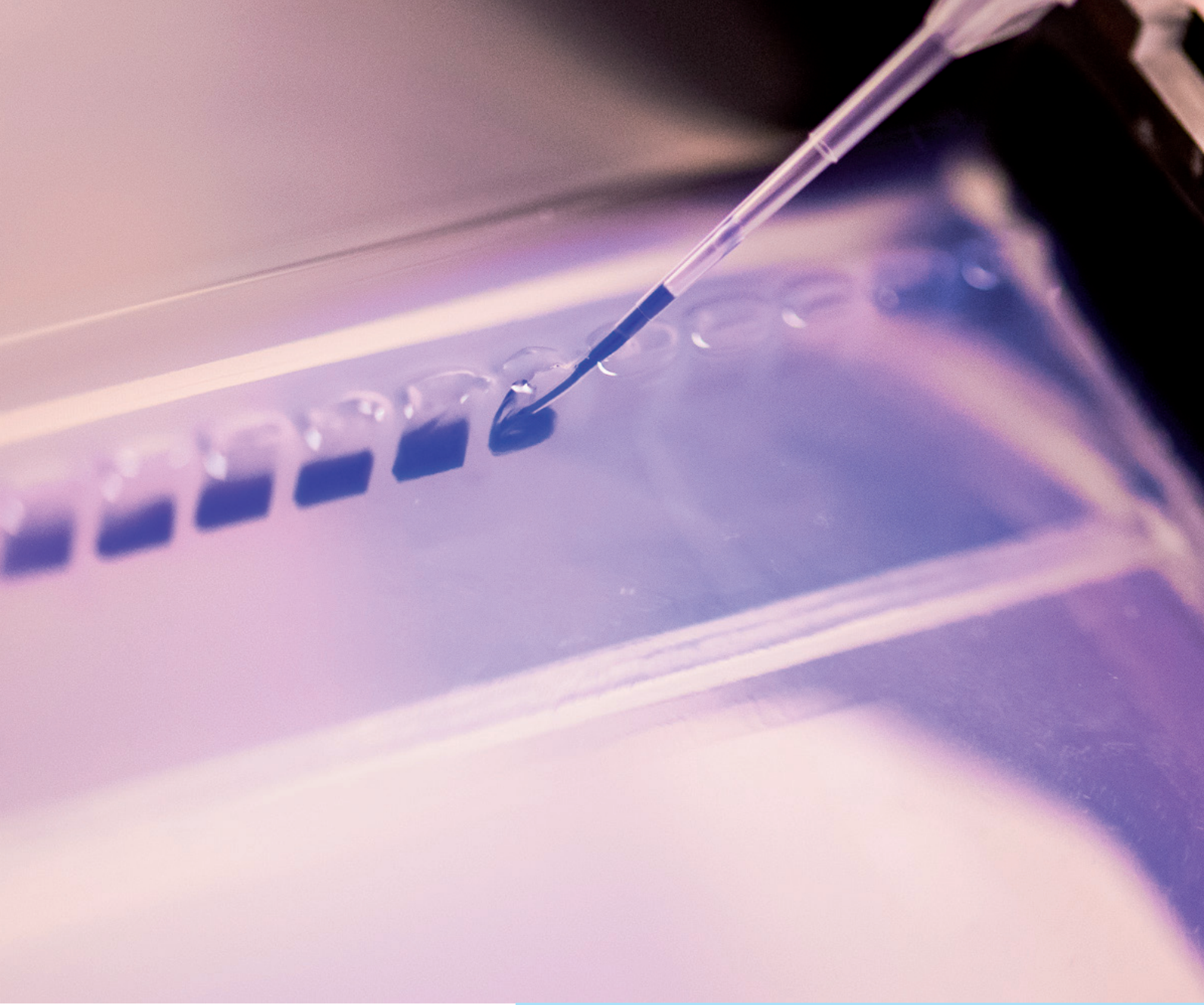
"In-depth characterization of cellular and molecular mechanisms during embryonic development and disease paves the way towards organ bioprinting and therapeutic testing."

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

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

Staff members

Emeritus: Pierre J. Courtoy • **Postdoctoral Fellow:** Tongsong Wang • **PhD Students:** Jonathan Degosserie, Léolo Gonay, Giuseppina Grieco, Charlotte Heymans, Virginie Janssens, Catherine Spourquet • **Undergraduate Student:** Ophélie Delcorte • **Research Assistant:** Pascale Lemoine • **Technical Assistant:** Abdelkader El Kaddouri • **Administrative Support:** Aimée-Lys Rusesabagina



Infections and Inflammations

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

Jean-François Collet

Bacterial Stress Responses

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

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

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

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

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

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

Staff members

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

Jean-Paul Coutelier

Infections & Immunity

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

The possibility for evoluted organisms to survive infections depends on the ability of their immune system to eliminate the pathogenic agent. Therefore, specialized responses, involving different subsets of immune cells such as cytolytic lymphocytes, T helper and B lymphocytes and macrophages, the molecules that allow those cells to communicate, and the products of those interactions, including antibodies, have been elaborated. Since distinct infectious agents induce different responses, infections result 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.

"Modulation of the host immune microenvironment by LDV infection triggered NK cell activation and IFN-γ production, resulting in the inhibition of the development of some tumors such as plasmacytoma and mesothelioma."

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, not only in antiviral antibodies that were more efficient to protect mice against a fatal polioencephalomyelitis, but also in immunoglobulins with an antigenic target unrelated to viral proteins. LDV-induced response includes also an early production of Type 1 interferon (IFN); transient production of pro-inflammatory cytokines, including IL-6 and IL-12; an enhancement of macrophage phagocytic activity; a transient NK cell activation, characterized by enhanced IFN-γ production and cytolytic activity; and a shift in T helper lymphocyte differentiation towards the Th1 cell subset.

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

We wish next to extend this analysis of the relationship between infectious agents and the immune microenvironment to parasitic diseases. Using animal models and clinical studies, we will determine whether helminth infections affect the severity of malaria through modulation of the host gut microbiota and the induction of T helper and regulatory responses. We will also analyze the consequences of Plasmodium infection on immune-mediated concomitant host diseases.

Staff members
PhD Students: Mélanie Gaignage, Mohamed Mandour •
Research Assistant: Michaël Moray

LUDWIG CANCER RESEARCH
Brussels

Jean-Christophe Renauld &
Laure Dumoutier

Inflammatory Disorders & Cytokines

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

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

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

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

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

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

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

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

Staff members
Emeritus: Jacques Van Snick • **Postdoctoral Fellows:** Perrine Cochez, Muriel Lemaire • **PhD Students:** Elisabeth Losdyck, Camille Michiels • **Undergraduate Students:** Mathilde Choteau, Ariane Sablon • **Research Assistants:** Pamela Cheou, Emilie Hendrickx • **Administrative Support:** Geneviève Schoonheydt

Thomas Michiels

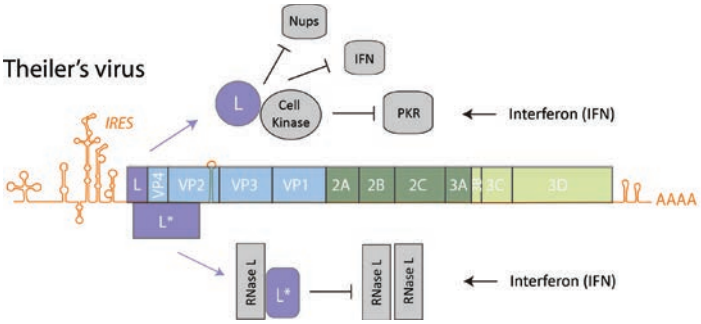
Viral Persistence

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

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

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

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



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

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

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

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

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

Staff members

Guest Investigators: Eric Freundt, Yohei Hayashi • **PhD Students:** Teresa Cesaro, Melissa Drappier, Sophie Jacobs, Michael Peeters • **Research Assistants:** Stéphane Messe, Muriel Minet, Fanny Wavreil • **Technical Assistant:** Christian Miserez

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

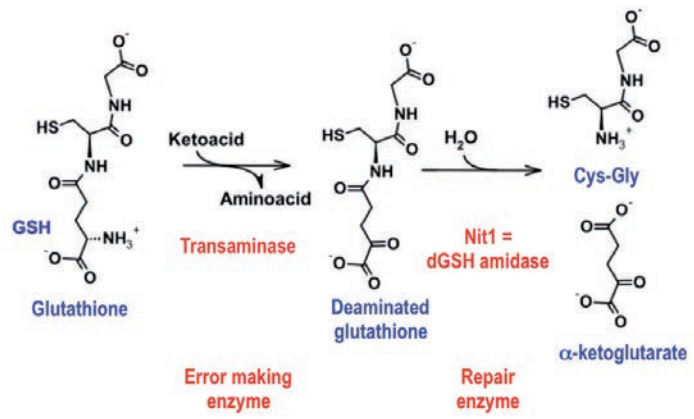
Metabolite Repair

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

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

These findings led us to identify additional metabolite repair enzymes. One of the last two that we described is a phosphatase that is indispensable to destroy two side-products, erythronate-4-phosphate and L-2-phospholactate, made by two major enzymes of glycolysis. Erythronate 4-phosphate is a strong inhibitor (Ki < 1 µM) of 6-phosphogluconate dehydrogenase, while L-2-phospholactate inhibits the synthesis of the glycolytic regulator fructose-2,6-bisphosphate. Absence of the phosphatase causes dramatic perturbations of sugar metabolism.



The last repair enzyme that we described (Figure) is known as Nit1, and its function has remained an enigma since its discovery about 20 years ago. We found that Nit1 is an amidase that serves to destroy a damaged form of glutathione, deaminated glutathione (dGSH), in which the amino group of the glutamyl moiety has been replaced by a keto group. dGSH results from slow side activities catalyzed by numerous transaminases. Nit1-deficient mice excrete dGSH and therefore lose a substantial amount of cysteine in urine.

Staff members

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

Etienne Marbaix &
Patrick Henriet

Endometrium Physiopathology

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

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

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

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

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

Staff members
PhD Students: Monika Lamba Saini, Charlotte Thieffry •
Undergraduate Students: Mauriane Maja, Marine Trifin •
Administrative Support: Aimée-Lys Rusesabagina

Mark Rider

Protein Phosphorylation

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

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

AMPK acts as a sensor of cellular energy status activated by an increase in the AMP/ATP ratio as occurs during muscle contraction/exercise. The role of AMPK in the cell is to maintain ATP by stimulating ATP-producing pathways and at the same time inhibiting energy-consuming biosynthetic pathways. AMPK has emerged as an attractive therapeutic drug target for treating metabolic disorders. In collaboration with the pharmaceutical company AstraZeneca (Mölndal, Sweden), we investigated whether inhibition of AMP metabolizing enzymes could be a means of achieving or potentiating AMPK activation. Mainly using genetic knockout mouse models, however, we showed that inhibition of AMP-metabolizing enzymes in skeletal muscle would not be a viable strategy for increasing AMPK activity and glucose uptake for the treatment of type 2 diabetes.

Therefore, we took advantage of a potent small-molecule direct AMPK activator called compound '991' to explore AMPK function. Treatment of skeletal muscles with compound 991 efficiently activated AMPK and elicited metabolic effects in muscle that are appropriate for treating type 2 diabetes by stimulating glucose uptake and increasing fatty acid oxidation. Metformin was previously shown to antagonize glucagon-stimulated cyclic AMP signaling in liver, independently of AMPK. However, using compound 991, we provided a novel alternative mechanism by which AMPK antagonizes hepatic glucagon signaling, with implications for lowering liver glucose production in diabetes. Over the years, we have made other significant contributions to the field by discovering new targets downstream of AMPK, such as eukaryotic elongation factor 2 to inhibit protein synthesis, myosin light-chain kinase to inhibit smooth muscle contraction, liver glycogen synthase to inhibit hepatic glycogen synthesis and the FYVE domain-containing phosphatidylinositol 5-kinase to promote skeletal muscle glucose transport.

"Using compound 991, we provided a novel alternative mechanism by which AMPK antagonizes hepatic glucagon signaling, with implications for lowering liver glucose production in diabetes."

In addition to our work on AMPK, we run the protein mass spectrometry (MS) facility on the Brussels campus of UCL. The development of MS techniques for protein analysis has been an important asset for our Institute and the University. Since the acquisition of an electrospray ion-trap mass spectrometer in 1997, the use of MS for our research and collaborations has led to well over 100 publications.

Staff members

Senior Investigator: Didier Vertommen (Platform Manager) • **Postdoctoral Fellows:** Aphrodite Choumessi, Manuel Johanns • **PhD Student:** Sheng-Ju Chuang • **Undergraduate Students:** Annabel Calvert (University of Bristol), Isabel de Rojas (University of Madrid), Joanna Sitek (University of Warsaw) • **Research Assistants:** Gaëtan Herinckx, Nusrat Hussain, Roxane Jacobs, Michaël Moray • **Technical Assistant:** Freddy Abrassart • **Administrative Support:** Aimée-Lys Rusesabagina

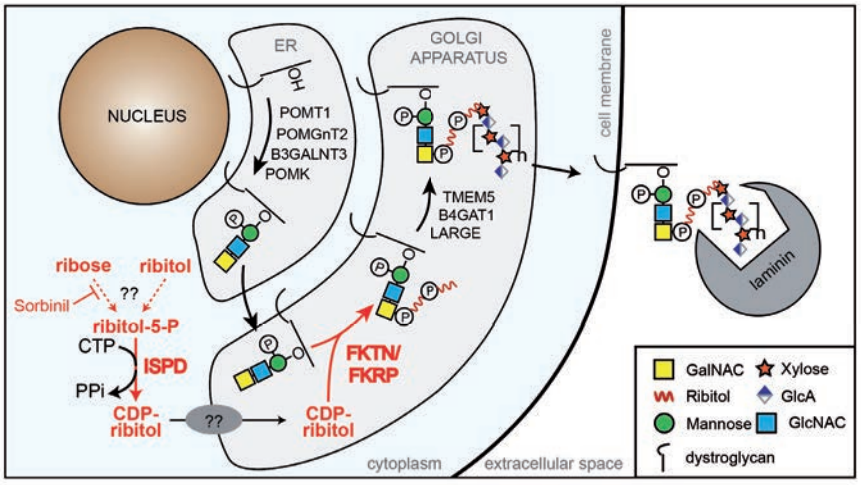
Guido Bommer

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

Cancer Metabolism

The local 'success' of a cancer cell is measured by its ability to proliferate and survive better with the available nutrients than its neighboring cancerous cells. Like any other cell, a cancer cell needs to maintain cellular integrity and fulfill baseline housekeeping functions. All cell types need to synthesize ATP by breaking down nutrients in pathways such as glycolysis, citric acid cycle and mitochondrial oxidative phosphorylation. In addition, proliferating cells in general and cancer cells in particular need to generate 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.

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.



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

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

Selected Publications

Françoise Bontemps & Eric Van Den Neste

1. Van Den Neste E, Cardoen S, Offner F, Bontemps F. Old and new insights into the mechanisms of action of two nucleoside analogs active in lymphoid malignancies: fludarabine and cladribine. Int J Oncol. 2005;27:1123-34.

2. Smal C, Vertommen D, Bertrand L, Ntamashimikiro S, Rider M, Van Den Neste E, Bontemps F. Identification of in vivo phosphorylation sites on human deoxycytidine kinase. Role of Ser-74 in the control of enzyme activity. J Biol Chem. 2006;281:4887-93.

3. Smal C, Van Den Neste E, Maerevoet M, Poire X, Theate I, Bontemps F. Positive regulation of deoxycytidine kinase activity by phosphorylation of Ser-74 in B-cell chronic lymphocytic leukaemia lymphocytes. Cancer Lett. 2007;253:68-73.

4. de Viron E, Knoops L, Connerotte T, Smal C, Michaux L, Saussoy P, Vannuffel P, Beert E, Vekemans MC, Hermans C, Bontemps F, Van Den Neste E. Impaired up-regulation of polo-like kinase 2 in B-cell chronic lymphocytic leukaemia lymphocytes resistant to fludarabine and 2-chlorodeoxyadenosine: a potential marker of defective damage response. Br J Haematol. 2009;147:641-52.

5. de Viron E, Michaux L, Put N, Bontemps F, Van Den Neste E. Present status and perspectives in functional analysis of p53 in chronic lymphocytic leukemia. Leuk Lymphoma. 2012; 53:1445-51.

6. Amsailale R, Van Den Neste E, Arts A, Starczewska E, Bontemps F, Smal C. Phosphorylation of deoxycytidine kinase on Ser-74: Impact on kinetic properties and nucleoside analog activation in cancer cells. Biochem Pharmacol. 2012;84:43-51.

7. Amsailale R, Beyaert M, Smal C, Janssens V, Van Den Neste E, Bontemps F. Protein phosphatase 2A regulates deoxycytidine kinase activity via Ser-74 dephosphorylation. FEBS Lett. 2014;7588:727-32.

8. Beyaert M, Starczewska E, Van Den Neste E, Bontemps F. A crucial role for ATR in the regulation of deoxycytidine kinase activity. Biochem Pharmacol. 2016;100:40-50.

9. Starczewska E, Beyaert M, Michaux L, Vekemans MC, Saussoy P, Bol V, Arana Echarri A, Smal C, Van Den Neste E, Bontemps F. Targeting DNA repair with aphidicolin sensitizes primary chronic lymphocytic leukemia cells to purine analogs. Oncotarget. 2016;7:38367-79.

10. Beyaert M, Starczewska E, González Pérez AC, Vanlangendonck N, Saussoy P, Tilman G, De Leener A, Vekemans MC, Van Den Neste E, Bontemps F. Revaluation of ATR signaling in primary resting chronic lymphocytic leukemia cells: evidence for pro-survival or pro-apoptotic function. Oncotarget. 2017. doi: 10.18632/oncotarget.18144.

Stefan Constantinescu

1. Chachoua I, Pecquet C, El-Khoury M, Nivarthi H, Albu RI, Marty C, Gryshkova V, Defour JP, 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.

2. Balligand T, Achouri Y, Pecquet C, Chachoua I, Nivarthi H, Marty C, Vainchenker W, Plo I, Kralovics R, Constantinescu SN. Pathologic activation of thrombopoietin receptor and JAK2-STAT5 pathway by frameshift mutants of mouse calreticulin. Leukemia. 2016;30:1775-8.

3. Leroy E, Dusa A, Colau D, Motamedi A, Cahu X, Mouton C, Huang LJ, Shiau AK, Constantinescu SN. Uncoupling JAK2 V617F activation from cytokine-induced signaling by modulation of JH2 αC helix. Biochem J. 2016;473:1579-91.

4. Favale F, Messaoudi K, Varghese LN, Boukour S, Pecquet C, Gryshkova V, Defour JP, Albu RI, Bluteau O, Ballerini P, Leverger G, Plo I, Debili N, Raslova H, Favier R, Constantinescu SN*, Vainchenker W*. An incomplete trafficking defect to the cell-surface leads to paradoxical thrombocytosis for human and murine MPL P106L. Blood. 2016;128:3146-58. (*equal contribution)

5. Kapralova K, Horvathova M, Pecquet C, Fialova Kucerova J, Pospisilova D, Leroy E, Kralova B, Milosevic Feenstra JD, Schischlik F, Kralovics R, Constantinescu SN* & Divoky V*. Cooperation of germ line JAK2 mutations E846D and R1063H in hereditary erythrocytosis with megakaryocytic atypia. Blood. 2016;28:1418-23. (*equal contribution)

6. Leroy E, Defour JP, Sato T, Dass S, Gryshkova V, Marlar SM, Staerk J, Constantinescu SN*, Smith SO*. His499 regulates dimerization and prevents oncogenic activation by asparagine mutations of the human thrombopoietin receptor. J Biol Chem. 2016;291:2974-87. (*equal contribution)

7. Defour JP, 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.

8. Pecquet C, Diaconu CC, Staerk J, Girardot M, Marty C, Royer Y, Defour JP, Dusa A, Besancenot R, Giraudier S, Villeval JL, Knoops L, Courtoy PJ, Vainchenker W, Constantinescu SN. Thrombopoietin receptor down-modulation by JAK2 V617F: restoration of receptor levels by inhibitors of pathologic JAK2 signaling and of proteasomes. Blood. 2012;119:4625-35.

9. Staerk J, Defour JP, 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.

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. 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.

2. 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. 2017; epub ahead of print. (doi: 10.1038/gim.2017.104) (*equal contribution)

3. Coomans de Brachène A, Dif N, de Rocca Serra A, Bonnineau C, Velghe AI, Larondelle Y, Tyteca D, Demoulin J-B. PDGF-induced fibroblast growth requires monounsaturated fatty acid production by stearoyl-CoA desaturase. FEBS Open Bio. 2017;7:414-23.

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

5. 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.

6. Arts FA, Velghe AI, Stevens M, Renauld J-C, Essaghir A, Demoulin J-B. Idiopathic basal ganglia calcification-associated PDGFRB mutations impair the receptor signalling. J Cell Mol Med. 2015;19:239-48.

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. 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:pii.91438.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

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.

Sophie Lucas

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

2. 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.

3. 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.

4. Cuende J, Lienart 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.

5. Huygens C, Lienart 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.

6. 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.

7. 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.

Benoît Van den Eynde

1. Ma W, Zhang Y, Vigneron N, Stroobant V, Thielemans K, van der Bruggen P, Van den Eynde BJ. Long-peptide cross-presentation by human dendritic cells occurs in vacuoles by peptide exchange on nascent MHC class I molecules. J Immunol. 2016;196:1711-20.

2. 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.

3. 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; in press.

4. 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.

5. Dalet A, Robbins PF, Stroobant V, Vigneron N, Li YF, El-Gamil M, Hanada K-i, Yang JC, Rosenberg SA, Van den Eynde BJ. An antigenic peptide produced by reverse splicing and double asparagine deamidation. Proc Natl Acad Sci USA. 2011;108:E323-331.

6. 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.

7. 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.

8. 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.

9. 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.

10. Uyttenhove C, Pilotte L, Théate I, Stroobant V, Colau D, Parmentier N, Boon T, Van den Eynde BJ. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. Nat Med. 2003;9:1269-74.

Pierre van der Bruggen

1. 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.

2. Demotte N, Bigirimana R, Wieërs G, Stroobant V, Squifflet J-L, Carrasco J, Thielemans K, Baurain J-F, Van Der Smissen P, Courtoy PJ, van der Bruggen P. A short treatment with galactomannan GM-CT-01 corrects the functions of freshly isolated human tumor infiltrating lymphocytes. Clin Cancer Res. 2014;20:1823-33.

3. Demotte N, Wieërs G, Van Der Smissen P, Moser M, Schmidt CW, Thielemans K, Squifflet J-L, Weynand B, Carrasco J, Lurquin C, Courtoy PJ, van der Bruggen P. A galectin-3 ligand corrects the impaired function of human CD4 and CD8 tumor infiltrating lymphocytes and favors tumor rejection in mice. Cancer Res. 2010;70:7476-88.

4. 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.

5. Carrasco J, Godelaine D, Van Pel A, Boon T, van der Bruggen P. CD45RA on human memory CD8 T cells is a marker for the time elapsed since the last antigenic stimulation. Blood. 2006;108:2897-905.

6. Schultz E, Chapiro J, Lurquin C, Claverol S, Burlet-Schiltz O, Warnier G, Russo V, Morel S, Lévy F, Boon T, Van den Eynde B, van der Bruggen P. The production of a new MAGE-3 peptide presented to cytolytic T lymphocytes by HLA-B40 requires the immunoproteasome. J Exp Med. 2002;195:391-9.

7. Chaux P, Vantomme V, Stroobant V, Thielemans K, Corthals J, Luiten R, Eggermont A, Boon T, van der Bruggen P. Identification of MAGE-3 epitopes presented by HLA-DR molecules to CD4+ T lymphocytes. J Exp Med. 1999;189:767-77.

8. Mandruzzato S, Brasseur F, Andry G, Boon T, van der Bruggen P. A CASP-8 mutation recognized by cytolytic T lymphocytes on a human head and neck carcinoma. J Exp Med. 1997;186:785-93.

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. Tyteca D, D'Auria L, Van Der Smissen P, Medts T, Carpentier S, Monbaliu JC, de Diesbach P, Courtoy PJ. Three unrelated sphingomyelin analogs spontaneously cluster into plasma membrane micrometric domains. Biochim Biophys Acta. 2010;1798:909-27.

2. D'Auria L, Van Der Smissen P, Bruyneel F, Courtoy PJ*, Tyteca D*. Segregation of fluorescent membrane lipids into distinct micrometric domains: Evidence for phase compartmentation of natural lipids?. PLOS One. 2011;6:e17021. (*equal contribution)

3. D'Auria L, Fenaux M, Aleksandrowicz P, Van Der Smissen P, Chantrain C, Vermylen C, Vikkula M, Courtoy PJ, Tyteca D. Micrometric segregation of fluorescent membrane lipids: relevance for endogenous lipids and biogenesis in erythrocytes. J Lipid Res. 2013;54:1066-76.

4. D'Auria L, Deleu M, Dufour S, Mingeot-Leclercq M-P, Tyteca D. Surfactins modulate the lateral organization of fluorescent membrane polar lipids: a new tool to study drug:membrane interaction and assessment of the role of cholesterol and drug acyl chain length. Biochim Biophys Acta. 2013;1828:2064-73.

5. Carquin M, Pollet H, Veiga-da-Cunha M, Cominelli A, Van Der Smissen P, N'Kuli F, Emonard H, Henriet P, Mizuno H, Courtoy PJ, Tyteca D. Endogenous sphingomyelin segregates into submicrometric domains in the living erythrocyte membrane. J Lipid Res. 2014;55:1331-42.

6. Carquin M, Conrard L, Pollet H, Van Der Smissen P, Cominelli A, Veiga-da-Cunha M, Courtoy PJ, Tyteca D. Cholesterol segregates into submicrometric domains at the living erythrocyte membrane: evidence and regulation. Cell Mol Life Sci. 2015;72:4633-51.

7. 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.

8. Mound A, Lozanova V, Warnon C, Hermant M, Robic J, Guere C, Vie K, Lambert de Rouvroit C, Tyteca D, Debacq-Chainiaux F, Poumay Y. Non-senescent keratinocytes organize in plasma membrane submicrometric lipid domains enriched in sphingomyelin and involved in re-epithelialization. Biochim Biophys Acta. 2017;1862:958-71.

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. 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.

Miikka Vikkula

1. Seront E, Limaye N, Boon LM, Vikkula M. La rapamycine ouvre l'ère des thérapies ciblées dans les malformations veineuses. Méd Sci (Paris). 2016;32:574-8.

2. Havelange V, Pepermans X, Ameye G, Théate I, Callet-Bauchu E, Barin C, Penther D, Lippert E, Michaux L, Mugneret F, Dastugue N, Raphaël M, Vikkula M, Antoine-Poirel H. Genetic differences between paediatric and adult Burkitt lymphomas. Br J Haematol. 2016;173:137-44.

3. Persu A, Evenepoel L, Jin Y, Mendola A, Ngueta G, Yang W-Y, Gruson D, Horman S, Staessen JA, Vikkula M. STK39 and WNK1 are potential hypertension susceptibility genes in the BELHYPGEN cohort. Medicine (Baltimore). 2016;95:e2968.

4. Goffinet L, Oussalah A, Guéant-Rodriguez RM, Chery C, Basha M, Avogbe PH, Josse T, Jeannesson E, Rouyer P, Flayac J, Gerard P, Le Touze A, Bonin-Goga B, Goga D, Simon E, Feillet F, Vikkula M, Guéant JL. Cystathionine β-synthase genetic variant rs2124459 is associated with a reduced risk of cleft palate in French and Belgian populations. J Med Genet. 2016;53:828-34.

5. Castrén E, Salminen P, Vikkula M, Pitkäranta A, Klockars T. Inheritance patterns of Infantile Hemangioma. Pediatrics. 2016;138:e20161623.

6. Dompmartin A, Revencu N, Boon LM, Vikkula M. Disorders affecting cutaneous vasculature. In: Griffiths C et al, eds. Rook's Textbook of Dermatology, Part 6/Chapter 73. 9th ed, John Wiley & Sons. 2016.

7. 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)

8. 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.

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

10. Wassef M, Blei F, Adams DM, Alomari A, Baselga E, Berenstein A, Burrows P, Frieden I, Garzon M, Lopez-Gutierrez J-C, Lord D, Mitchel S, Powell J, Prendiville J, Vikkula M; ISSVA Board and Scientific Committee. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. Pediatrics. 2015;136:e203-14.

Charles De Smet

1. 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 post-infarction remodeling. JCI Insight. 2017;2:91810

2. 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.

3. 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.

4. Van Tongelen A, Loriot A, De Backer O, De Smet C. Application of CRISPR/cas9-directed homologous recombination to the generation of human tumor cells with conditional knockout of an X-linked microRNA locus. Gene Technol. 2015;4:1000124.

5. 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)

6. 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.

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

9. Loriot A, Reister S, Parvizi KG, Lysy PA, De Smet C. DNA methylation-associated repression of cancer-germline genes in human embryonic and adult stem cells. Stem Cells. 2009;27:822-4.

10. 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.

11. 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. Viceconte N, Dheur MS, 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.

2. Koskas S, Decottignies A, Dufour S, Pezet M, Verdel A, Vourc'h C, Faure V. Heat shock factor 1 promotes TERRA transcription and telomere protection upon heat stress. Nucleic Acids Res. 2017;45:6321-33.

3. 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.

4. 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)

5. 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)

6. Van Beneden A, Arnoult N, Decottignies A. Telomeric RNA expression: length matters. Front Oncol. 2013;3:178.

7. 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)

8. Mattiussi M, Tilman G, Lenglez S, Decottignies A. Human telomerase represses ROS-dependent cellular responses to Tumor Necrosis Factor-alpha without affecting NF-kappaB activation. Cell Signal. 2012;24:708-17.

9. Tilman G, Arnoult N, Lenglez S, Van Beneden A, Loriot A, De Smet C, Decottignies A. Cancer-linked satellite 2 DNA hypomethylation does not regulate Sat2 non-coding RNA expression and is initiated by heat shock pathway activation. Epigenetics 2012;7:903-13.

10. Tilman G, Loriot A, Van Beneden A, Arnoult N, Londoño-Vallejo JA, De Smet C, Decottignies A. Subtelomeric DNA hypomethylation is not required for telomeric sister chromatid exchanges in ALT cells. Oncogene. 2009;28:1682-93.

Frédéric Lemaigre & Patrick Jaquemin

1. 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.

2. 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.

3. 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.

4. Cordi S, Godard C, Saandi T, Jacquemin P, Monga SP, Colnot S, Lemaigre FP. Role of β-catenin in development of bile ducts. Differentiation. 2016;91:42-9.

5. Augereau C, Lemaigre FP, Jacquemin P. Extraction of high-quality RNA from pancreatic tissues for gene expression studies. Anal Biochem. 2016;500:60-2.

6. Demarez C, Hubert C, Sempoux C, Lemaigre FP. Expression of molecular differentiation markers does not correlate with histological differentiation grade in intrahepatic cholangiocarcinoma. PLoS One. 2016;11:e0157140.

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. Hanley J, Dhar DK, Mazzacuva F, Fiadeiro R, Burden JJ, Lyne AM, Smith H, Straatman-Iwanowska A, Banushi B, Virasami A, Mills K, Lemaigre FP, Knisely AS, Howe S, Sebire N, Waddington S, Paulusma CC, Clayton P, Gissen P. Vps33b is crucial for structural and functional hepatocyte polarity. J Hepatol. 2017;66:1001-11.

9. Gérard C, Tys J, Lemaigre FP. Gene regulatory networks in differentiation and direct reprogramming of hepatic cells. Semin Cell Dev Biol. 2017;66:43-50.

10. 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 2017; epub ahead of print (doi: 10.1002/hep.29475).

Wen-Hui Lien

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

2. 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.

3. 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.

4. 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.

5. 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.

6. Bock C, Beerman I, Lien WH, Smith ZD, Gu H, Boyle P, Gnirke A, Fuchs E, Rossi DJ, Meissner A. DNA methylation dynamics during in vivo differentiation of blood and skin stem cells. Mol Cell. 2012;47:633-47.

7. 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.

8. 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.

9. 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.

10. Wang W, Jossin Y, Chai G, Lien WH, Tissir F, Goffinet A. Feedback regulation of apical progenitor fate by immature neurons through Wnt7, Celsr7 and Fzd3 signaling. Nat Commun. 2016;7:10936.

Christophe Pierreux

1. 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.

2. Viceconte N, Dheur M-S, Majerova E, Pierreux CE, Baurain J-F, van Baren N, Decottignies A. Limited replicative potential of melanoma metastases unable to maintain telomere length. Cell Rep. 2017;19:2529-43.

3. 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)

4. 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)

5. Dupasquier S, Delmarcelle AS, Marbaix E, Cosyns JP, Courtoy PJ, Pierreux CE. Validation of housekeeping genes and impact on normalized gene expression in clear renal cell carcinoma: critical reassesment of ZONAB/CSDA expression. BMC Mol Biol. 2014;15:9.

6. Delmarcelle AS, Villacorte M, Hick AC, Pierreux CE. An ex vivo culture system to study thyroid development. J Vis Exp. 2014;6(88).

7. 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.

8. 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.

9. 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.

10. Lima WR, Parreira KS, Devuyst O, Caplanusi A, N'Kuli F, Marien B, Van Der Smissen P, Alves PM, Verroust P, Christensen EI, Terzi F, Matter K, Balda MS, Pierreux CE*, Courtoy PJ*. ZONAB promotes proliferation and represses differentiation of proximal tubules epithelial cells. J Am Soc Nephrol. 2010;21:478-88. (*equal contribution)

Jean-François Collet

1. Arts IS, Vertommen D, Baldin F, Laloux G, Collet J-F. Comprehensively characterizing the thioredoxin interactome in vivo highlights the central role played by this ubiquitous oxidoreductase in redox control. Mol Cell Proteomics. 2016;15:2125-40.

2. Lafaye C, Van Molle I, Tamu Dufe V, Wahni K, Boudier A, Leroy P, Collet J-F, Messens J. Sulfur denitrosylation by an engineered Trx-like DsbG enzyme identifies nucleophilic cysteine hydrogen bonds as key functional determinant. J Biol Chem. 2016;291:15020-8.

3. Szewczyk J, Collet J-F. The journey of lipoproteins through the cell: one birthplace, multiple destinations. Adv Microb Physiol. 2016;69:1-50.

4. Zhang Y, Agrebi R, Bellows LE, Collet J-F, Kaever V, Gründling A. Evolutionary adaptation of the essential tRNA methyltransferase TrmD to the signaling molecule 3',5'-cAMP in bacteria. J Biol Chem. 2017;292:313-27.

5. Ezraty B, Gennaris A, Barras F, Collet J-F. Oxidative stress, protein damage and repair in bacteria. Nat Rev Microbiol. 2017;15:385-96.

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

7. 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.

8. Depuydt M, Leonard SE, Vertommen D, Denoncin K, Morsomme P, Wahni K, Messens J, Carroll KS, Collet J-F. A periplasmic reducing system protects single cysteine residues from oxidation. Science. 2009;326:1109-11.

9. 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.

10. Williamson JA, Cho SH, Ye J, Collet J-F, Beckwith JR, Chou JJ. Structure and multistate function of the transmembrane electron transporter CcdA. Nat Struct Mol Biol. 2015;22:809-14.

Jean-Paul Coutelier

1. 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.

2. 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.

3. 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.

4. 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; epub ahead of print. (doi: 10.1002/iid3.187)

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. Meite M, Léonard S, El Azami El Idrissi M, Izui S, Masson PL, Coutelier J-P. Exacerbation of autoantibody-mediated hemolytic anemia by viral infection. J Virol. 2000;74:6045-9.

8. 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.

9. 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.

10. 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.

Jean-Christophe Renauld & Laure Dumoutier

1. Steenwinckel V, Louahed J, Orabona C, Huaux F, Warnier G, McKenzie A, Lison D, Levitt R, Renauld J-C. IL-13 mediates in vivo IL-9 activities on lung epithelial cells but not on hematopoietic cells. J Immunol. 2007;178:3244-51.

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

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

4. 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.

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. 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.

7. 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.

8. 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.

9. Martin JC, Wolk K, Beriou G, Abidi A, Witte-Händel E, Louvet C, Kokolakis G, Drujont L, Dumoutier L, Renauld J-C, Sabat R, Josien R. Limited presence of IL-22 binding protein, a natural IL-22 inhibitor, strengthens psoriatic skin inflammation. J Immunol. 2017;198:3671-8.

10. 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.

Thomas Michiels

1. 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.

2. 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.

3. Rakus K, Ronsmans M, Forlenza M, Boutier M, Piazzon MC, Jazowiecka-Rakus J, Gatherer D, Athanasiadis A, Farnir F, Davison AJ, Boudinot P, Michiels T, Wiegertjes GF, Vanderplasschen A. Conserved fever pathways across vertebrates: a herpesvirus expressed decoy TNF-α receptor delays behavioral fever in fish. Cell Host Microbe. 2017;21:244-53.

4. Sorgeloos F, Lardinois C, Jacobs S, van Kuppeveld FJ, Kaspers B, Michiels T. Neurotropism of Saffold virus in a mouse model. J Gen Virol. 2016;97:1350-5.

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

6. 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.

7. 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.

8. Delhaye S, Paul S, Blakqori G, Minet M, Weber F, Staeheli P, Michiels T. Neurons produce type I interferon during viral encephalitis. Proc Natl Acad Sci USA. 2006;103: 7835-40.

Emile Van Schaftingen & Maria Veiga-da-Cunha

1. Nolting K, Park JH, Tegtmeyer LC, Zühlsdorf A, Grüneberg M, Rust S, Reunert J, Du Chesne I, Debus V, Schulze-Bahr E, Baxter RC, Wada Y, Thiel C, van Schaftingen E, Fingerhut R, Marquardt T. Limitations of galactose therapy in phosphoglucomutase 1 deficiency. Mol Genet Metab Rep. 2017;13:33-40.

2. Barbier T, Machelart A, Zúñiga-Ripa A, Plovier H, Hougardy C, Lobet E, Willemart K, Muraille E, De Bolle X, Van Schaftingen E, Moriyón I, Letesson JJ. Erythritol availability in bovine, murine and human models highlights a potential role for the host aldose reductase during Brucella infection. Front Microbiol. 2017;8:1088.

3. Gold WA, Sobreira N, Wiame E, Marbaix A, Van Schaftingen E, Franzka P, Riley LG, Worgan L, Hübner CA, Christodoulou J, Adès LC. A novel mutation in GMPPA in siblings with apparent intellectual disability, epilepsy, dysmorphism, and autonomic dysfunction. Am J Med Genet A. 2017;173:2246-50.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. Barbier T, Collard F, Zúñiga-Ripa A, Moriyón I, Godard T, Becker J, Wittmann C, Van Schaftingen E, Letesson JJ. Erythritol feeds the pentose phosphate pathway via three new isomerases leading to D-erythrose-4-phosphate in Brucella. Proc Natl Acad Sci USA. 2014;111:17815-20.

10. Veiga-da-Cunha M, Chevalier N, Stroobant V, Vertommen D, Van Schaftingen E. Metabolite proofreading in carnosine and homocarnosine synthesis: molecular identification of PM20D2 as β-alanyl-lysine dipeptidase. J Biol Chem. 2014;289:19726-36.

Etienne Marbaix & Patrick Henriet

1. 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

Mark Rider

1. Rider MH, Bertrand L, Vertommen D, Michels PA, Rousseau GG, Hue L. 6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase: head-to-head with a bifunctional enzyme that controls glycolysis. Biochem J. 2004;381:561-79.

2. Horman S, Vertommen D, Heath R, Neumann D, Mouton V, Woods A, Schlattner U, Wallimann T, Carling D, Hue L, Rider MH. Insulin antagonizes ischemia-induced Thr172 phosphorylation of AMP-activated protein kinase alpha-subunits in heart via hierarchical phosphorylation of Ser485/491. J Biol Chem. 2006;281:5335-40.

3. Lai YC, Kviklyte S, Vertommen D, Lantier L, Foretz M, Viollet B, Hallén S, Rider MH. A small-molecule benzimidazole derivative that potently activates AMPK to increase glucose transport in skeletal muscle: Comparison with effects of contraction and other AMPK activators. Biochem J. 2014;460:363-75.

4. Horman S, Browne G, Krause U, Patel J, Vertommen D, Bertrand L, Lavoinne A, Hue L, Proud C, Rider MH. Activation of AMP-activated protein kinase leads to the phosphorylation of elongation factor 2 and an inhibition of protein synthesis. Curr Biol. 2002;12:1419-23.

5. Plaideau C, Lai Y-C, Zanou N, Kviklyte S, Lofgren L, Andersén H, Vertommen D, Gailly P, Hue L, Bohlooly M, Hallén S, Rider MH. Pharmacological inhibition of AMP-deaminase in skeletal muscle during contraction: effects on purine nucleotide concentrations and AMPK activation in comparison with genetic Ampd1 deletion. Chem Biol. 2014;21:1497-510.

6. 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.

7. 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.

8. Liu Y, Lai YC, Hill EV, Tyteca D, Carpentier S, Ingvaldsen A, Vertommen D, Lantier L, Foretz M, Dequiedt F, Courtoy PJ, Erneux C, Viollet B, Shepherd PR, Tavaré JM, Jensen J, Rider MH. Phosphatidylinositol 3-phosphate 5-kinase (PIKfyve) is an AMPK target participating in contraction-stimulated glucose uptake in skeletal muscle. Biochem J. 2013; 455:195-206.

9. Tossounian MA, Pedre B, Wahni K, Erdogan H, Vertommen D, Van Molle I, Messens J. Corynebacteruin diphteriae methionine sulfoxide reductase A exploits a unique mycothiol redox relay mechanism. J Biol Chem. 2015;290:11365-75.

10. Rider MH, Waelkens E, Derua R, Vertommen D. Fulfilling the Krebs and Beavo criteria for studying protein phosphorylation in the era of mass spectrometry-driven kinome research. Arch Physiol Biochem. 2009;15:298-310.

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.

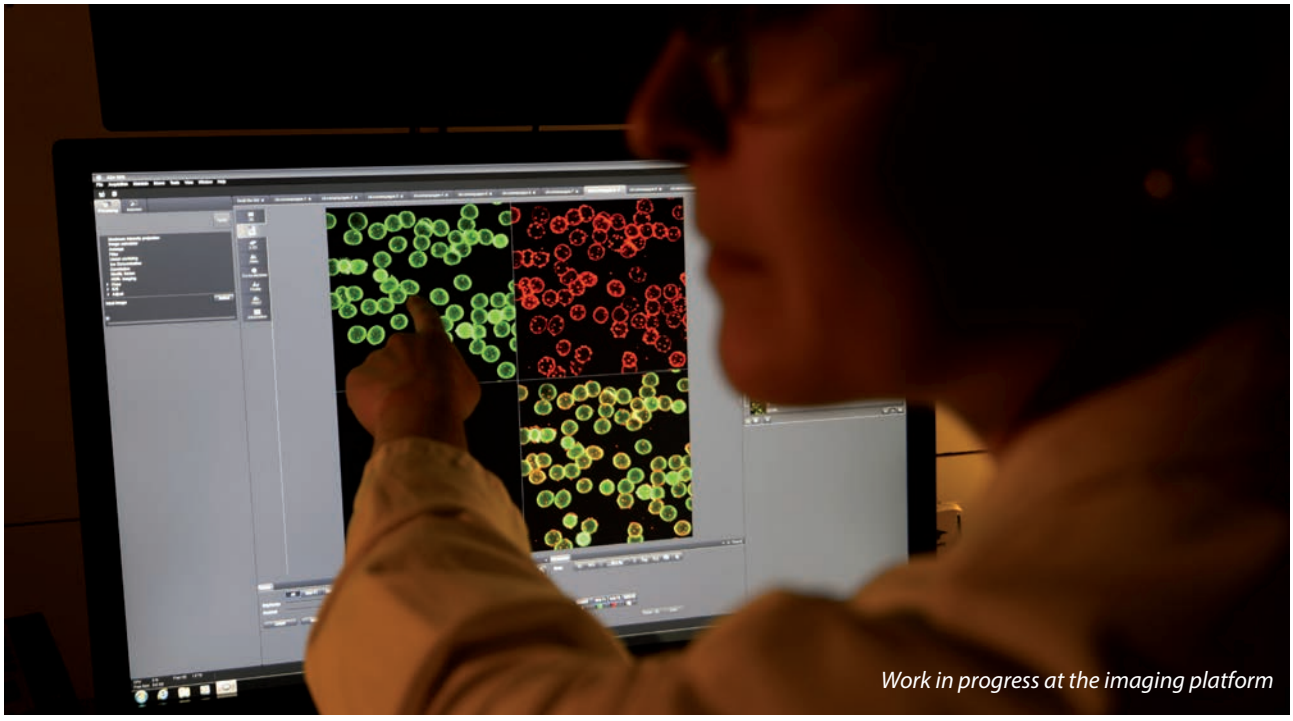
6. Bommer GT, MacDougald OA. Regulation of lipid homeostasis by the bifunctional SREBF2-miR33a locus. Cell Metab. 2011;13:241-7.

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.



Work in progress at the imaging platform

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. P. Coulie and is run by Dr. N. Dauguet.
[W] http://www.deduveinstitute.be/flow-cytometry-and-cell-sorting

Genomics

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

Imaging

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

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 Prof. M. Rider and is run by Dr. D. Vertommen, together with Prof. P. Morsomme and Dr. H. Degand at the Institute of Life Sciences (University of Louvain).
[W] http://uclouvain.be/en/research-institutes/isv/massprot

Transgenesis

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

Prizes, Awards and Honors

to Thierry BOON • ITOC Lifetime Achievement Award

Assigned in 2017 by the Cancer Drug Development Forum and the Society for Immunotherapy of Cancer to "…one of the most renowned researchers in the field of anti-cancer vaccines".

to Stefan CONSTANTINESCU • Prix quinquennal des sciences médicales fondamentales 2011-2015

Awarded every five years by the Belgian government to a Belgian researcher for the best published work in basic medical sciences.

to Stefan CONSTANTINESCU • Special Recognition Award from the A*Star Experimental Therapeutics Centre, Singapore

Assigned in 2017 on the occasion of its 10th anniversary to a scientist that promoted research at the Centre via collaborative research.

to Patrick JACQUEMIN • Prix Henri Fauconnier 2014-2016

Awarded every three years to a Belgian researcher by the Académie royale de Médecine for a work aiming at the cure of cancer, tuberculosis or "any other social scourge".

to Géraldine LALOUX • Prix d'Alvarenga, de Piauhy 2016

Awarded every year to a Belgian researcher by the Académie royale de Médecine for the best thesis on a medical topic.

to Nisha LIMAYE • Prix Lambertine Lacroix 2016

Awarded every other year by the FNRS to a Belgian researcher aged 50 or less, for a translational research on cardio-vascular diseases.

During the academic year 2016-2017, Laurence BOON became President of the International Society for the Study of Vascular Anomalies for the period 2016-2018; Jean-François COLLET was elected Member of the Académie royale de Belgique, Classe des Sciences; Stefan CONSTANTINESCU became Vice-President of the Federation of European Academies of Medicine for the period 2017-2020, as well as Honorary Member of the Romanian Academy, and was appointed Consultant interne at the Service of Hematology of University Hospital Saint-Luc; Wen-Hui LIEN was elected to the Board of the Belgian Society for Stem Cell Research; the University of Oxford conferred the title of Professor of Tumour Immunology on Benoît VAN DEN EYNDE; and Miikka VIKKULA was promoted Full Member of the Académie royale de Médecine de Belgique.

PhD Theses - August 2016 to July 2017

Géraldine DESSILLY • *Impact des polymorphismes génétiques de la P-glycoprotéine sur le transport des immunosuppresseurs et des inhibiteurs de tyrosine kinases* • Promoter: V. Hautfroid

Perrine COCHEZ • *AhR and Ccr6 are not required for IL-22 production in imiquimod-induced psoriasis model* • Promoter: L. Dumoutier

Eliza STARCZEWSKA • *From analysis of purine analogue activation to the development of new therapeutic strategies in chronic lymphocytic leukaemia* • Promoter: F. Bontemps

Joanna SZEWCZYK • *The Escherichia coli stress sensor protein RcsF: stress sensing mechanism and subcellular targeting unravelled* • Promoter: J.-F. Collet

Emilie LEROY • *Secondary site mutations restoring physiologic function for JAK2 V617F and identification of novel allosteric sites in oncoproteins: new therapeutic opportunities for blood malignancies* • Promoter: S. Constantinescu

David SCHRÖDER • *Tumor-specific CD8 T cells in a primary human breast carcinoma: a detailed analysis* • Promoter: P. Coulie

Isabelle ARTS • *How bacterial thioredoxin proteins make or break disulfides* • Promoter: J.-F. Collet

Amina HOUDDANE • *Role of Akt/PKB and PFKFB isoenzymes in the control of glycolysis, cell proliferation and protein synthesis in mitogen-stimulated thymocytes* • Promoter: M. Rider

Manuel JOHANNS • *AMPK in the control of hepatic glucagon signalling and protein synthesis* • Promoter: M. Rider

Florence ARTS • *PDGFRB mutations cause infantile myofibromatosis and other human congenital diseases* • Promoter: J.-B. Demoulin

Aurélie VAN TONGELEN • *Identification of a novel cancer-germline transcript within the miRNA harboring GABRA3 gene. Epigenetic alterations of the locus in tumors* • Promoter: C. De Smet

Olivier DEDOBBELEER • *La protéine GARP participe à l'activation du TGF-β dans les lymphocytes B humains et contrôle la production d'IgA* • Promoter: S. Lucas.

Lectures & Scientific Events - August 2016 to July 2017

21st Heremans Memorial Lecture

Hidde PLOEGH • *Boston Children's Hospital & Harvard Medical School, Boston, USA*

A biochemical exploration of the immune system: from atomic resolution to non-invasive imaging in vivo

(podcast: https://www.youtube.com/watch?v=RkXViCHR4FE)

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

Shu S. CHNG • *Singapore Center for Environmental Life Sciences Engineering, National University of Singapore*

Bacterial outer membrane lipid trafficking and homeostasis

Radek SKODA • *University Hospital Basel, Switzerland*

Molecular pathogenesis and stem cell characteristics of myeloproliferative neoplasms

Agnieszka CHACINSKA • *International Institute of Molecular and Cell Biology, Warsaw, Poland*

Protein trafficking at the crossroads to mitochondria

Harris BERNSTEIN • *National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland, USA*
The assembly of the autotrans porter family of bacterial outer membrane proteins

Kerwyn C. HUANG • *School of Medicine, University of Stanford, CA, USA*
Curvature sensing of the bacterial cytoskeleton dictates cell-shape maintenance and cell-size control

Susanna MANDRUZZATO • *Istituto Oncologico Veneto & University of Padova, Italy*
Immune evasion in cancer: role of myeloid-derived suppressor cells

Bruno ANDRE • *Institute of Molecular Biology and Medicine, Université Libre de Bruxelles, Gosselies, Belgium*
Lateral segregation, ubiquitylation and endocytosis of amino acid transporters in yeast

James BARDWELL • *Howard Hughes Medical Institute, University of Michigan, Ann Arbor, MI, USA*
Visualizing chaperone mediated protein folding

Fernando M. BELMONTE • *Center for Molecular Biology Severo Ochoa, Madrid, Spain*
Signaling in epithelial morphogenesis and patterning in tubular organs

Dirk DRASDO • *INRIA Paris, France & Interdisciplinary Centre for Bioinformatics, University of Leipzig, Germany*
Mathematical multi-level modeling of liver regeneration at histological scales: from data to models and back

Rune HARTMANN • *Aarhus Research Center for Innate Immunity, University of Aarhus, Denmark*
The dual role of type III interferon in the antiviral defense and control of pathogenic inflammation

Dagmar IBER • *Swiss Institute of Bioinformatics & ETH Zurich, Switzerland*
From networks to function - Computational models of organogenesis

Richard MORIGGL • *Ludwig Boltzmann Institute for Cancer Research & University of Veterinary Medicine Vienna, Austria*
Insights into graded STAT5 activity levels are linked with metabolic glucose sensing with consequences for blood cancers

Carsten BERNDT • *Faculty of Medicine, Heinrich-Heine University & Life Science Center, Düsseldorf, Germany*
Redoxins in plants, fish, man, and reindeers - Christmas research

Diana MATHEOUD • *School of Medicine, University of Montréal, QC, Canada*
Mitochondrial antigen presentation (MitAP) in Parkinson's disease and autoimmunity

Paul MONGA • *School of Medicine, University of Pittsburgh, PA, USA*
Cellular and molecular basis of hepatobiliary repair: a Wnt-beta-catenin perspective

Stanislas GORIELY • *Institute for Medical Immunology, Université Libre de Bruxelles, Gosselies, Belgium*
Regulation of inflammation and tumorigenesis by ARE-mediated mRNA decay

Michele MISHTO • *Berlin Institute of Health & Institute of Biochemistry, University of Medicine-Charité, Berlin, Germany*
Proteasome-catalysed peptide splicing and its biological implications

Juliane LIEPE • *Center for Integrative Systems Biology and Bioinformatics, Imperial College, London, UK*
From in silico to the clinic: methods to study proteasome-catalysed peptide splicing

Alexandra VAN KEYMEULEN • *Institute of Interdisciplinary Research in Human and Molecular Biology, ULB, Belgium*
Deciphering the cellular hierarchy of the mammary gland and its relation with breast cancer initiation

Mohamad ASSI • *M2S Laboratory, University of Rennes 2, France*
The impact of physical activity and antioxidants on signaling pathways involved in tumor growth and skeletal muscle wasting

Patrick GUNNING • *Centre for Medicinal Chemistry, University of Toronto Mississauga, ON, Canada*
Targeted and covalent modification of STAT3/5 proteins: lessons learned

Lucy GODLEY • *Center for Clinical Cancer Genetics, University of Chicago, IL, USA*
Clinical implications of familial leukemia syndromes

Chantal DESDOUETS • *Institut Cochin, University Paris-Descartes, France*
Liver polyploidy: Dr Jekyll or Mr Hide?

Marc PALLARDY • *Faculty of Pharmacy, University Paris-Sud, France*
The challenges of assessing immunotoxicity and immunogenicity of biopharmaceuticals

Jonathan VAN EYLL • *Bioinformatics and New Medicine, UCB Pharma, Braine-l'Alleud, Belgium*
Mechanistic causal reasoning to decipher complex transcriptomics signatures

Bengt HALLBERG • *Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Sweden*
ALK in cancer biology

Sine R. HADRUP • *Veterinary Institute, Technical University of Denmark, Copenhagen, Denmark*
Novel strategies for mapping the repertoire of tumor reactive T cells

Régis JOSIEN • *Center for Research in Transplantation and Immunology, University of Nantes, France*
IL-22BP controls IL-22 actions during inflammation and steady state

Daniel OLIVE • *Institut Paoli-Calmettes, University of Aix-Marseille, France*
Role of BTN3A, novel activators of the Vg9Vd2 T cells, in cancer

Inaugural Plenary Lecture - Princess Lilian Foundation Visiting Professorship 2016-2017
Daniel KAHNE • *Harvard Medical School, Cambridge, MA, USA*
From penicillin to the PEZ™ machine

Alain TRAUTMANN • *Institut Cochin, University Paris-Descartes, France*
Conflicting signals, a useful notion for cancer treatments

Catherine P.-J. LU • *Howard Hughes Medical Institute, Rockefeller University, New York, NY, USA*
How does skin decide to grow hairs or sweat glands? Epithelial-mesenchymal signaling crosstalk from mouse to human

Marc GRAILLE • *Ecole polytechnique, University Paris-Saclay, France*
The devil is in the methyl: generation and degradation of methylated RNAs

Nadège BERCOVICI • *Institut Cochin, University Paris-Descartes, France*
Cooperation between T lymphocytes and myeloid cells during tumor regression induced in mouse models

Robert H. SILVERMAN • *Lerner Research Institute, Cleveland Clinic, OH, USA*
Roles of viral and host double-stranded RNA, OAS and RNase L in the control of virus replication and cell death

Sven POTELLE • *University of Lille 1, France*
TMEM165, a new regulator of Golgi Mn2+ homeostasis involved in congenital disorders of glycosylation

Clément BARJON • *Saint-Antoine Research Center, University Paris-Sud, France*
IL-21 promotes the development of a regulatory subset of γδ T cells expressing CD73

Javier RAMIREZ • *Saint-Antoine Research Center, University Paris-Sud, France*
Multidisciplinary study of FcgRII in autoimmunity

Begona HERAS • *La Trobe Institute for Molecular Science, La Trobe University, Melbourne, VIC, Australia*
Bacterial virulence factors: structures, infection mechanisms and development of antibacterials

---

"Stunning" Meeting: PhD Day of the SFMBBM Graduate School, organized by graduate students from J.-F. Collet's lab
Main speakers: James BARDWELL *(Howard Hughes Medical Institute, University of Michigan, USA)*, Helen SAIBIL (*Birkbeck College, London, UK)*, Anne BERTOLOTTI *(University of Cambridge, UK)* & Alexander HEUCK *(Institute of Molecular Pathology, Vienna, Austria)*

> *The "Structure et Fonctions des Macromolécules Biologiques, Bioinformatique et Modélisation" Graduate School brings together teams from five Belgian universities and two foreign laboratories.*

Princess Lilian Foundation Visiting Professorship 2016-2017: awarded to Prof. Daniel KAHNE from Harvard Medical School, and hosted by J.-F. Collet
Program: inaugural lecture, international mini-symposium, meetings with researchers from Belgian universities working in the fields of microbiology, chemistry and pharmacology

> *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.*

Visit of Prof. Eric LANDER from the Broad Institute of MIT & Harvard, hosted on our campus by Sophie Lucas, as part of his election to an honorary doctorate at the University of Louvain.
Program: plenary lecture and meeting with graduate students from the University of Louvain

PhD Day

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

de Duve Institute

Directorate

Emile Van Schaftingen, Director
Frédéric Lemaigre
Benoît Van den Eynde
Miikka Vikkula

General Services

Administration

Serge Thibaut (Finance and Administration Manager) • Yolande de Crayencour and Isabelle de Duve (External Relations) • Francisca Voermans (Research Project Coordinator) • Nathalie Krack (Administrative Coordinator) • Julie Klein (Administrative Assistant) • Marjorie Decroly (Accountant)

Informatics Support

Jean-Pierre Szikora and Jacques Vanclève

Technical Support

Alain Buisseret (Manager) • Dan Coman, Kéoprasith Souvannaraj, André Tonon (Technical Assistants)

Board of Directors

Luc Bertrand (President) • Henri Beaufay • Vincent Blondel • Thierry Boon-Falleur • François Casier • Etienne Davignon • Emmanuel de Beughem • Jacques Melin • Dominique Opfergelt • Jean-Christophe Renauld • Jacques van Rijckevorsel • Maurice Velge

Scientific Council

Dario Alessi (University of Dundee, UK) • Michael Hall (Biozentrum Basel, Switzerland) • Bernard Malissen (Centre d'Immunologie Marseille-Luminy, France) • Gilbert Vassart (Université Libre de Bruxelles, Belgium)

Ludwig Cancer Research

Director

Benoît Van den Eynde

Research Groups

Stefan Constantinescu
Jean-Christophe Renauld
Benoît Van den Eynde
Pierre van der Bruggen

General Services

Administration

Dario Florean (HR Manager) • Pierre-Olivier Seroen (Administrator) • Aline Bien, Fanny Florean, Carine Lemoine, Magali Moraine, Geneviève Schoonheydt, Auriane Sibille (Accountants and Administrative Assistants)

Informatics Support

Jo Lejeune and Jacques Vanclève

Technical Support

Alain Buisseret (Manager) • Jean-Luc Germis (Technician) • André Tonon (Assistant to the Manager) • Evelyne Corbisier, Pascale De Vleeschouwer, Samira Jebari, Olivier Maes, Pascale Mahieu-Gaudy, Keoprasith Souvannaraj, Ioanis Spanoudis, Marcos Suarez (Technical Assistants)

Pre-clinical Research Resources Group

Guy Warnier (Group Head) • Gilles Gaudray (Deputy Group Head) • Lionel Crikeler, Julien Gossiaux, Laurent Hermanns, Marius Ilisei, Quentin Lechien (Technical Assistants)

LUDWIG CANCER RESEARCH
Brussels

B1.74.03
Avenue Hippocrate 74
B-1200 Brussels, Belgium
[T] +32 (2) 764 74 59
[F] +32 (2) 762 94 05

Supporting Organizations

- Académie de Recherche et d'Enseignement Supérieur
- Belgian Ministry of Health, Plan Cancer
- Belgian Science Policy Office
- Centre du Cancer, Cliniques universitaires Saint-Luc
- Cystinosis Research Foundation
- European Commission
- European Research Council
- Fédération Wallonie-Bruxelles
- Fondation contre le Cancer
- Fondation Roi Baudouin
- Fondation Salus Sanguinis
- Fonds Jacques Goor
- Fonds Joseph Maisin
- Fonds National de la Recherche Scientifique
- Les avions de Sébastien
- Loterie Nationale
- MPN Research Foundation, USA
- National Institutes of Health, USA
- Région Bruxelles-Capitale
- Région Wallonne
- Télévie
- Université catholique de Louvain
- Worldwide Cancer Research

WELBIO Laboratories

The following laboratories are supported by Welbio:

Development & Expansion Council (DEC)

Baron Bertrand, President

Fellowship and/or Laboratory Sponsors

Mr P. Berend • Mr J. Berteau • Baron & Baronne L. Bertrand • Mrs R. Boon-Falleur • Mr & Mrs A. Bouckaert • Mrs C. Delori • Mrs H. Delori • Mr P. Delori • Mrs R. Haegelsteen • Mr & Mrs A. Lacroix • Mr & Mrs D. Mathieu • Baron & Baronne Ch.-A. Peers de Nieuwburgh • Baronne Peterbroeck • Chevalier A. de Selliers • Vicomte P. de Spoelberch • Vicomte Th. de Spoelberch • Dr J. Troquet • Mrs J. Van Cauwenberghe • Baron M. Velge • Fonds Jacques Goor • Fonds Maurange

Members

Mr & Mrs Ch. Adriaenssen • Mr & Mrs B. Auxenfans • Mr & Mrs J.-N. Bossé • Chevalier Bourseaux • Mr M. Bragard • Mr & Mrs M. Carlier • Mr Fr. Casier • Dr J.-M. Collette • Mrs Y. Collinet • Mr & Mrs B. Cosyns • Mr D. Dalibot • Vicomte E. Davignon • Mr & Mrs J. Delen • Pr P. De Smet • Baron & Baronne V. de Dorlodot • Mr D. de Duve • Mr L. de Duve • Mr O. de Duve • Baron S. Emsens • Mr della Faille de Leverghem • Baronne de Gerlache de Gomery • Mr & Mrs L. Grandchamp des Raux • Mr J.-P. Gueret • Mr R. Havaux • Mr J. Hollenfeltz du Treux • Mrs Homans-de Visscher • Mr O. Huaux • Mr & Mrs M. Huynen • Mrs A. Jacobs van Merlen • Mr & Mrs L. Jacobs van Merlen • Comte & Comtesse de Kerchove de Denterghem • Mr & Mrs Ph. Lammerant • Mr J.-M. Legrand • Comte J. de Liedekerke • Mr A. Merckx • Mr L.-Ch. de Mol • Mrs de Moreau de Gerbehaye • Jhr & Mrs J. van Rijckevorsel • Dr F. Robert • Dr P. Saillez • Mr D. Solvay • Vicomte A. de Spoelberch • Vicomte G. de Spoelberch • Vicomte N. de Spoelberch • Vicomte R. de Spoelberch • Mr & Mrs E. Struye de Swielande • Mr E. Van Baren • Mr N. Van Baren • Baron & Baronne G. de Vaucleroy • Mr & Mrs J. de Vaucleroy • Mr Ph. de Visscher • Mr P. Winssinger • Mr & Mrs L. Willame • Mrs A. Wittmann • Chevalier G. de Wouters d'Oplinter •
ACKERMANS & VAN HAAREN • BANK DELEN • BELFIUS • BNP PARIBAS FORTIS • CABLERIE D'EUPEN • CBC/KBC • CHEMITEX • DIM FUNDS • FONDATION CONTRE LE CANCER • KYMOVE • GROUPE EDMOND DE ROTHSCHILD EUROPE • GROUPE LHOIST • ING • L'OREAL • LINKLATERS • LOTERIE NATIONALE • MERCIER VANDERLINDEN • NEWTON BIOCAPITAL • PUILAETCO • SOCIETE GENERALE • SOPARTEC • WHITE & CASE

Steering Committee DEC

Baron Bertrand, President

Members

Pierre Coulie • Yolande de Crayencour • Isabelle de Duve • Olivier de Duve • Olivia de Schorlemer • Vincianne Delvigne • Sophie Lammerant • Jean-Marc Legrand • Irène Mathieu • Juliette Siaens • Marie Speeckaert • Georges Van den Berghe • Emile Van Schaftingen • Aurélie Wijnants

Acknowledgements

In 2016, 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 2016 the Institute has been able to allocate the following fellowships, entirely supported by our donors :

The «Haas-Teichen» fellowship was attributed to Angela Queisser (Germany),

the «Maurange» fellowship to Anita Roy (India),

the «Pierre M» fellowship to Ha-Long Phuoc Nguyen (USA),

and an ICP fellowship has been awarded to Mohamad Assi (Lebanon).

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

Luc Bertrand
President of the Development and Expansion Council

de Duve
INSTITUTE

www.deduveinstitute.be