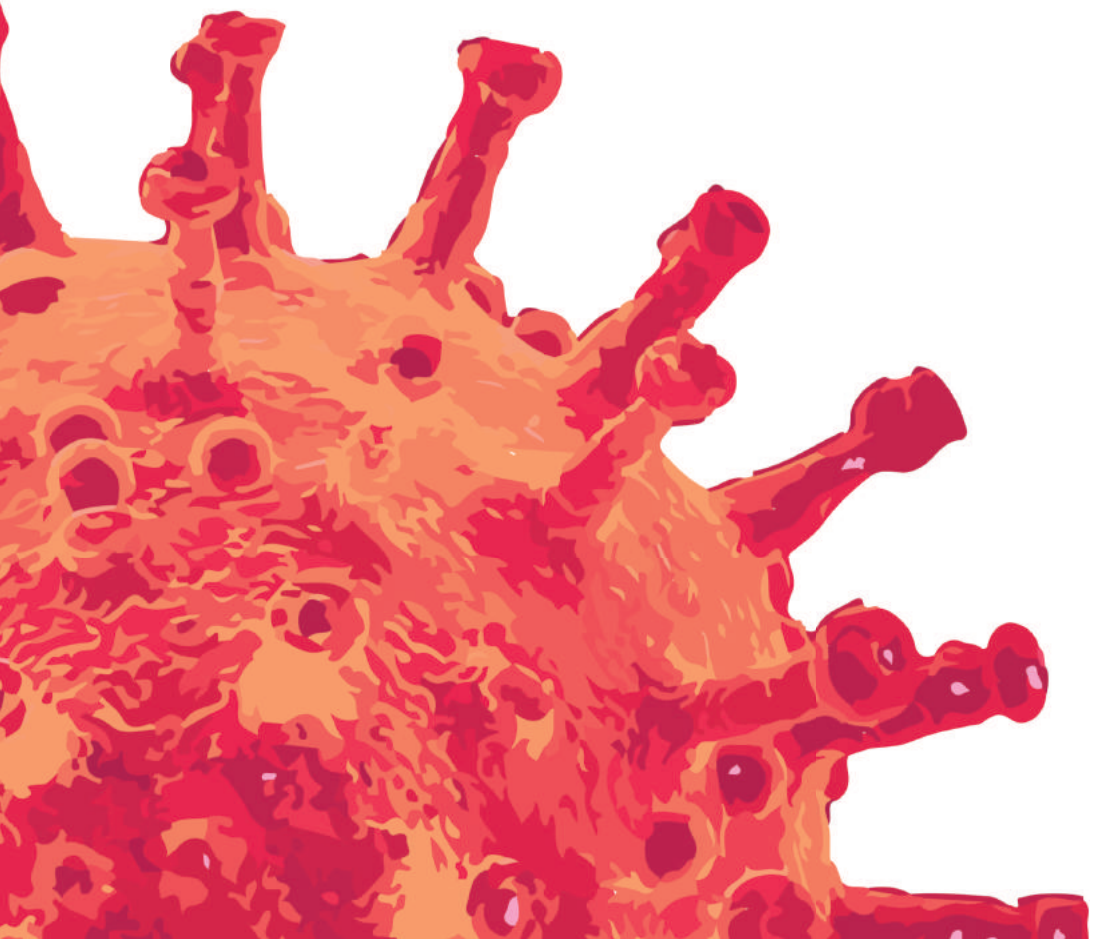
SCIENTIFIC REPORT 2020

de Duve INSTITUTE

de Duve Institute &
Ludwig Cancer
Research - Brussels



LUDWIG CANCER RESEARCH
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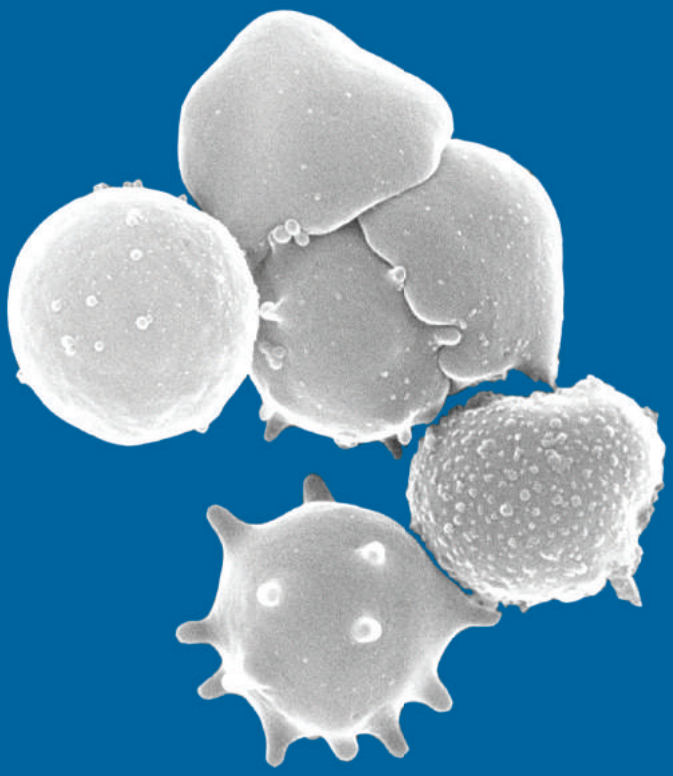

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Picture: Scanning electron microscopy picture of red blood cells (imaging platform, Tyteca's group)

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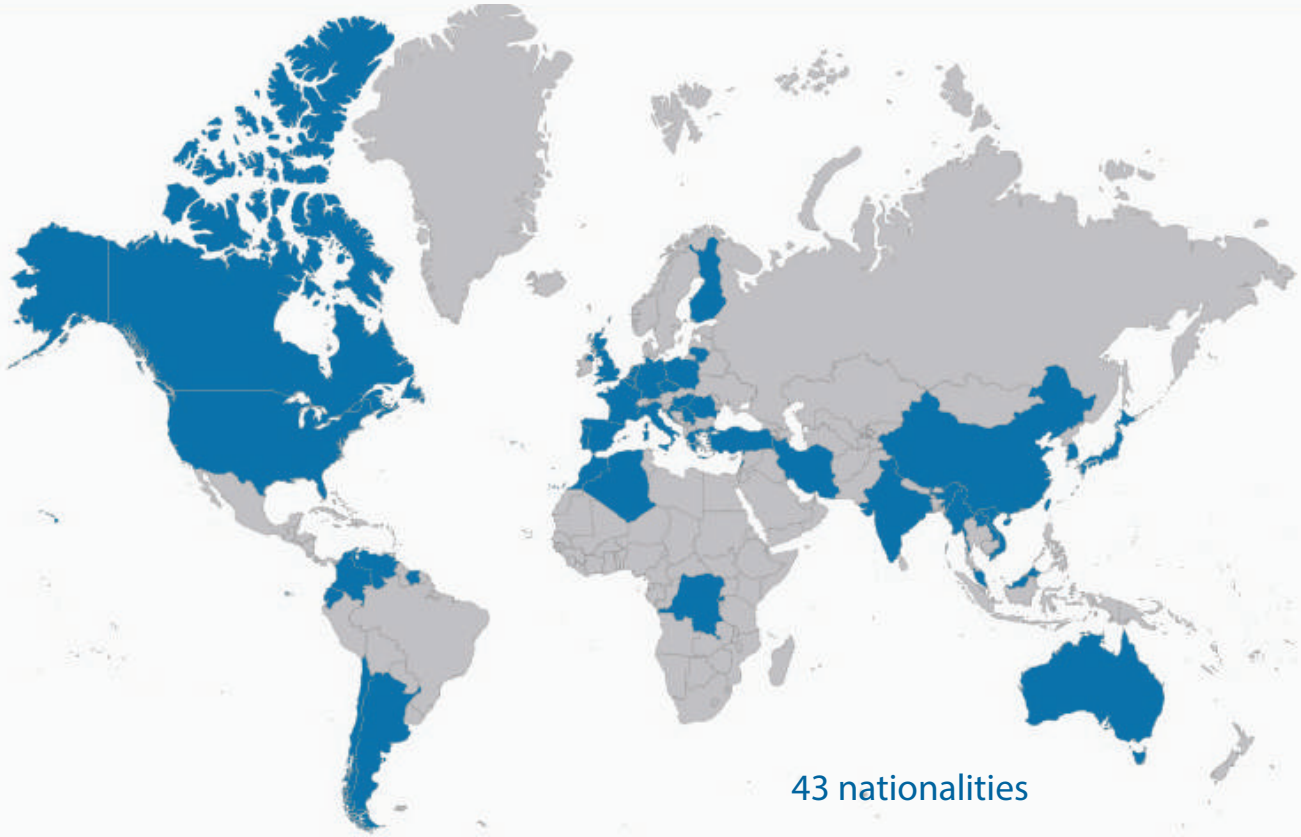


43 nationalities

309 members

45% 55%

101 PhD students

37 postdoctoral students

113 publications

Most international lectures were postponed due to the Covid-19 pandemic

6 technology platforms

8000 m^2

From the Director

The year 2020 was a special year for every institution, and de Duve Institute was no exception. We mourned the loss to Covid-19 of Serge Thibaut, our just-retired Administrative and Financial Director, and of Maurice Velge, a faithful support of the Institute and member of the Board of Directors. Our deepest sympathies go to their families.

Because of the pandemic, we stopped most experimental research for about three months, converted to teleworking, and only progressively resumed experiments during the summer. This forced pause obviously delayed the progress of a number of projects. However, on the positive side, it also gave our scientists more time to think, to analyze and reflect on their results, to publish their findings, to explore new concepts and elaborate new projects.

An important new endeavor of the Institute that was launched in 2020 was the collaboration of the group of Jean-François Collet with the Japanese group Kaneka-Eurogentec, a world leader in the production of biomedicines. Most of them are produced in bacteria, and the aim of the collaboration is to leverage the expertise of Jean-François Collet in bacteria to improve the production of biomedicines. A particular focus of Jean-François Collet is to study the cell envelope of Gram-negative bacteria (see pages 12 and 34). His work may help developing new antibiotics, which are critically needed to face the serious threat of the emergence of multi-resistant bacteria. As a testimony to the quality and importance of his work, Jean-François Collet was awarded this year the prestigious quinquennial FNRS Scientific Prize Joseph Maisin for basic biomedical sciences 2016-2020.

Another important event for the Institute was the inception of a new research group led by Nick van Gastel, a promising young investigator returning from Harvard University and studying the interactions between leukemic cells and their environment in the bone marrow. You can read about his research on page 14.

Numerous important discoveries were made by our scientists and were published in a record number of 113 publications this year. These included the development of improved approaches of cancer immunotherapy (pages 12 and 21, page 22), the discovery of the genetic cause of primary lymphedema (pages 13 and 27) and of rare blood cancers (pages 13 and 18), and the discovery of an efficient treatment for an orphan disease causing congenital neutropenia (page 40). These are only examples, and you will find many other biomedical findings detailed in this report.

Benoit Van den Eynde

About the Institute

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

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

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

In 1978 the Ludwig Institute for Cancer Research decided to base its Belgian branch within the walls of de Duve Institute. A fruitful collaboration between the two institutions has been pursued ever since, and is today embodied in the full structural support of two research groups within de Duve Institute.

The ambition of de Duve Institute is to pursue 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 de Duve Institute to remain at the forefront of European research. We are extremely grateful to all those who support the Institute.

Research Highlights

Steering a double-edged sword

Twenty years ago, young PhD student Laure Dumoutier discovered a new cytokine, named IL-22. This cytokine appeared a potent protein with two sides: essential in the response to infections, but disastrous in some chronic diseases. Today, she tries to find a way to block the bad effects, while keeping the good ones.

Laure Dumoutier is a researcher in heart and soul. At school she was already riveted by science and doing experiments, dreaming to find new things that might help people. She went to study Biomedical Science at UCLouvain, knowing a PhD study would be the next step. During her master thesis at the nearby Louvain Drug Research Institute, she showed her high motivation. She wanted to do molecular biology, a topic no one at the lab knew much about. Persisting in her choice, she worked from 8 to 22 to get a good result.

During her master thesis she had collaborated with Jamila Louahed, a post-doc of de Duve Institute. When she went there to thank her with a box of chocolates, she bumped into the group leader of the post-doc, Jean-Christophe Renauld. He complimented her on her hard-working attitude. She didn't hesitate and asked him whether there was a position available in his group. Soon after, she started her PhD study in the lab where she today, 20 years later, heads her own research group. "Thanks to a box of chocolate, I found the perfect place for me", she says.

The group of Jean-Christophe Renauld studied cytokines, small proteins that function as intercellular messengers. The group focused on interleukins (IL), a subgroup of cytokines that – mostly – messages between different white blood cells (leukocytes). They play an important role in regulating immune responses. Laure Dumoutier's first goal was to find the mediator of the activity of IL-9, a regulator of a variety of blood cells. Within six months she had an exciting result: she found a new gene, which seemed related to a cytokine. Continuing to research on this gene, she discovered a new cytokine, called IL-22. "We failed to find the mediator of IL-9, but we did find something else. I believe that's crucial in research: catching the fact that you are in front of something new, even if it's not what you are looking for." This serendipitous discovery was the first of many findings on this new cytokine by Laure Dumoutier and Jean-Christophe Renauld. They made discoveries on its receptor and how it exerts its effects inside cells. While other labs also studied the cytokine, it became clear that IL-22 is a potent messenger acting on epithelial cells, which are found in the skin and the intestines, and has an important role in psoriasis and bowel diseases.

Meanwhile, Jean-Christophe Renauld became more involved in managing tasks at the university and Laure Dumoutier gradually took over responsibilities of running the lab. In 2008 she was appointed FNRS researcher. From then on, she developed her own research track, though still closely linked to 'her cytokine', IL-22. She successfully set up joint research with Prof. Marie Baeck from the Dermatology Department of University Hospital Saint-Luc. They investigate the immune response in biopsies from patients with skin diseases, such as psoriasis, allergic contact dermatitis and chronic spontaneous urticaria. Their

"The dream would be to block the detrimental role of IL-22, without affecting its beneficial effects."

multiple discoveries about the role of cytokines in these chronic diseases, provide leads for better treatments.

The more research on IL-22 increased, it became clear that the protein has two sides. It has a positive role in protecting the liver and the intestines during inflammation; however, its extensive production in psoriasis and colon cancer has harmful consequences. "The dream would be to block the detrimental role, without affecting the beneficial effects", Laure Dumoutier says. She sees a possible way to do this, based on an earlier discovery. "IL-22 exerts its effects by activating STAT3 through its receptor. It can do so in the conventional way, which involves phosphorylated tyrosines on the cytokine receptor. Many cytokines activate STAT3 this way. We observed that IL-22 can also activate STAT3 in an alternative, tyrosine-independent manner, which acts on another part of STAT3. We showed that this unconventional STAT3 pathway induced by IL-22 is responsible for skin lesions observed in the psoriasis model. If we can block this alternative activation, we might be able to slow down the STAT3 activation induced by IL-22, thereby stopping the harmful effects, but still allowing the beneficial effects."

In collaboration with the group of Oliver Hantschel of the university of Marburg, her lab recently succeeded in blocking this alternative STAT3 activation route. The two teams used monobodies, which are small proteins that mimic antibodies. These monobodies can fix, with a high affinity, the part of STAT3 that is involved in the unconventional activation mechanism. In lung epithelial cells, they showed that the monobodies indeed diminish the activity of STAT3 induced by IL-22.

High IL-22 expression and STAT3 activity is not only observed in psoriasis and bowel diseases, but also frequently in other auto-immune diseases and cancers. Drugs that inhibit IL-22 or STAT3 are thus highly sought after, but have so far not been developed successfully. The monobodies are however not directly a clinical solution, says Laure Dumoutier: "The challenge is how to deliver them inside the cells: they are too big to enter. Methods are being sought to favor their entry, but this is not easy." Her team will in a next step try to crystallize the complex of a part of the IL-22 receptor and STAT3 to characterize the interactions between the two proteins. "This may help to develop small molecules that are able to disturb unconventional STAT3 activation induced by IL-22. Small molecules can easily enter into cells, so this may be a faster track."

Mapping the escape routes of a virus

Viruses have evolved clever strategies to evade the immune system of their host. Thomas Michiels tries to get insight in these strategies, to counteract the pathogenicity of viruses, but also to better understand the immune responses.

Biologist Thomas Michiels started his scientific career studying bacteria. He did his PhD with Prof. Guy Cornelis, in microbiology on the Woluwe campus of UCLouvain, doing research on bacterial transposons and on Yersinia enterocolitica, bacteria that cause gastroenteritis. This led to the discovery of the type III secretion system of bacteria. He got acquainted to virology in his postdoc studies at the Institut Pasteur in Paris. When, in 1992, he got the opportunity to start a new group at de Duve Institute, he chose to continue studying viruses. "During my research on bacteria, I got too much focused on certain aspects of bacteriology and lost contact with the world of eucaryotes. Studying viruses that infect eucaryotes, including humans, was a way to reconnect to human cell biology", he says. Though today, he adds, research on bacteria has evolved and also addresses their interaction with human cells. And sometimes the fields unexpectedly come together: "We recently encountered a viral protein that acts in human cells exactly as a protein produced by bacteria, that I studied during my PhD."

The group of Thomas Michiels tries to understand how cells react to viruses and how viruses escape these responses of the cell. The goal is not only to increase the knowledge about the actions of viruses, but also to gain new insights in the way human cells function. "Viruses are able to hijack important mechanisms of the cell. By studying viruses, we can better understand how our own cells and our immune system work." His group uses Theiler's virus as a model in their studies. This is a mouse virus with the ability to persist in the central nervous system and which causes lesions that are reminiscent of human multiple sclerosis. He has been studying the virus for almost 30 years now. "Following this single virus has led me to many different tracks. A virus interacts with various types of cells and interferes with multiple cellular pathways."

One of these tracks led him to an important discovery on IFN- λ, a specific type of interferon. Interferons are a group of proteins that play an important role in the cellular defense against a virus. Thomas Michiels' group discovered that IFN-λ mainly acts on epithelial cells, the cells that form the outer surface of our body, like in our skin, intestines, blood vessels and lungs. They are the first cells a virus encounters when it enters a body and IFN-λ is therefore the first line of defense against viruses that infect the lungs and intestines, such as SARS-CoV-2.

Thomas Michiels is fascinated by the strategies that viruses have developed to escape immune defences. "Viruses are fooling the cell by modifying cellular pathways. They produce proteins that hijack cellular enzymes, thereby forcing the enzyme to change their classic job. Different viruses disturb cellular processes in different ways, but often they use the same trick: the phosphorylation of an enzyme." In Theiler's virus, his group has characterized how

"Viruses produce proteins that hijack cellular enzymes, thereby forcing the enzyme to change their classic job."

two proteins, encoded for by the viral genome, disturb the immune response in its host in multiple ways. "They change the traffic of proteins between the nucleus and cytosol. They modulate the interferon production and they prevent the cell to sense the presence of the virus."

The diversity of viruses is enormous: in their genomes, structures, as well as in the ways they interfere with their hosts. "Each virus has its own specificities. Therefore, there will not be a single therapy that can be used against all viruses, we will not find a magic bullet." A kind of broad-spectrum drug could however work against a group of viruses, if similarities can be found. An EOS (Excellence Of Science) project, led by Thomas Michiels, aims to compare the cellular reactions to different viruses. In this project, funded by F.R.S.-FNRS and FWO, the group collaborates with teams of UGent, ULiège and KU Leuven. "We hope to focus on common pathways, however we found that they have quite different strategies. There are some common points, but there is more divergence than we expected." The teams did however find a common pattern on the polymerases of positive RNA viruses. Positive RNA viruses have the particularity to synthesize their own polymerases, which are the enzymes that carry out the replication of the genome. The common pattern identified on these enzymes seems a druggable target. "A drug that will act on this site might inhibit the replication of several viruses. A PhD student in my group investigates this promising route."

Last year has been turbulent for Thomas Michiels and fellow virologists. The Covid pandemic has turned the public eye on their work. "Everyone now sees the importance of studying viruses", says Thomas Michiels. This has been different in the past. "Before the pandemic, Corona viruses were little studied. There was little funding available, as it was considered an animal disease. We should not neglect any field." If the crisis has made one thing clear, it is the value of fundamental research, he adds: "The development of the vaccines in such a short time is impressive. It is the result of years and years of research. When HIV emerged, there was a delay of two years between the appearance of the disease and the identification of the virus. A lot has changed since then. We have learned about how viruses replicate, how they act in the cell, and there have been many technical advancements. Basic research has been instrumental in the incredibly fast development of the vaccines."

Printing a pancreas

3D printing of an organ may sound like science fiction. But after the successful printing of a mouse thyroid, the group of Christophe Pierreux now aims to bioprint a mouse pancreas. As partner in an EU project, the group provides the 3D maps of the architectural organization of the organ, which constitute the basic instructions for the printer.

The third time is a charm for Christophe Pierreux and de Duve Institute. He first joined the Institute in 1993, to do his master thesis in biology from UNamur. After six months of research at the Ludwig Institute for Cancer Research in London, he returned to the Institute for his PhD thesis. Finally, following two years of postdoctoral training in London, he came back again, this time to stay for good.

These first years of his scientific life, in the group of Guy Rousseau and Frédéric Lemaigre, were crucial to his career. "I was the first student of Frédéric and could not have had better training", Christophe Pierreux says. His research topic evolved from gene regulation to embryonic development and organogenesis, which are still his areas of interest today. In 2007 he started his own group in the environment of Pierre Courtoy, whom he succeeded after his retirement. His prime attention shifted to the architecture of tissues in the embryo. "I'm amazed by the perfect and precise structure-function relationships acquired by organs during embryonic development. Look at a mouse: in 20 days you have a complete organism, that can breathe and eat."

Christophe Pierreux tries to unlock our understanding on how organs are formed. He describes the process in which some progenitor cells grow, differentiate, migrate and mix, to form particular structures like branched ducts. He focuses on the pancreas and the thyroid gland. "These two organs are very similar in the early stages of their embryonic development, but then they differentiate and form specific structures, like open branched ducts or closed spheres, necessary for their mature functions." The pancreas helps to regulate blood sugar levels by producing hormones like insulin and glucagon, and it secretes digestive enzymes into the intestines. The thyroid makes hormones that control the metabolism rate, thereby regulating body temperature and weight. Using leading-edge imaging techniques in combination with ex vivo and in vivo models, the group characterizes the organization of the two organs, as well as the intercellular communication. "Developing organs like the pancreas and the thyroid interact with their environment. The blood vessels, for example, are more than passive nutritive pipes delivering oxygen and nutrients to the developing organs; they also communicate with the developing organs, providing instructive signals to mature", he explains.

In 2014, Christophe Pierreux' research took an unexpected turn. His group had just published an article on the development of the thyroid gland, when he was approached by a Russian company, specialised in 3D bioprinting. "They wanted to use our knowledge on tissue organization to bioprint a thyroid. At first, I was skeptical, but they visited our lab and convinced me to participate in the project." They succeeded to print a functional thyroid, starting from thyroid and endothelial progenitor cells,

"3D printed pancreas units would better mimic the 3D architecture and the various cell populations of the pancreas."

clustered in spheroids, as building blocks. Christophe Pierreux' group provided the spheroids and the map of the 3D organization, the Russian company bioprinted the thyroid. "Within four days after the printing, the spheroids had fused and a vasculature was developing within the bioprinted construct. The construct was then implanted in a mouse with no thyroid, and in three weeks' time, it produced hormones and regulated the body temperature. It functioned as a normal thyroid gland."

After the successful printing of the thyroid, Christophe Pierreux' team moved to the next challenge: the bioprinting of a mouse pancreas. "A more complicated and challenging job. The pancreas is composed of at least seven different cell types – where there are only two in the thyroid – and it has two distinct functions: the endocrine function, which produces hormones regulating glycemia, and the exocrine function, which produces and transports digestive enzymes to the intestine. Precision in placing the cells will be key." This research is part of a European project, called Pan3DP, in which the team collaborates with partners from England, Israel, Switzerland and France. The task of Christophe Pierreux' group is to generate a 3D atlas of the pancreas: the description of all cell types in space and time, including their signalling interactions. "The 3D bioprinter is like an inkjet printer, with cells in the cartridges and instructing signals as bio-ink. We must accurately describe what happens in nature since our map of the tissue will give the instructions to the bioprinter." The goal of the project is to generate small 3D units of the pancreas for biomedical research purposes. It could be used for studying the biology and diseases of the pancreas, such as diabetes, pancreatitis or pancreatic cancer, or drug toxicity. "Such pancreatic units would be much better than the 2D cell cultures used today, because they would better mimic the 3D architecture and the various cell populations of the pancreas. These units could also reduce laboratory animal use."

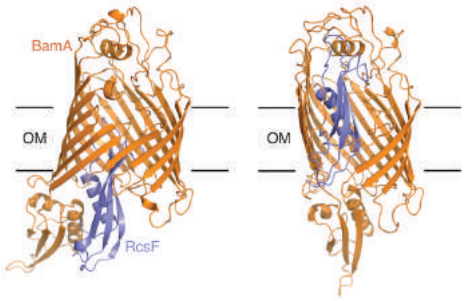
At this stage, the project does not aim for clinical applications, but should be a proof-of-concept for later applications. In the future, printing a human pancreas or islets of Langerhans might be conceivable for transplantations or regenerative medicine, says Christophe Pierreux: "Transplantation of islets with insulin-producing cells, is used as a therapy in diabetes but it is still rare and not always accepted by the patient's body. Continued research and progress in stem cell research and 3D bioprinting, and their combinations, could lead to a better solution."

More about the Pan3DP project:
https://www.pan3dp-project.eu

In a nutshell

An image of the bacterial defense in action

Many pathogenic bacteria, such as Salmonella, E. coli, and Pseudomonas, are gram-negative bacteria, which means that they are surrounded by two membranes. These membranes act as defense walls and antibiotics have to break through them to kill bacteria.



Embedded in these walls are protein complexes called BAM (β-barrel assembly machinery), which are essential parts of the assembly and defense systems in all gram-negative bacteria. They are crossing points for the protein-soldiers who come out of the bacterial fortification to monitor the surroundings. If BAM is successfully blocked, bacteria cannot survive.

BAM is therefore an attractive target for the development of new antibiotics, but its mode of operation remains poorly understood. This is where Jean-François Collet's team, in collaboration with VUB and the University of Leeds, has taken a big step forward. They studied the interaction of BAM and the lipoprotein RcsF, one of the protein soldiers that help the bacterium combating stress. Using a technique called protein crystallography, the teams managed to take a snapshot of BAM exporting RcsF through the outer perimeter wall. The picture shows how RcsF is lodged deep inside the barrel-like structure of BAM. They also proposed, with a simulation, how the BAM complex is moving to push and pull RcsF to the outside surface.

This 3D image of BAM provides valuable information on the remarkable bacterial mechanism and offers a new angle of attack for antibiotic treatment. Finding new antibiotics is imperative, as more and more bacteria become resistant to existing antibiotics, which forms a threat to human health.

Reference

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A new immunotherapy against cancer

'Classic' cancer therapies directly target cancer cells. Immunotherapies, on the other hand, target the patient's healthy immune cells, stimulating them and causing them to kill cancer cells. Immunotherapies have growing success, in particular in melanoma and lung cancer patients, but today only work in a minority of patients with metastatic cancer.

Regulatory T cells (Tregs), a subpopulation of T cells that suppress the actions of other T cells, play a significant role in hindering the body's immune response to tumors. Sophie Lucas and her team have been studying Tregs in the context of cancer since 2004. They discovered that the immunosuppressive actions of Tregs are due to the production of TGF-β1, a powerful cytokine that inhibits neighboring immune cells. They also elucidated how Tregs produce active TGF-β1, which involves GARP, a protein anchored in the Treg membrane. The lab succeeded to find an antibody that is able to block TGF-β1 activation by GARP and thus prevents Tregs from sending their blocking signals.

In their recent work, they combined the Treg-blocking antibodies with another proven immunotherapy (anti-PD1 antibodies) to treat cancerous mice. The combined treatments regressed tumors in many more mice than each antibody administered separately. They also showed that their antibodies specifically enhance the anti-tumor activity of T cells in the tumor, which suggests that the treatment may have little adverse effects. The results have led to the first tests of the new treatment in cancer patients in a clinical study (phase I) by a pharmaceutical company.

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NEW GENETIC CAUSES OF PRIMARY LYMPHEDEMA IDENTIFIED

The laboratory of Miikka Vikkula identified a novel gene responsible for primary lymphedema, a strongly invalidating chronic disease that predisposes to infections, and results from abnormal development and function of the lymphatic system. By using whole-exome sequencing, they were able to discover mutations in a gene called ANGPT2 in patients with lymphedema.

ANGPT2 encodes the angiopoietin-2 molecule, a ligand of the TIE2 receptor. Angpt2 had previously been shown to influence lymphatic development in mice, but this is the first time that mutations in this gene are found to cause a disease in human beings. Among the identified mutations, one deletes one copy of the entire gene, whereas four others are amino acid substitutions.

The lab collaborated with the group of Kari Alitalo in Finland, who analyzed in detail the mutant proteins. They were able to show that three of the mutants are not properly secreted, even hampering partially the secretion of the protein produced from the remaining normal allele and thus having a so-called 'dominant-negative effect'. The fourth one is hyperactive, inducing increased proliferation of dilated lymphatic vessels. The identification of the genetic causes of primary lymphedema is essential for proper diagnosis of patients and more precise genetic counseling, and opens a novel pathway for developing treatments (the long-term goal of the Vikkula lab).

With the help of its large international network of collaborators, including the Center for Vascular Anomalies and the Center for Medical Genetics of the University Hospital Saint-Luc, the team has collected samples from over 900 patients (and their family members) suffering from lymphedema, and they continue to recruit more patients.

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A POSSIBLE NEW TARGET FOR TREATMENT OF RARE BLOOD CANCERS

Myeloproliferative neoplasms (MPNs) are a group of rare blood cancers in which excess blood cells are produced in the bone marrow. Essential thrombocythemia (ET), one such neoplasm, is driven by mutations in the gene called MPL, which encodes the thrombopoietin receptor (TPOR). These mutations lead to ligand-independent dimerization of the receptor into a continuously signaling conformation.

In 2018, collaborators of Stefan Constantinescu identified two ET patients that harbored non-canonical double mutations in MPL, namely L498W-H499C and H499Y-S505N. Using biochemical and signaling assays along with partial saturation mutagenesis, the team of Stefan Constantinescu showed that L498W is an activating mutation potentiated by H499C and that H499Y enhances the activity of the canonical S505N mutation found in MPNs.

To understand the mechanisms underlying the activity of the new mutants, the team showed that L498W, H499C and the double L498W-H499C mutant activated a truncated TPOR mutant lacking the extracellular domain, indicating that these mutations act on the transmembrane-cytosolic domain segments of the TPOR.

Using structure-guided mutagenesis, the team identified the upstream amino acid W491 as a key residue required for activation by multiple oncogenic MPL mutations. They also drew parallels between the ET mutations and the mechanism by which eltrombopag, a small molecule TPOR agonist used for patients with low platelets, activates TPOR. Structural data pointed to a common dimerization and activation path for TPOR that is shared between eltrombopag and canonical and non-canonical activating TPOR mutations that all depend on W491. The latter being an extracellular exposed residue, it could become a target for therapeutic intervention.

Reference

Levy G, Carillo S, Papoular B, Cassinat B, Zini J.M, Leroy L, Varghese L, Chachoua I, Defour J-P, Smith SO & Constantinescu SN. MPL Mutations in essential thrombocythemia uncover a common path of activation with eltrombopag dependent on W491. Blood. 2020;135:948-53.

New cellular metabolism group

The bone marrow is the 'blood cell factory' of our body. Different types of bone marrow cells work together to produce billions of blood cells a day. The new group of Nick van Gastel tries to understand how these cells communicate with each other to run these processes smoothly, and what goes wrong when leukemia develops.

Nick van Gastel discovered his passion for fundamental experimental research during his bioengineering study at the universities of Antwerp and Ghent. He thus opted for a doctorate at KU Leuven, where he also did two years of post-doc research, after which he left for Harvard University in Boston. When, after five years, he and his family wanted to return to Belgium, he seized the opportunity to start a research group at de Duve Institute. It is the unconditional attention for fundamental research that makes the Institute appeal to him. "I strongly believe that the sheer interest in understanding how a system works is the basis for real breakthroughs in medical treatment."

What will your group study?

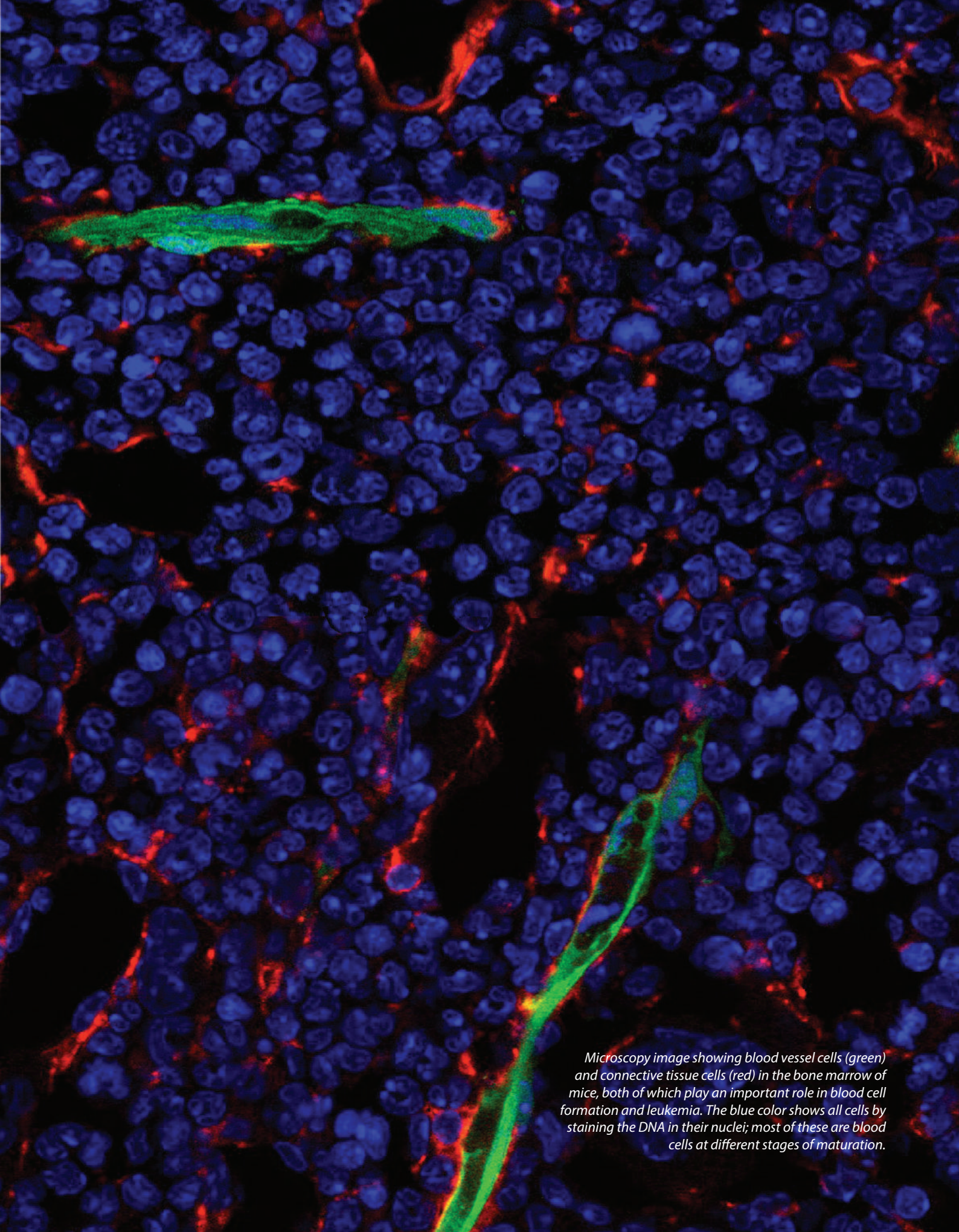
"The bone marrow is located inside our bones, especially in the pelvis, breastbone, ribs, and vertebrae. Here, all our blood cells are made, starting from blood stem cells. But these cells cannot do this on their own. The correct functioning of blood cell production relies on the interactions with other cell types in the bone marrow microenvironment such as bone cells, blood vessel cells, immune cells and connective tissue cells. We study how these cells interact with each other. We are particularly interested in communication via metabolites, which are the products of biochemical reactions in a cell to convert nutrients into energy and primary molecules. Bacteria are known to use metabolites as communication signals to respond to environmental stress or coordinate growth. In complex organisms such as mammals, metabolites also have a role in cellular communication. However, little is known about its extent and importance."

How is your research related to diseases?

"In malignant blood tumors, such as leukemia, blood stem cells start to grow out of control and no longer form normal blood cells. It is known that cells in the bone marrow microenvironment are involved in the development and progression of these diseases. By comparing normal and leukemic blood cell production, we aim to identify changes in metabolic communication systems that can be targeted to reduce the growth of leukemia cells or improve the efficacy of current treatment methods such as chemotherapy. The knowledge can also be useful to improve bone marrow transplantation."

How will your group tie in within the institute?

"We are working closely together with the group of Stefan Constantinescu, who studies signaling in blood cancers. I also plan to collaborate with the groups specialized in the field of metabolism and immunology. Like this, I hope that my group can be a valuable addition to the institute!"



Microscopy image showing blood vessel cells (green) and connective tissue cells (red) in the bone marrow of mice, both of which play an important role in blood cell formation and leukemia. The blue color shows all cells by staining the DNA in their nuclei; most of these are blood cells at different stages of maturation.

Research Groups

Cancer

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

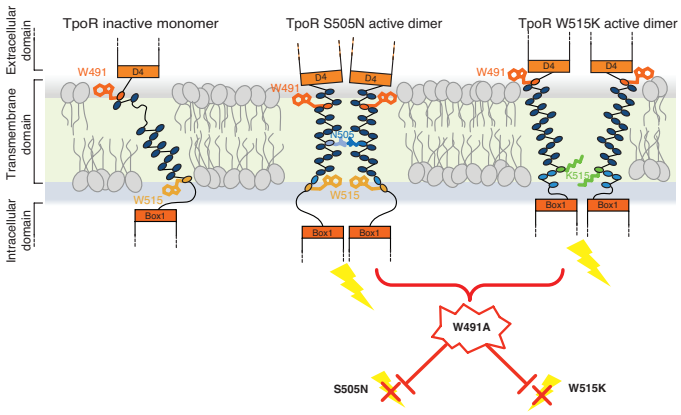
Stefan Constantinescu

LUDWIG CANCER RESEARCH
Brussels

Cell Signaling & Molecular Hematology

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

Formation of blood requires small proteins, denoted as cytokines, such as erythropoietin, thrombopoietin, interleukins or interferons. These proteins induce survival, growth and differentiation of blood precursors. They act by binding on the surface of target cells to 'receptors', which function like 'antennae' that transmit a signal to the cell interior. We study how these specific receptors assemble on the membrane and couple at the cell interior to other proteins, such as Janus Kinases (JAKs), which are absolutely required to transmit a signal. We found that mutations in JAKs or in receptors themselves, such as the receptor for thrombopoietin (TpoR/MPL) confuse the cells and make them grow indefinitely, leading to blood cancers, specifically myeloproliferative neoplasms (MPNs). Our hypothesis is that a curative treatment needs a JAK2 V617F-specific inhibitor. To this end, we delineated the circuit of JAK2 kinase activation by the V617F acquired mutation in the pseudokinase domain that could be a target for specific inhibition. The same strategy is taken for mutants in the TpoR that we discovered in 2006, where mutations in W515 just after the transmembrane domain activate the receptor. This year we reported that a region of the extracellular sequence containing residue W491 just upstream of the transmembrane sequence is required for stabilization of oncogenic forms of TpoR, and for their ligand independent activity (Figure). Importantly, this region is not required for physiologic function of TpoR in response to the ligand Tpo. Thus, this region can become a target for therapy as it is accessible to both small molecules and protein therapeutics.



The extracellular domain sequence containing W491 above the transmembrane domain is required for activation of TpoR by oncogenic S505N (middle) and W515K (right) mutations, while the non-mutated receptor is monomeric (left).

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

In order to pursue our aims, we use molecular biology approaches like extensive mutagenesis as well as functional assays as readouts for structural determinants, biophysical approaches, as well as in vivo transgenesis, microscopy and fractionation, mouse bone marrow transplantation, as well as investigation of primary patient cells.

Staff members
Clinical Investigator: Jean-Philippe Defour • **Senior Investigators:** Didier Colau, Christian Pecquet • **Guest Investigator:** Pierre De Meyts • **Postdoctoral Fellows:** Audrey de Rocca Serra, Leila Varghese • **PhD Students:** Alina Alexandru, Sarah Bailly, Harsh Goyal, Gabriel Levy, Nicolas Papadopoulos, Gaëlle Vertenoeil • **Research Assistants:** Lidvine Genet, Céline Mouton, Yacine Rahmani, Madeleine Swinarska • **Technical Assistant:** Florin Militaru

Jean-Baptiste Demoulin

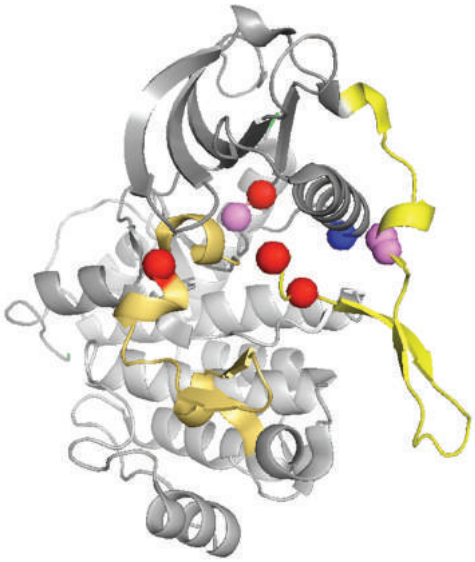
Cancer Signaling

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

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

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

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



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

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

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

Staff members

Clinical Investigator: Violaine Havelange • **Postdoctoral Fellow:** Emeline Bollaert • **PhD Students:** Boutaina Boulouadnine, Guillaume Dachy, Emilie Guérit, Ariane Sablon • **Undergraduate Students:** Joanne Péters, Constance Pirson • **Research Assistants:** Sandrine Lenglez, Virginie Vandewalle • **Administrative Support:** Geneviève Schoonheydt

Pierre Coulie

Human Tumor Immunology

Cancer immunotherapy is a breakthrough but only for a minority of cancer patients. We explore important parameters of the very early stages of the development of anti-tumor T cell immune responses, notably antigenicity and inflammation.

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

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

One project focuses on T cells present within human breast tumors. We observed that anti-tumor T cells were often absent from these tumors, the simplest explanation being that T cells have nothing to recognize on breast tumor cells. Now we study the earliest stage of breast cancer, the so-called in situ carcinomas, asking whether anti-tumor immunity would not be stronger there than in more advanced tumors. Thus far we have no clear evidence for that, and instead we observed activated regulatory T cells, which are known to suppress immune responses. We study also bladder carcinomas, trying to understand the mechanism behind the clinical efficacy, in some patients, of instillations of live BCG, the bacteria that constitute the anti-tuberculosis vaccine.

Another project deals with inflammation, which is normally a local response to microbes or various types of cellular stress. Inflammation depends on soluble factors, notably cytokines including IL-1β. In nascent cancer, inflammatory signals are faint and probably often absent. Increasing them locally could induce or increase anti-tumor T cell responses. In this context, we study the secretion of IL-1β by monocytes, another type of white blood cells and an important source of IL-1β. Monocytes can secrete IL-1β while they die, thus releasing their intracellular content. However we have observed that under certain conditions monocytes secrete IL-1β but do not die. We try to understand the mechanism of this secretion. Using CRISPR-Cas9 libraries we identified genes involved in this secretion. Several of them encode proteins associated with autophagy. Specifically blocking or increasing this secretion could have important medical applications in chronic inflammatory diseases or cancer, respectively.

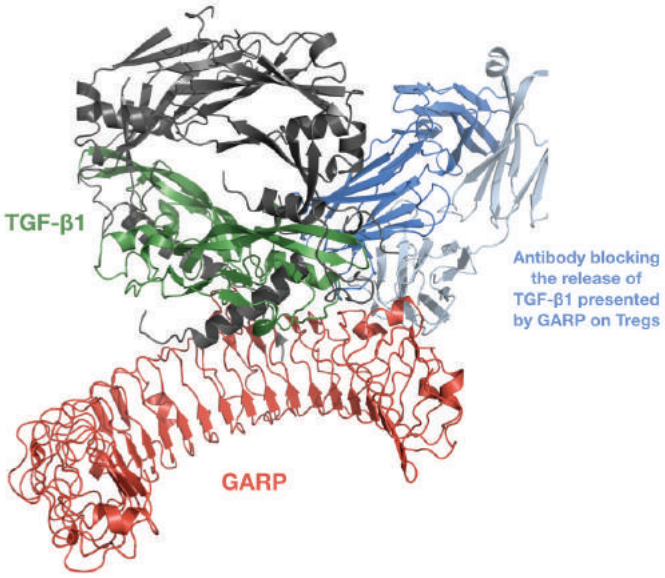
Staff members
Senior Investigators: Nicolas Dauguet (Platform Manager), Tiphanie Gomard, Nicolas van Baren • **PhD Students:** Walther Brochier, Alix Devaux, Charlotte Wautelet • **Research Assistants:** Gérald Hames, Catherine Muller, Nathalie Remy, Athina-Elena Somerhausen • **Administrative Support:** Suzanne Depelchin

Sophie Lucas

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

Regulatory T cells & TGF-β

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



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

We try to identify the mechanisms by which Tregs suppress immune responses. We found that Tregs produce a protein called TGF-β1, which acts as an inhibitory messenger on immune cells. We also found that production of the immunosuppressive TGF-β1 requires another Treg protein called GARP. In all cell types, production of TGF-β1 is highly regulated and often requires accessory proteins. Tregs are among the very few cell types to produce TGF-β1 in a manner that depends on GARP. We developed tools (e.g. monoclonal antibodies) that bind GARP and block TGF-β1 production by Tregs. We explore in mouse models whether these tools could be used as drugs to block Treg immunosuppression in patients suffering from cancer. Recently, we published encouraging results in mouse models of cancer indicating that anti-GARP antibodies favor the elimination of tumors when they are combined to another approach of cancer immunotherapy known as PD1/PD-L1 blockade. The latter is the best currently available immunotherapeutic approach, but it is still insufficiently efficient when used on its own in most patients. We used x-ray crystallography to solve the 3D structure of a protein assembly comprising GARP, TGF-β1 and a blocking antibody (Figure). This allowed us to understand how GARP presents TGF-β1 for activation on Tregs, and how our antibody actually blocks this process. Our antibodies were licensed to a pharmaceutical company, and a clinical trial was initiated in March 2019. We are now participating to the trial, in collaboration with University Hospital Saint-Luc and Prof. J.-P. Machiels. We will have the opportunity to study in depth the anti-tumor immune responses that may occur in the few patients who will receive the anti-GARP antibodies that were developed in our laboratory.

Staff members

Postdoctoral Fellows: Clément Barjon, Mélanie Gaignage, Purnima Gupta, Stéphanie Liénart, David Schröder • **PhD Students:** Charlotte Bertrand, Grégoire de Streel, Julien Devreux, Mathieu Jamez, Fanny Lambert, Sara Lecomte, Pierre Van Meerbeeck, Xuhao Zhang • **Undergraduate Student:** Marine Redaelli • **Research Assistants:** Fatima Benhaddi, Noora Bleeckx, Nicolas Chalon • **Administrative Support:** Emmanuelle Hemelrike

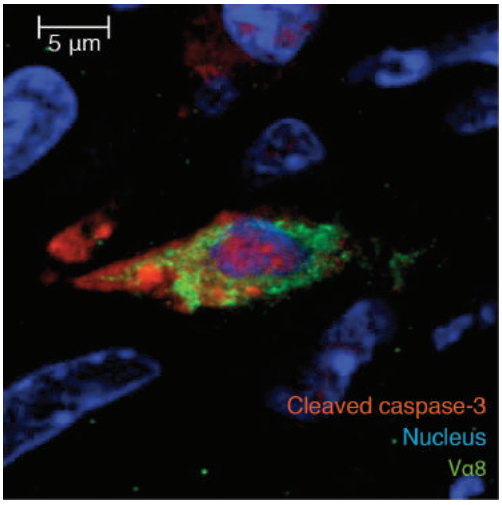
Benoit Van den Eynde

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 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 observed that tumors can selectively induce the death of T lymphocytes by apoptosis, and can produce immunosuppressive factors such as tumor-growth factor beta (TGFβ). Tumors also paralyze T lymphocytes by starving them of key amino acids, such as tryptophan. They do so by expressing enzymes, such as indoleamine dioxygenase (IDO) and tryptophan dioxygenase (TDO), which rapidly degrade tryptophan. We try to develop therapeutic strategies that can block these immunosuppressive mechanisms and thereby improve the clinical efficacy of cancer immunotherapy.

Staff members

Senior Investigators: Vincent Stroobant, Nathalie Vigneron • **Postdoctoral Fellows**: Joanna Abi Habib, Veronica Finisguerra, Wenbin Ma, Stefan Naulaerts, Jingjing Zhu • **PhD Students:** Raphaël Bombart, Tereza Dvorakova, Violette Ferrari, Simon Klaessens, Dorian Lapaille, Julie Lesenfants, Pierre-Florent Petit, Marie Solvay • **Undergraduate Students:** Manon Dalcq, Pierre-Hubert Desimpel • **Research Assistants:** Giuseppe Attardo, Loubna Boudhan, Martin Doyen, Matteo Formenti, Minh Phuong Le, Luc Pilotte, Bénédicte Tollet • **Administrative Support:** Isabelle Grisse

Pierre van der Bruggen

T Lymphocyte Dysfunction

We study the interactions between cancer cells and the human immune system. We ask why tumor-infiltrating lymphocytes (TILs) are often unable to eliminate tumors, and aim to find strategies to overcome this challenge.

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

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

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

Today, we remain dedicated to studying T cells and the different immunosuppressive mechanisms that operate in human tumors. Tumor-infiltrating T cells (TILs) are often dysfunctional, and we focus on three factors that might limit TIL function: extracellular galectins, TIL exhaustion and myeloid-derived suppressor cells (MDSCs). We discovered that extracellular galectin-3 secreted by tumor cells and macrophages binds glycoproteins at the T cell surface, which blocks human TIL functions.

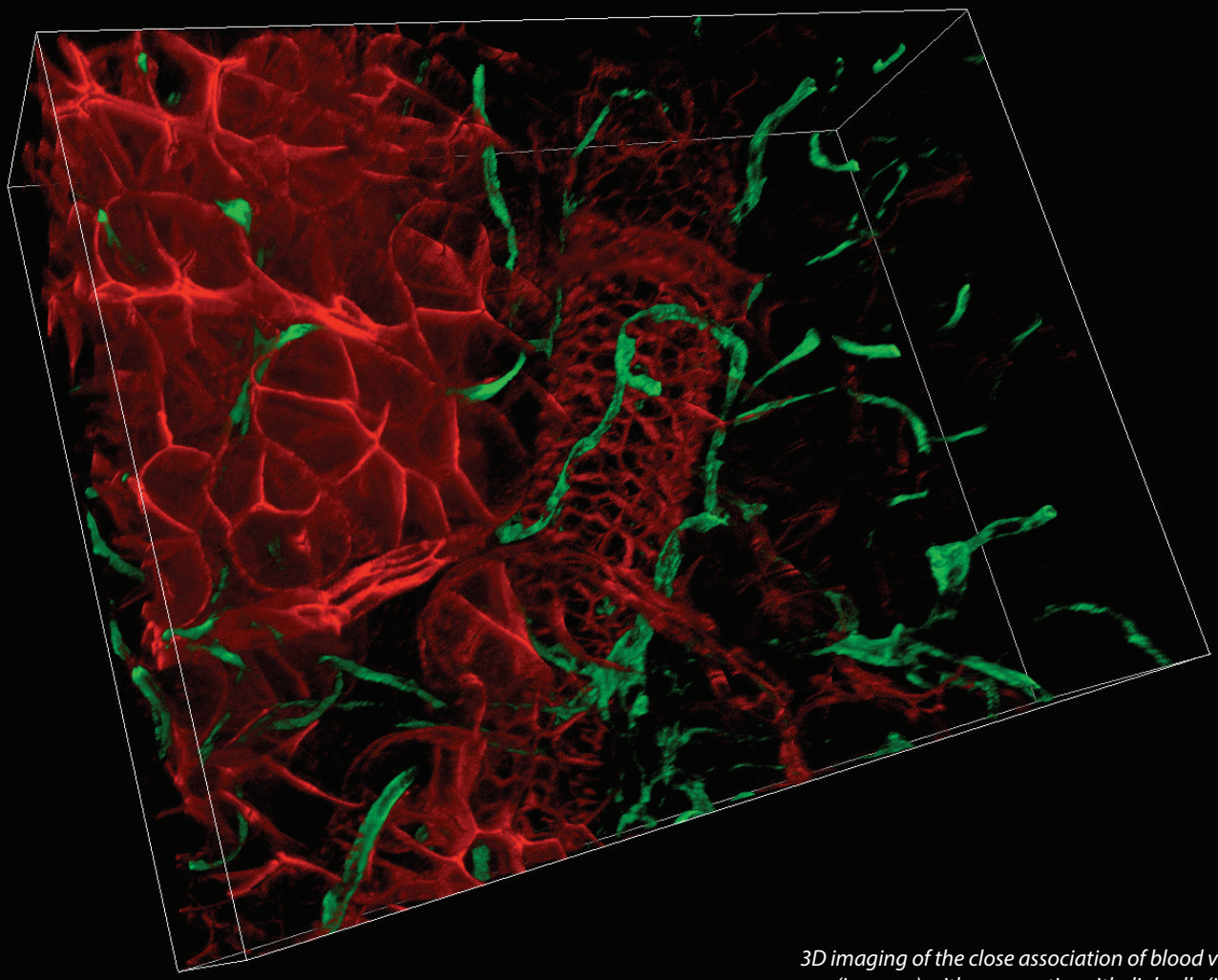
TILs become less functional in tumors, a phenomenon often named exhaustion. We are characterizing in-depth CD8 T cells infiltrating human tumors functionally, phenotypically and molecularly. We abrogate or increase the expression of specific transcription factors to study how they contribute to or prevent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

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

Most of our clinical samples are obtained from patients suffering from ovarian cancer. This deadly disease is often diagnosed at an advanced stage and patients receive chemotherapy before surgery. However, today it is still impossible to predict if and how a patient will respond to chemotherapy. To explain the heterogeneous responses to chemotherapy, we collect samples before and after treatment, and we study the immune cells, the tumor microenvironment and the genetics of the tumors. We dream to identify factors that could predict therapeutic outcomes or be targeted to improve the clinical management of future patients.

Staff members

Postdoctoral Fellow: Annika Bruger • **PhD Students:** Thibault Hirsch, Mathieu Luyckx, Shufeng Nan, Damien Neyens, Christophe Vanhaver • **Undergraduate Student:** Emmanuel Mbida • **Research Assistants:** Alexandre Bayard, Céline Duhamel, Claude Wildmann • **Administrative Support:** Isabelle Grisse



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

Genetics and Development

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

Donatienne Tyteca

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

Membrane Biology

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

"Elucidating the role of membrane lipids in disease paves the way towards use as diagnostic biomarker and manipulation for therapeutical benefit."

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

Lipid domains and membrane biophysical properties are deregulated in RBCs from patients suffering from spherocytosis and elliptocytosis, two genetic RBC deformability disorders (coll. B. Brichard & C. Lambert, University Hospital Saint-Luc). Hence, some lipid domains are lost upon RBC storage at 4°C, suggesting they could represent sites susceptible to vesiculation. In agreement with this hypothesis, extracellular vesicles released by stored RBCs exhibit various lipid compositions and are released by different mechanisms. The relevance of those observations to RBC vesiculation in blood bags before transfusion is currently tested (coll. Croix-Rouge de Belgique). Similar approaches are developed to determine the biogenesis and significance of erythroid cell-derived extracellular vesicles in erythroleukemia, a rare type of acute myeloid leukemia with poor prognosis (coll. V. Havelange).

Like RBC squeezing, cell migration and invasion also require cell shape remodelling. We explore whether and how membrane biophysical properties and lipid domains are altered in breast cancer and contribute to cell invasion. The malignant cells exhibit higher plasma membrane but lower cytocortex stiffness (coll. D. Alsteens) and a higher surface cholesterol content. The decrease of cholesterol content specifically inhibits invasion of the malignant cells, opening the possibility to target this lipid by a pharmaceutical approach. Extension to muscular cell migration and fusion into myotubes is ongoing, as a prerequisite to understand Duchenne myopathy.

Staff members

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

Nisha Limaye

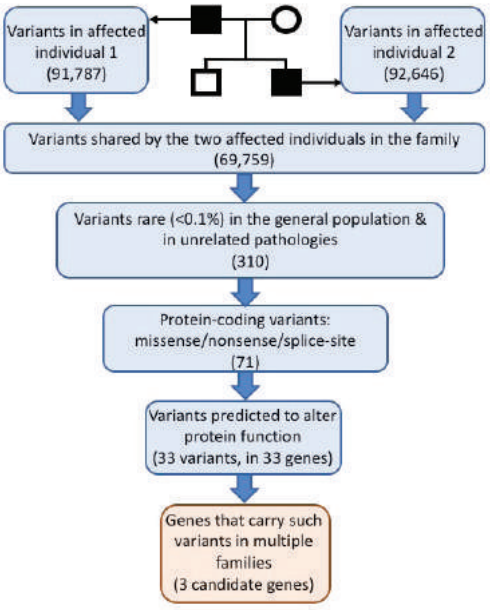
Genetics of Autoimmunity & Cancer

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

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

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

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



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

Once we identify a genetic variant that we hypothesize may cause disease, we test for functional evidence of its impact: we induce cells to express the faulty version of the gene, and study how this changes their appearance, behavior and function. We also screen patients with non-inherited ('sporadic') forms of the same disease for the gene or the biological pathway it participates in, to assess for how widespread a role it plays. Ultimately, by understanding the genetic and molecular bases of these rare diseases, we seek to better predict, prevent, and treat them.

Staff members
Guest Investigator: Gaëlle Tilman • **PhD Students:** Cécile Boulanger, Elsa Khoury, Hiba Maalouf, Pierre Maus • **Undergraduate Student:** Jean-Christophe Debray • **Research Assistant:** Delphine Nolf

Miikka Vikkula

Human Genetics

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

The bases of many disorders remain unknown, and treatments are often aimed at alleviating symptoms. We try to identify the causes of vascular tumors and malformations, lymphedema, and cleft lip and palate. We also collaborate in studies on arterial diseases (fibromuscular dysplasia), cancers (angiosarcoma, breast cancer), and diabetes. This research is based on blood and tissue samples collected from patients in collaboration with clinical expert centers worldwide, and especially with University Hospital Saint-Luc. We generate large amounts of data of the patient's genome using high-throughput DNA and RNA sequencing, and analyze them with our own specialized bioinformatics tool Highlander. We manage the UCLouvain Genomics Platform and an important computational cluster.

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

With our work, we have identified several genes that are mutated and cause inherited forms of vascular malformations. We have also discovered that the much more common non-hereditary forms are often due to somatic mutations. Due to these mutations, the PI3K/AKT or the RAS/MAPK signaling pathway is abnormally activated. Using mouse as model, we discovered that the time of occurrence of the mutation during development plays a crucial role in defining lesion development. With our murine model for venous malformations, we demonstrated that the mTOR inhibitor rapamycin can control expansion of lesions. We also demonstrated its effectiveness in patients and a phase III European trial, called 'VASE', is ongoing and coordinated by Prof. L. Boon at University Hospital Saint-Luc.

More recently, we have generated a model for arteriovenous malformation, and it is being tested for efficiency with medical treatments.

A large part of our efforts is dedicated to understanding lymphedema, which causes chronic swelling of legs and arms and predisposition to infections. We have discovered several genes that can be mutated and predispose to lymphedema. In 2020, we added a completely new gene and signaling pathway to the ever increasing picture of underlying causes. Altogether, 29 genes are now known, explaining about 30% of the cases. Our current work focuses on identification and explanation for the other 70%.

Another area of interest to us is cleft lip with or without cleft palate. They are one of the most frequent congenital malformations. Using our genomic approach we aim at identifying underlying causes to develop better diagnostics, prevention and future management. We currently develop novel bioinformatic tools to study these complex diseases.

Staff members

Clinical Investigators: Laurence Boon (Plastic Surgeon), Daniel Manicourt (Rheumatologist) • **Senior Investigators:** Pascal Brouillard (Platform Manager), Raphaël Helaers • **Postdoctoral Fellows:** Ha-Long Nguyen, Angela Queisser, Reza Salimi • **PhD Students:** Murat Alpaslan, Mirta Basha, Simon Boutry, Martina De Bortoli, Eleonore Pairet, Peyman Ranji, Nassim Homayun Sepehr, Matthieu Schlögel, Stanislas Smadja • **Undergraduate Student:** Joanna Colot • **Research Assistants:** Bill Brancart, Fabrice Cahay, Dominique Cottem, Audrey Debue, Séverine Gonze, Liliana Niculescu • **Technical Assistants:** Mourad El Kaddouri, Danny Plessiet • **Administrative Support:** Liliana Niculescu, Mina Todorovic

Charles De Smet

Epigenetics in Cancer

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

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

"Altered DNA methylation patterns in tumors often lead to aberrant activation of genes that normally display specific expression in germline cells."

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

Several CG genes were found to encode proteins that display oncogenic properties, and are therefore considered as potential targets for anti-cancer therapies. It is expected indeed that therapies directed against proteins expressed almost exclusively in tumors and germline cells will have only little side effects in cancer patients. Our group also isolated a CG gene (*CT-GABRA3*) that is not translated into a protein, but carries a clustered pair of miRNAs (miR-105 and miR-767). These miRNAs were found to promote tumor development, notably by favoring the formation of distant metastases.

More recently, we made the surprising observation that several CG genes produce long non-coding transcripts that overlap downstream promoters and thereby trigger their hypermethylation. Another consequence of CG gene activation in tumors is therefore the epigenetic repression of neighboring genes, which include tumor suppressor genes.

In order to determine the full spectrum of gene activations induced by genome demethylation in tumors, we performed a computational analysis of transcriptomic and methylomic data from lung cancer. This led to the identification of new transcripts activated by DNA demethylation in tumors, the majority of which are germline specific. Interestingly, we also identified two groups of transcripts that display specific expression in the lower digestive tract and in stratified epithelia. Current work aims at determining the profile of activation of these transcripts in other types of tumors, and at evaluating their possible association with tumor progression.

Staff members
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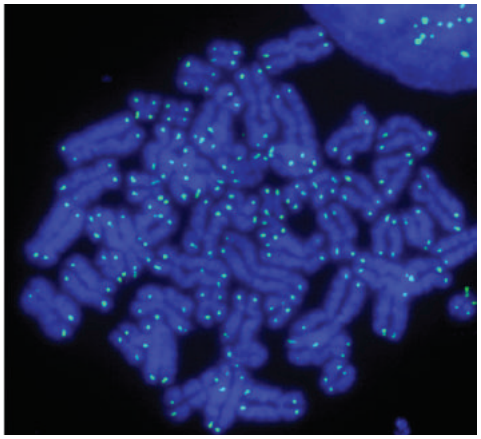
Anabelle Decottignies

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 & Epigenetics

Telomeres are specialized protective protein-RNA-DNA structures at chromosome ends and shorten with successive cell divisions until they get too short, leading to a permanent exit from cell cycle and cellular senescence.

Most cancer cells avoid telomere shortening. In 90% of tumors, telomerase expression is reactivated. In embryonic stem cells, telomerase counteracts telomere shortening, but its expression is lost upon cell differentiation. Sarcomas or central nervous system tumors (including pediatric tumors), however, frequently activate a telomerase-independent mechanism, called ALT (Alternative Lengthening of Telomeres), based on homologous recombination events. As ALT is not active in normal cells, this offers interesting perspectives for targeted cancer therapy. Thanks to a powerful genetic system, we identified TSPYL5 as a possible specific anti-ALT target. In collaboration with chemists, we are currently working on the identification of anti-TSPYL5 drugs. The same screen led us to discover new unexpected non-canonical roles for the h*TR* subunit of telomerase in the regulation of DNA damage response at telomeres.



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

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

Another part of our research focuses on TElomeric Repeat-containing RNA species, dubbed TERRA, which contribute to telomere protection. We discovered that the AMPK/PGC1-α metabolic pathway, activated by endurance exercise, promotes human telomere transcription through NRF1, suggesting a role for antioxidant defenses. We recently characterized mouse TERRA species and demonstrated their non-telomeric origin, highlighting important differences between human and mouse.

Finally, we study cellular ageing, notably in the context of premature ageing diseases linked to defective telomere maintenance (telomeropathies). We studied the cellular defects induced by telomeropathy-linked *PARN* loss-of-function. Telomeropathy diagnosis is achieved through telomere length measurement in blood cells using a technique called Flow-FISH, which was not available in Belgium. Last year, we set up Flow-FISH in collaboration with University Hospital Saint-Luc and enrolled about 500 healthy volunteers to establish the standard curves. The technique is now used by Belgian clinicians. These curves allowed us to show that most severely affected COVID-19 patients are characterized by short telomeres, further supporting the link between telomere length and resistance against viral infections.

Staff members

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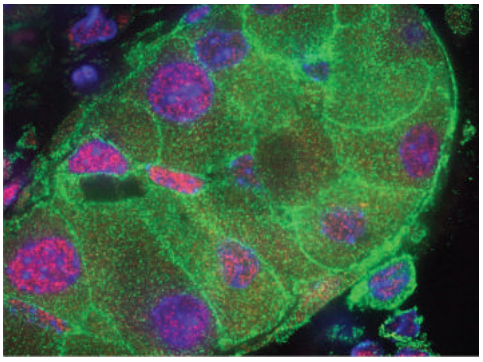
Frédéric Lemaigre &
Patrick Jacquemin

Cell Differentiation

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

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



Immunolabelling of the pancreas of a mutant mouse showing the presence of the Kras oncogene at the cell membrane (green) and of an activated Jak signaling pathway (red). Cell nuclei were labelled in blue.

The main cell types of the liver are the hepatocytes, which exert the metabolic functions of the organ, and the cholangiocytes, which delineate the bile ducts. We investigate the transcriptional networks that drive hepatocyte and cholangiocyte development in the embryo and identified several regulators of normal hepatocyte and biliary development, e.g. HNF6 – discovered in our laboratory –, and TGFβ signaling.

Parallel to our research on development, we investigate the differentiation switches occurring during transition from normal to precancerous and eventually invasive cancer states. In our studies of liver cancer, we developed an original mouse model of cholangiocarcinoma that faithfully reproduces the sequential steps of tumorigenesis in humans. In pancreas, we study the cell type of origin of pancreatic ductal adenocarcinoma (PDAC), i.e. acinar or duct cells, and the signaling cascades promoting formation of precancerous lesions and their evolution to cancer. Recently we identified the duct cells as the cell type of origin for a neoplastic lesion giving rise to PDAC. We also highlighted a post-translational mechanism regulating the activity of the KRAS oncogene in PDAC initiation.

Finally, we address the need of quantitative approaches by using mathematical modeling of gene networks, which we investigate in pancreas and liver. This resulted in the design of a mathematical model that predicts the behavior and drug response of a gene network involved in hepatocellular cancer. This mathematical approach also helped us to better understand the respective roles of EGFR and ERBB2 signaling receptors in PDAC.

Staff members

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Wen-Hui Lien

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

Signaling Crosstalk

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

In mammals, Wnt signaling pathways, including canonical and non-canonical Wnt signaling, regulate diverse processes, such as cell proliferation, differentiation, migration and polarity. Canonical Wnt signaling, referred as Wnt/β-catenin signaling, is known as an important pathway that regulates developmental processes, tissue regeneration and cancers. While Wnt/β-catenin signaling has been extensively studied, the functions of non-canonical Wnt pathways are still underappreciated. Our group uses skin as a model system to investigate the roles of non-canonical Wnt pathways mediated by receptor tyrosine kinase-like orphan receptor 2 (ROR2) in the regulation of skin stem cells and tumorigenesis.

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

Wnt signaling is shown to regulate adult stem cells, but exactly how it functions and for what purpose has been a matter of much debate. We conduct loss-of-function approaches by generating mutant mouse models to determine how ROR2-dependent Wnt signaling regulates skin development and hair follicle regeneration. Using the cell culture system, 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 the main regulators involved in non-canonical Wnt signaling pathways and to use them as therapeutic targets to treat cancer and other diseases.

Staff members

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

Christophe Pierreux

Epithelial Differentiation

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

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

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

Our group aims at understanding how epithelial cells of the thyroid and the exocrine pancreas organize and differentiate in response to signals from their environment. We have shown that thyroid and pancreatic progenitors first form a tridimensional mass of proliferating, non-polarized epithelial cells. Then, epithelial cells polarize and form monolayers that adopt a structure tailored to the organ's function: multiple independent closed spheres, or follicles, in the thyroid, or a single, highly branched network of ducts and acini in the exocrine pancreas. We demonstrated the importance of VEGF signaling during thyroid and pancreas formation and uncovered a perfusion-independent function of blood vessels, mediated by paracrine signals from endothelial cells. Our work on epithelial-endothelial relationship has been instrumental to pave the way towards thyroid bioprinting and we are now working on building a precise 3D atlas of the embryonic pancreas for bioprinting. We are also studying a sophisticated communication system that uses small (~100 nanometers) vesicles to transfer information between cells. During thyroid development, we uncovered the role of these extracellular vesicles in intercellular communications aiming at building the thyroid follicles. We are now investigating the messages contained in extracellular vesicles specifically released by thyroid cells in cancer and in thyroid diseases.

We are also investigating epithelial homeostasis in adult organs. On the one hand, we studied the blood vessels during pancreatitis, a condition mainly affecting our western countries, and found important remodeling of the vasculature. We are now studying the molecular mechanisms causing these tissular changes. On the other hand, we also addressed the pathophysiology of cystinosis, a multisystemic lysosomal disease due to defective lysosomal membrane cystine/H+ antiporter, cystinosin. We found that the disease first manifests by a kidney Fanconi syndrome, largely caused by megalin-dependent cystine accumulation in kidney lysosomes. We are now investigating the possibility to translate our basic discoveries into a simple diet-based therapy for cystinosis.

Staff members

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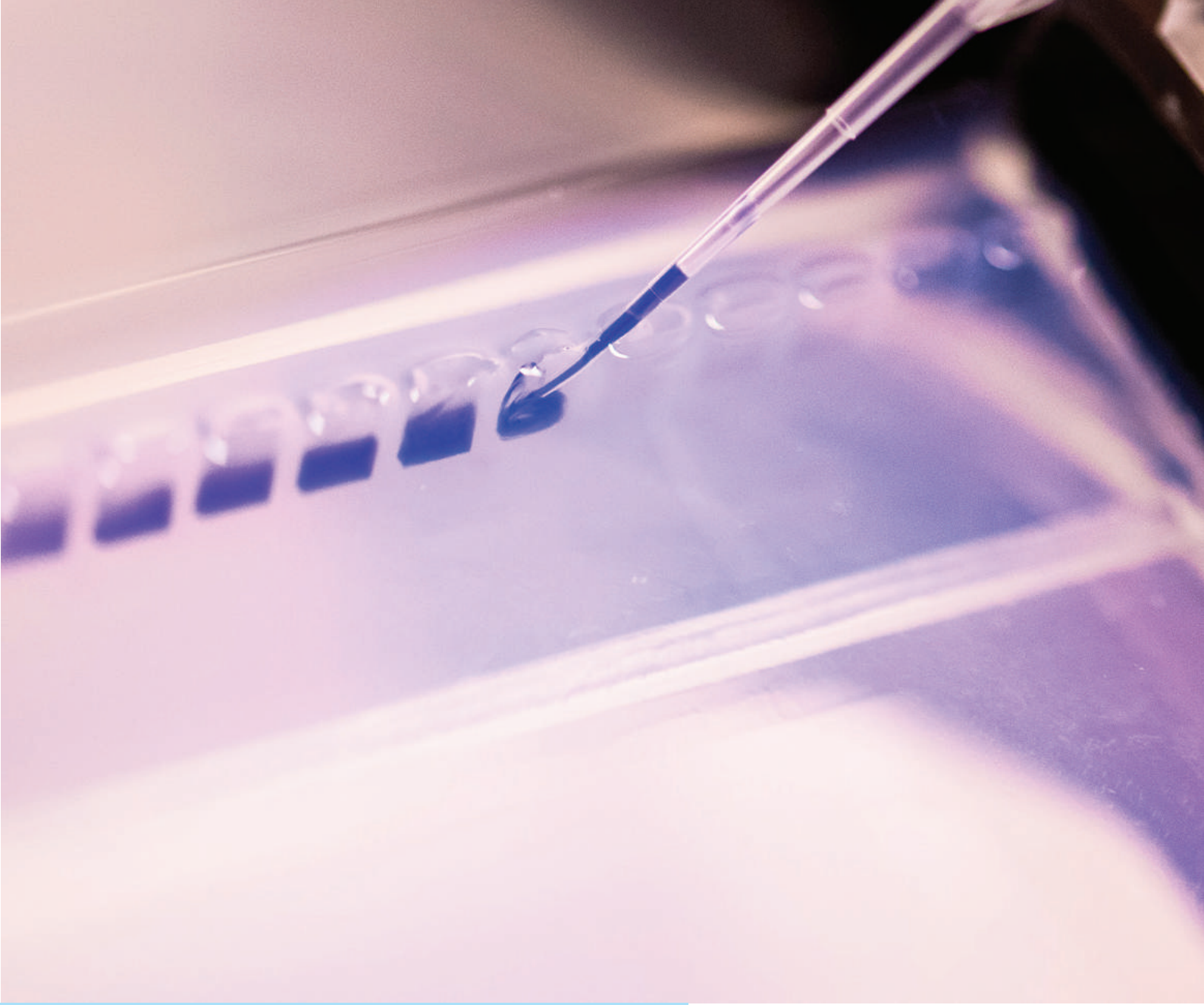


Our body deals with viral or bacterial infections by inflammatory responses of the immune system. Our groups investigate how viruses modulate the body's immune reactions, or escape from them. We also address the worrying emergence of bacteria resistant to all available antibacterial agents. When inflammation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

Infections and Inflammation

Jean-François Collet

Bacterial Stress Responses

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

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

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

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

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

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

Staff members

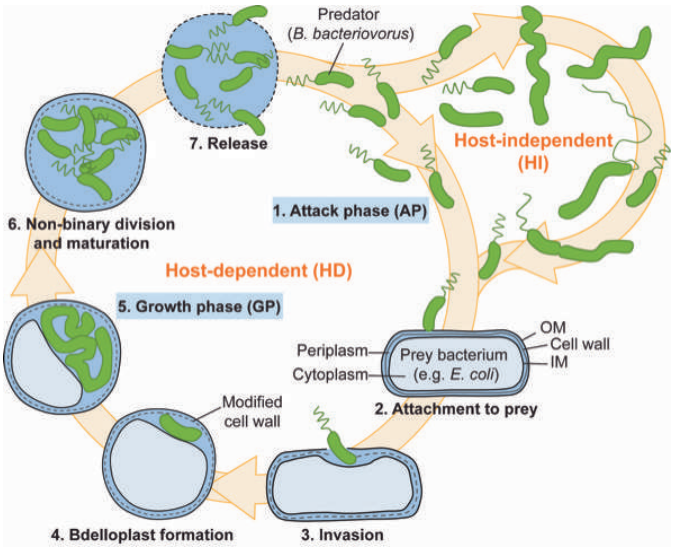
Senior Investigators: Seung Hyun Cho, Pauline Leverrier • **Guest Investigators:** Bogdan Iorga, Hiroyuki Kanamaru • **Postdoctoral Fellows:** Abir Asmar, Michaël Deghelt, Antoine Delhaye, Alexandra Gennaris, Alexandre Marbaix, Chi Nguyen • **PhD Students:** Naemi Csoma, Kilian Dekoninck, Emile Dupuy, Jessica El Rayes, Elisa Pierre, Raquel Rodriguez Alonso, Alexandre Thurman • **Undergraduate Student:** Emmanuelle Latour • **Research Assistant:** Carla Aspite, Asma Boujtat

Géraldine Laloux

Bacterial Cell Biology

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

Acquiring fundamental knowledge on the cell biology of bacteria is a prerequisite for many clinical applications, including the fight against pathogenic strains, the development of solutions to the problem of antibiotic resistance, and the appropriate use of bacteria with beneficial roles in the human body. In our group, we study how bacteria organize their cellular content in space and time to achieve complex lifestyles, using a combination of bacterial genetics, molecular biology, live fluorescence microscopy and quantitative image analysis at the single-cell level.



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

We focus on the predatory bacterium *Bdellovibrio bacteriovorus* for two main reasons: (i) *Bdellovibrio* is a promising complement to classical antibiotics, since it kills other Gram-negative bacteria (including antibiotic-resistant and biofilm-forming pathogens), while being harmless for eukaryotic (e.g. human) cells; (ii) *Bdellovibrio* has an astounding cell cycle (Figure), which challenges the paradigm of binary cell division in bacteria: while most model species produce two cells per generation, *Bdellovibrio* releases larger and variable numbers of descendants. How cellular processes are orchestrated to govern the sophisticated biology of *Bdellovibrio* is largely unknown. Yet, discovering the molecular determinants underlying the cell cycle of this micro-predator is critical to understand how it kills and thrives inside its prey.

In 2020, we discovered that the single chromosome of *Bdellovibrio* (its genetic material) is compacted to an unprecedented level when the bacterium is outside its prey, and partially decondenses during the growth phase inside the prey. We are now investigating the molecular cues and physiological role of this unique cell-cycle-dependent organization. We also revealed the complex dynamics of chromosome replication and segregation, which led us to propose a model that explains how *Bdellovibrio* produces variable, odd or even numbers of daughter cells that do not follow a canonical exponential pattern. Moreover, we developed methodologies to quantitatively assess predation efficiency. In parallel, we examine the function of proteins that keep the content of the bacterial cell in order and we investigate the mechanisms of non-binary division and its regulation (i.e. how and when the cell divides at multiple locations along its length). For all projects, we constantly develop new analytic tools to extract quantitative data from live microscopy images, at the single-cell and population levels.

Staff members

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Jean-Paul Coutelier

Infections & Immunity

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

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

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

Using lactate dehydrogenase-elevating virus (LDV), and other common mouse viruses, we were first to show that viruses triggered a specific type of response, now called Type 1, characterized by increased proportion of IgG2a antibodies that were more efficient to protect mice against a fatal polioencephalomyelitis. Some of these characteristics of the immune responses are found also after infection with intracellular parasites such as *Plasmodium*, whereas helminths, including *Schistosoma*, induce a completely different response. Infections result therefore in a bias in the immune microenvironment of the host, which often leads to alterations of responses elicited against non-infectious antigens and of concomitant diseases with an immune component.

In mice, LDV- and *Plasmodium*-modulated immune microenvironment resulted in an enhanced susceptibility to diseases concomitant to the infection, but of unrelated cause, such as septic shock, through macrophage activation leading to enhanced TNF production. These infectious agents triggered an increased production of soluble receptors for bacterial lipopolysaccharide, which might serve as early indicators of this enhanced susceptibility to develop shock. Similarly, autoantibody-mediated hemolytic anemia and thrombocytopenia were aggravated by viral infection because of enhanced phagocytosis of opsonized erythrocytes and platelets by activated macrophages. This could explain how Immune Thrombocytopenic Purpura develops in children after infection with diverse common viruses.

However, modulation of the host immune microenvironment by infections could also protect against immune-mediated diseases such as graft-versus-host response and experimental autoimmune encephalitis. Similarly, mouse NK cell activation and IFN-γ production triggered by LDV infection or by ligands of immune receptors that mimick infections resulted in the inhibition of the development of some tumors such as plasmacytoma and mesothelioma. In contrast, *Schistosoma* antigen decreased both IFN-γ production and plasmacytoma prevention. Similarly, a study of Egyptian myeloma patients suggested a preventive effect of viral infections, but an enhanced risk to develop cancer after *Schistosoma* infection.

Staff members

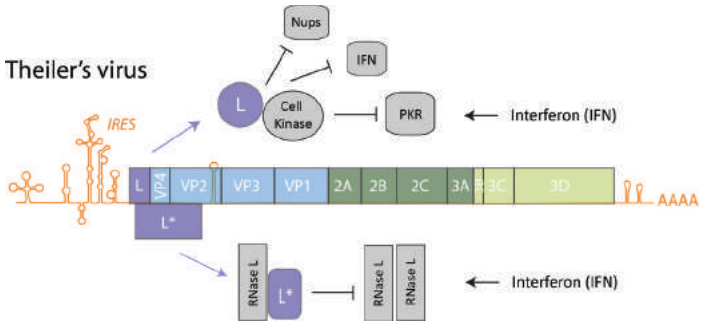
PhD Students: Jean d'Amour Mutoni, Ella Larissa Ndoricyimpaye, Pyone-Pyone Soe

Thomas Michiels

Viral Persistence & Interferon Response

Viruses developed fascinating strategies to hijack cellular signaling pathways and to counteract defenses of their host. Studying how viral proteins act provides insight into infection mechanisms as well as into important and physiological cellular processes.

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



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

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

• Theiler's virus 'leader' (L) protein: Theiler's virus is a mouse picornavirus that has a striking ability to persist in the central nervous system in the presence of a strong and specific immune response. We study how the L protein of this virus and of related cardioviruses interfere with innate immunity. Our recent data show that L can hijack cellular kinases. We currently study how hijacking such kinases contributes to innate immunity evasion.

• Interferon (IFN) response: One key molecule that can trigger IFN production by infected cells is double-stranded RNA (dsRNA). dsRNA is produced in infected cells, as a byproduct of viral replication. Cellular dsRNA sensing pathways participate in IFN production as well as in the activation of PKR, an antiviral enzyme. PKR activation is also observed in pathological conditions such as Aicardi-Goutières syndrome and systemic lupus erythematosus. We recently identified novel PKR phosphorylation sites that regulate PKR activation. Understanding the mechanisms leading to (aberrant) PKR activation is important to set up future therapeutic strategies that balance antiviral activities and risks of autoimmune effects.

• SARS-CoV-2: In view of the COVID-19 emergency, we embarked in basic researches related to the SARS-CoV-2 coronavirus, the COVID-19 agent. We set up an assay to test for the presence of protecting antibodies in patients or in vaccinated people. This work further prompted us to analyze the spike proteins determinants that define how the virus enters into cells. We also analyze polymerase properties that regulate viral replication with the hope that polymerase may be targeted by future antiviral agents.

Staff members

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Jean-Christophe Renauld &
Laure Dumoutier

Inflammatory Disorders & Cytokines

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

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

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

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

Recently, we investigated the role of IL-22 and IL-22-related cytokines in skin inflammatory disorders including psoriasis, allergic contact dermatitis and urticaria. In collaboration with the dermatology department of University Hospital Saint-Luc, we have shown that IL-22-related cytokines are highly expressed in the skin of patients with these three inflammatory diseases. These results strongly suggest that these cytokines are involved in skin inflammatory processes. Indeed, we have been able to show that in animal models of psoriasis, administration of an antibody blocking IL-22 activity is able to decrease some features such as scaly lesions and redness, demonstrating the deleterious role of this cytokine in the disease.

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

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

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

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

Metabolism and Hormones

Emile Van Schaftingen &
Maria Veiga-da-Cunha

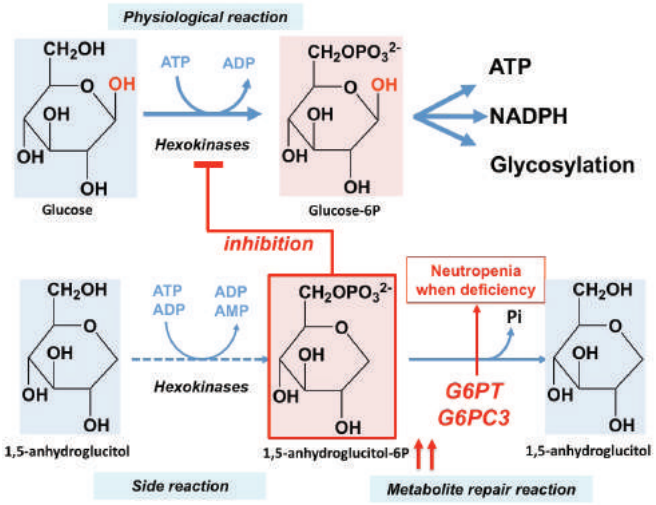
Metabolite Repair

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

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

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

Our work during the last ten years has been focused on the identification of additional metabolite repair enzymes. One of them, a highly conserved protein called Nit1, degrades a damaged form of glutathione, deaminated glutathione, which results from side activities of transaminases. Mice deficient in this enzyme eliminate deaminated glutathione in urine and therefore lose a substantial amount of cysteine every day. Others serve to eliminate toxic phosphate esters produced by glycolytic enzymes, an abnormal intermediate in lipid synthesis and an abnormal form of NADH.



The metabolite repair concept led us recently to understand the cause of the congenital neutropenia found in patients deficient in G6PC3, a phosphatase present in the endoplasmic reticulum, or deficient in G6PT (SLC37A4), the glucose-6-phosphate transporter of the endoplasmic reticulum. These two proteins collaborate to destroy 1,5-anhydroglucitol-6-P, an abnormal metabolite made in vivo by side activities of glucose-phosphorylating enzymes. Lack of dephosphorylation of 1,5-anhydroglucitol-6-P leads to its intracellular accumulation and, as a result, to strong inhibition of glucose phosphorylation. This is toxic to neutrophils and explains the patients' neutropenia. An inhibitor of the sodium-dependent glucose transporter SGLT2, which causes a depletion of 1,5-anhydroglucitol in serum, has been successfully used to treat the neutropenia in four patients.

Staff members

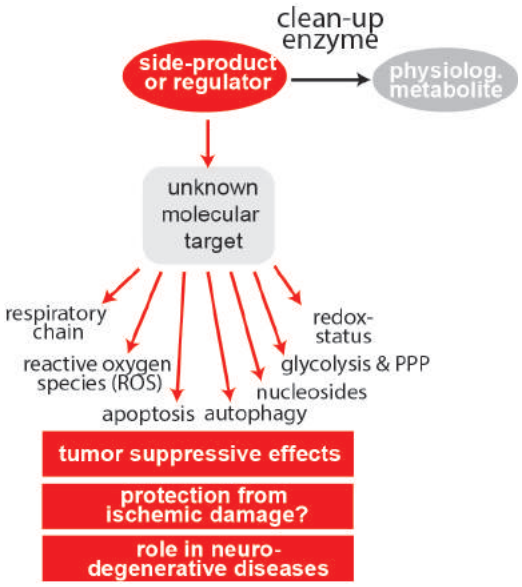
Senior Investigator: Elsa Wiame • **Guest Investigator:** Alessio Peracchi • **Postdoctoral Fellow:** Takfarinas Kentache • **Undergraduate Student:** Hernan Tirado • **Research Assistant:** Nathalie Chevalier • **Technical Assistant:** Karim Acherki • **Administrative Support:** Pauline Leverrier, Marie-Victoire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

Guido Bommer

Metabolism in Cancer & Other Diseases

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

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



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

We are investigating the role of a series of enzymes, for which we have reason to believe that they might be involved in the synthesis of regulatory molecules. In these studies, we use a combination of state-of-the-art metabolomics (GC-MS and LC-MS) and genetic manipulation of cell lines to understand the cellular effects of novel regulatory molecules. Classical enzymological studies (in collaboration with the laboratory of Emile Van Schaftingen and Maria Veiga-da-Cunha) on purified proteins are then used to understand the molecular basis of the observed effects. Eventually, we hope that our work will reveal novel therapeutic targets in cancer. Currently, we are particularly interested in several phosphatases that might serve to eliminate metabolic side-products or metabolic regulators.

While we strive to understand processes involved in cancer biology, we remain very much open to surprising discoveries. As such, we have recently discovered a novel post-translational modification of α-dystroglycan by ribitolphosphorylation. Furthermore, we are following-up on observations that suggest that so far unknown biochemical changes may contribute to the development of Parkinson's disease.

Staff members

Senior Investigator: Isabelle Gerin • **Postdoctoral Fellows:** Marina Bury, Joseph Dewulf, Sven Potelle • **PhD Students:** Francesco Caligiore, Isaac Heremans, Stéphanie Paquay, Benoît Ury • **Undergraduate Student:** Jean Jacobs, Aymeric Pinon • **Research Assistant:** Julie Graff

Mark Rider

Protein Phosphorylation

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

Metformin is the most prescribed drug used for the treatment of type 2 diabetes (T2D) and its effects can partly be explained by activation of AMP-activated protein kinase (AMPK), which is the main focus of our research. AMPK acts as a sensor of cellular energy status, activated by an increase in the AMP:ATP ratio, as occurs during hypoxia or muscle contraction/exercise. The role of AMPK in the cell is to maintain ATP by stimulating ATP-producing pathways and at the same time inhibiting energy-consuming biosynthetic pathways. Insulin, on the other hand, acts via protein kinase B (PKB) and stimulates anabolic pathways. AMPK is now a well recognized drug target for treating metabolic disorders such as T2D. We recently isolated two isoprenylated flavonoids from the roots of a plant, Dorstenia psilurus used in African traditional medicine, that activated AMPK. The compounds increased intracellular AMP:ATP by inhibiting the mitochondrial respiratory chain, increased skeletal muscle glucose uptake and inhibited hepatocyte glucose production. Moreover, the compounds lowered blood glucose when administered to insulin-resistant mice on a HFD, appropriate for the treatment of T2D. In white adipose tissue (WAT), we used inhibitors to show that PKB plays a major role in insulin-stimulated lipogenesis by controlling the phosphorylation state of key lipogenic enzymes. Our more recent unpublished work indicates that AMPK activation antagonizes insulin-stimulated lipogenesis in WAT to prevent lipid accumulation, a major cause of insulin resistance. Also in the liver, a panel of small-molecule AMPK activators inhibited glucagon-stimulated glucose production, pertinent for treating T2D, although one compound (991) had off targets effects by interfering with lactate/pyruvate metabolism and redox state.

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

In addition to our work on AMPK, we run the mass spectrometry (MS) protein analysis facility (MASSPROT) on the Brussels campus of UCLouvain. The acquisition by de Duve Institute of the High Resolution/Accurate Mass Orbitrap Lumos has enabled us to perform quantitative proteomics and increase our capabilities to study other protein modifications. Indeed, we have been able to improve our strategy for the quantitative measurement of differential changes in protein phosphorylation by studying insulin action in WAT. In collaboration with the group of S. Constantinescu, we showed that the glycosylation pattern of an immature thrombopoietin receptor participates in oncogenic transformation in myeloproliferative neoplasms. Within the framework of an EOS consortium, we quantitatively mapped the S-sulfenylated cysteines in *Arabidopsis* cells under H_2O_2 stress and thereby generated a comprehensive view of the plant S-sulfenylation landscape.

Staff members

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

Etienne Marbaix &
Patrick Henriet

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

Endometrium Physiopathology

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

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

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

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

Staff members
PhD Students: Charlotte Thieffry, Marie Van Wynendaele • **Undergraduate Student:** Caroline Dupuis • **Research Assistant:** Maxime Lingurski • **Administrative Support:** Aimée-Lys Rusesabagina

Computational Biology

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

Laurent Gatto

Computational Biology & Bioinformatics

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

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

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

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

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

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

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

Staff members

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

Selected Publications

Stefan Constantinescu

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Pierre Coulie

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Benoit Van den Eynde

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Technology Platforms

Flow Cytometry and Cell Sorting

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

Genomics

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

Imaging

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

Laboratory Animals

The platform produces mice under 'SPF' health status for academic research use, with no commercial purpose. It hosts 80 different mouse strains, both non-genetically and genetically modified, available under a very high sanitary status monitored via a sentinel program, for research teams of the University of Louvain and collaborators. The platform is managed by Prof. Sophie Lucas and is run by Dr. Pedro Gomez, with technical help from Pascale Bougard, Lionel Crikeler, Laurent Hermanns and Quentin Lechien.
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Mass Spectrometry

The platform provides proteomics services principally through gel-free approaches coupled to mass spectrometry. It specializes in the identification and quantification of proteins from complex samples, and can also provide data on the location of post-translational modifications, even in complex samples. The platform is managed by Profs. Jean-François Collet and Mark Rider and is run by Drs. Didier Vertommen and Sébastien Pyr dit Ruys.
[W] https://www.deduveinstitute.be/massprot-platform-mass-spectrometry

Transgenesis

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

Jean-François COLLET • Scientific Prize Joseph Maisin for basic biomedical sciences 2016-2020
Awarded every five years by the FNRS to a Belgian researcher for the best career, scientific quality and impact in basic biomedical sciences.

Jean-François COLLET • Francqui Chair 2019-2020 - Faculty of Sciences, University of Liège
Attributed every year by the Francqui Foundation to a Belgian professor invited by another Belgian university to give a 10-h teaching.

Stefan CONSTANTINESCU • Vice-President of the Académie royale de Médecine de Belgique for 2020

Anabelle DECOTTIGNIES • Oswald Vander Veken Prize 2020
Awarded every three years by the FNRS and the FWO to a European researcher, for an original contribution to the understanding of tumors of the locomotor apparatus, their causes, prevention, diagnosis and/or treatment.

Camille GOEMANS • Eugène Yourassowsky Prize 2020
Awarded every four years by the FNRS to a young Belgian researcher, to reward a doctoral thesis in the field of medical microbiology and infectious diseases (promoter: Jean-François Collet).

Wen-Hui LIEN • Selected by the Ministry of Science and Technology, Taiwan, to appear in a book about successful Taiwanese living abroad (*'Study and Go Abroad, Flip your Life'*, Commonwealth Publishing Group, 2020)

Nisha LIMAYE • Cristina Pivetta Prize 2020
Awarded every three years to a Belgian researcher by the Fonds pour la Recherche Scientifique en Rhumatologie for an original scientific work on systemic sclerosis.

Sven POTELLE and Benoît URY • Professor Christian Coërs Prize 2019
Awarded every year by the Académie royale de Médecine to a Belgian researcher aged 45 or less, to reward accomplished work or to encourage a particularly brilliant research project in the field of neuromuscular pathology.

Maria VEIGA-DA-CUNHA • d'Alvarenga, de Piauhy Prize 2020
Awarded every year to a Belgian researcher by the Académie royale de Médecine for the best thesis on a medical topic.

PhD Theses

Mohamed MANDOUR • *Modulation of early cancer growth by infectious agents through their interaction with the immune microenvironment* • Promoter: J.-P. Coutelier

Nora MEYERS • *Differential impact of the ERBB receptors EGFR and ERBB2 on the initiation of pancreatic intraepithelial neoplasia* • Promoter: P. Jacquemin, co-promoter: F. Lemaigre

Guillaume DACHY • *Genomic mechanisms of receptor-tyrosine kinase activation in myofibroma* • Promoter: J.-B. Demoulin, co-promoter: V. Havelange

Camille MICHIELS • *The C-terminal region of IL-22Ra: a novel potential therapeutic target for psoriasis* • Promoter: L. Dumoutier

Charlotte HEYMANS • *Role of laminin-111 in pancreatic acinar differentiation and of MarvelD3 in pancreas development and disease* • Promoter: C. Pierreux

Grégoire de STREEL • *Cancer immunotherapy with monoclonal antibodies blocking the GARP-dependent production of TGF-β1* • Promoter: S. Lucas

Matthieu SCHLÖGEL • *Identification of novel causes of lymphedema and lymphatic malformation, with phenotypic characterisation of patients* • Promoter: M. Vikkula, co-promoter: P. Brouillard

Lectures & Scientific Events

N.B. Due to the Covid-19 pandemic, all scientific events and most lectures had to be postponed or cancelled.

Jean-Paul VINCENT • *The Francis Crick Institute, London, UK*
Generation of signalling landscapes in a developing epithelium

Maxime ROSSI • *Institute for Medical Immunology, Université Libre de Bruxelles & University Hospital, Charleroi, Belgium*
Contribution of myeloid HO-1 to the modulation of renal ischemia-reperfusion injury

Denis WIRTZ• *Institute for NanoBiotechnology & Sidney Kimmel Cancer Center, Johns Hopkins University, Baltimore, MD, USA*
Targeting metastatic cancer

Nicolas GILLET• *Namur Research Institute for Life Sciences, University of Namur, Belgium*
The APOBEC3 cytidine deaminases: antiviral innate immune effectors with a genotoxic tendency

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Acknowledgements

In 2020, 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 2020, the Institute has been able to allocate the following fellowships, entirely supported by our donors:

the 'Haas-Teichen' fellowship to Angela Queisser (Germany), followed by Frédéric Sorgeloos (back from the United Kingdom),

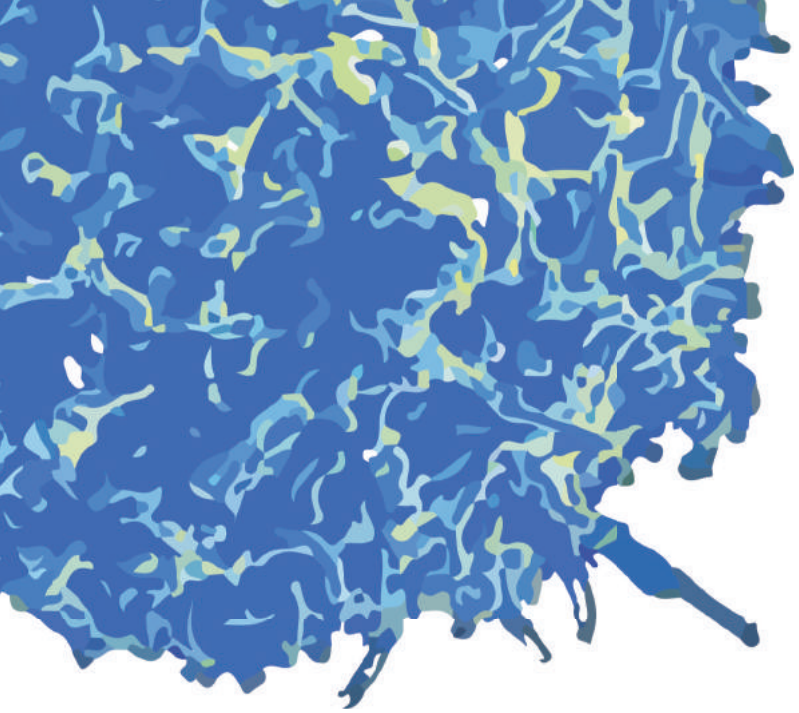
the 'Maurange' fellowship to Nicolas Capelli (France),

and a de Duve fellowship to Malak Haidar (Lebanon), as well as Maya Raghunandan (India) and Reza Salimi (Iran).

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

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

Luc Bertrand
Chairman of the Development and Expansion Council



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