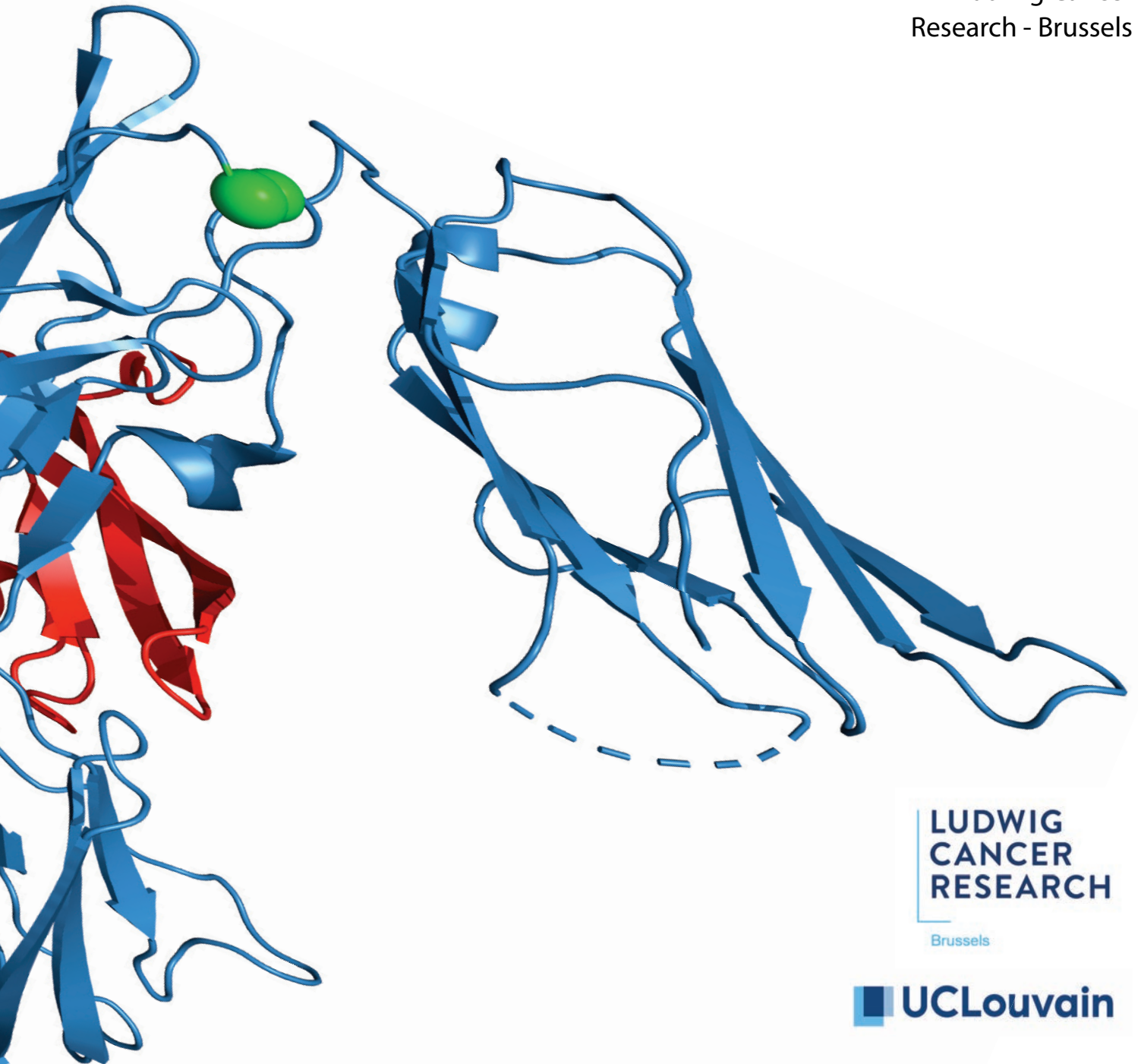


SCIENTIFIC REPORT 2021

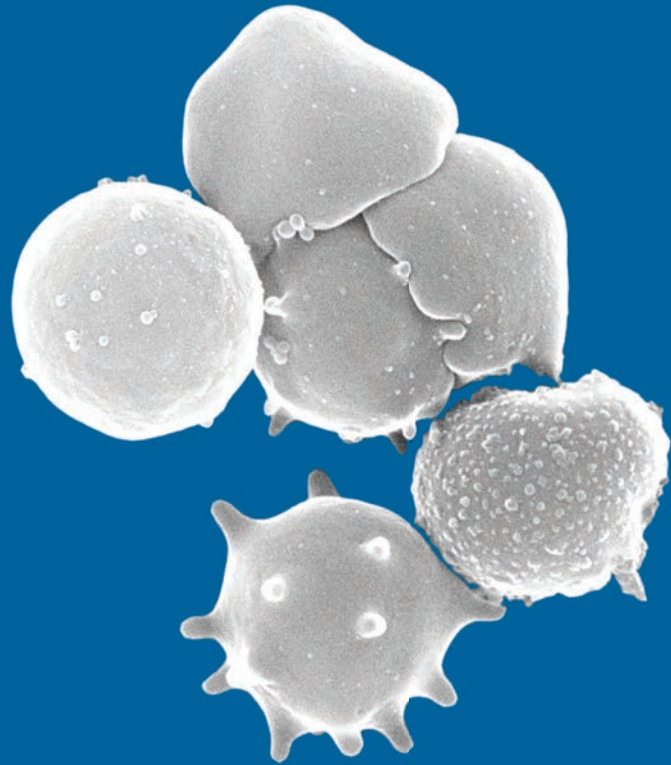


de Duve Institute &
Ludwig Cancer
Research - Brussels



LUDWIG
CANCER
RESEARCH
Brussels

UCLouvain



Avenue Hippocrate 75
B-1200 Brussels, BELGIUM

[T] + 32-2-764 75 50

[F] + 32-2-764 75 73

[E] deduve_institute@uclouvain.be

[W] www.deduveinstitute.be

Directors

Prof. Benoit Van den Eynde

Prof. Jean-François Collet

Prof. Sophie Lucas

Prof. Miikka Vikkula

Finance Manager

Pierre-Olivier Seroen

External Relations

Isabelle de Duve

Photographs

Jacky Delorme & Hugues Depasse

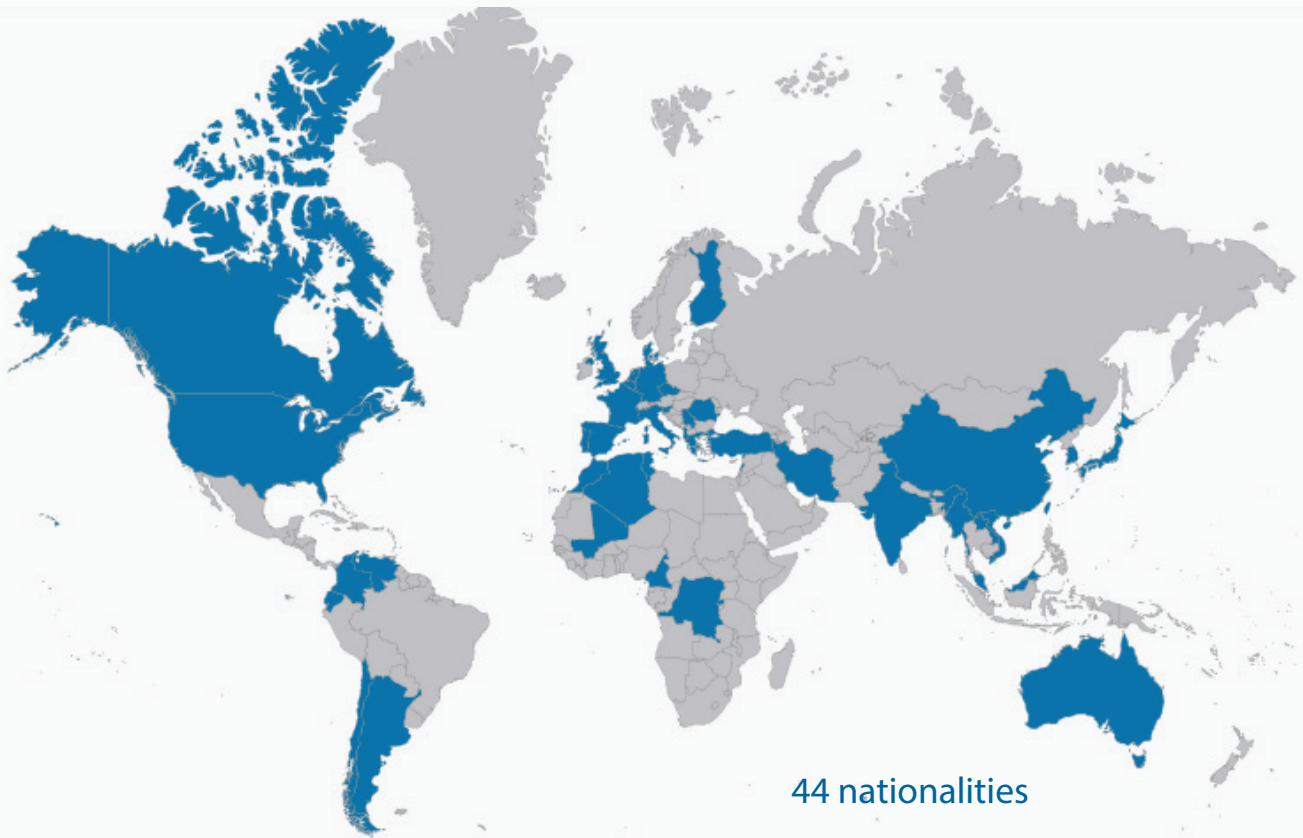
Research Highlights

Francisca Voermans

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

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

<p>2 KEY NUMBERS</p> <p>3 FROM THE DIRECTOR</p> <p>4 ABOUT THE INSTITUTE</p> <p>5 RESEARCH HIGHLIGHTS</p> <p>15 RESEARCH GROUPS</p> <hr style="border: 1px solid blue;"/> <p>46 SELECTED PUBLICATIONS</p> <p>57 TECHNOLOGY PLATFORMS</p> <p>58 PRIZES, AWARDS & HONORS</p> <p>59 PHD THESES</p> <p>60 LECTURES & SCIENTIFIC EVENTS</p> <p>61 MANAGEMENT</p> <p>62 SUPPORTING ORGANIZATIONS</p> <p>63 PRIVATE & CORPORATE FUNDING</p> <p>64 ACKNOWLEDGEMENTS</p>	<p style="text-align: right;">CANCER 16</p> <hr style="border: 1px solid green;"/> <p><small>LUDWIG CANCER RESEARCH</small> Stefan Constantinescu 17</p> <p>Nick van Gastel 18</p> <p>Jean-Baptiste Demoulin 19</p> <p>Pierre Coulie 20</p> <p>Sophie Lucas 21</p> <p><small>LUDWIG CANCER RESEARCH</small> Benoit Van den Eynde 22</p> <p>Pierre van der Bruggen 23</p> <p style="text-align: right;">GENETICS & DEVELOPMENT 24</p> <hr style="border: 1px solid red;"/> <p>Donatienne Tyteca 25</p> <p>Nisha Limaye 26</p> <p>Miikka Vikkula 27</p> <p>Charles De Smet 28</p> <p>Anabelle Decottignies 29</p> <p>Frédéric Lemaigre & Patrick Jacquemin 30</p> <p>Wen-Hui Lien 31</p> <p>Christophe Pierreux 32</p> <p style="text-align: right;">INFECTIONS & INFLAMMATION 33</p> <hr style="border: 1px solid blue;"/> <p>Jean-François Collet 34</p> <p>Géraldine Laloux 35</p> <p>Jean-Paul Coutelier 36</p> <p>Thomas Michiels 37</p> <p>Jean-Christophe Renault & Laure Dumoutier 38</p> <p style="text-align: right;">METABOLISM & HORMONES 39</p> <hr style="border: 1px solid magenta;"/> <p>Emile Van Schaftingen & Maria Veiga-da-Cunha 40</p> <p>Guido Bommer 41</p> <p>Mark Rider 42</p> <p>Etienne Marbaix & Patrick Henriët 43</p> <p style="text-align: right;">COMPUTATIONAL BIOLOGY 44</p> <hr style="border: 1px solid orange;"/> <p>Laurent Gatto 45</p>
---	--



317 members



104 PhD students



45 postdoctoral students



131 publications



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



6 technology platforms



8000 m²

I am thrilled to introduce this summary of research accomplishments at the de Duve Institute in the year 2021, which has seen a progressive return to normal operations in the wake of the pandemic.

In line with our motto “Deeper knowledge for better cures”, you will read in the research highlights (pages 6 to 14) how our scientists discovered the cause of several unexplained diseases. You will see that in a number of cases this understanding led to the identification of an effective therapy for previously incurable diseases, such as myofibromatosis (page 9) and rare inherited immune diseases (page 7). These cases exemplify the mission of the de Duve Institute, by showing how fundamental research can improve human health, sometimes through unexpected paths.

These are only examples, and you will find in this report many other exciting discoveries made by the different teams of researchers at the Institute. These teams comprise increasing numbers of young scientists: 104 PhD (doctorate) students and 45 postdoctoral fellows. Their findings were published in a record number of 131 scientific publications in 2021.

Another good news in 2021 has been the appointment of Nick van Gastel as a “Chercheur qualifié FNRS”, which is a coveted permanent position. Nick joined the Institute in July 2020 and is now a group leader studying metabolic regulation and the role of the bone marrow microenvironment in blood cell formation and leukemia, with the hope of developing new therapeutic strategies (page 18).

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.

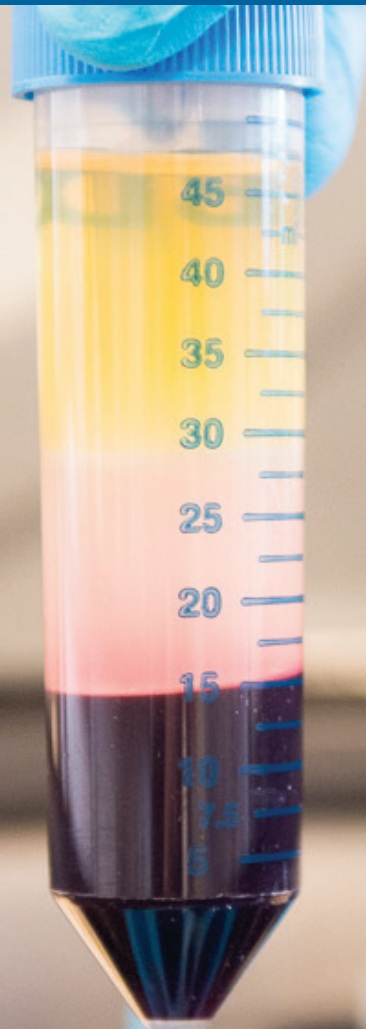
We value collaborative work and interdisciplinary research. The Institute functions in symbiosis with the Faculty of Medicine of the University of Louvain (UCLouvain) and many of its senior members hold a Faculty position and have teaching appointments. The influx of doctoral students and postdoctoral 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



OUT OF BALANCE

Our immune system operates on a delicate balance. It must respond quickly and rigorously, to stop invaders such as bacteria and viruses. But if it acts too vigorously, it may harm own, healthy tissue. Nisha Limaye studies diseases where the system is out of balance, in the hope of improving their diagnosis and treatment in the future.

The immune system is a complex machinery, involving many types of cells and molecules whose interactions are strictly regulated. The malfunction or absence of a critical molecule can disturb the balance of the system and lead to a variety of diseases. “These range from cancers, where the immune cells fail to kill the abnormal cancer cells, to autoimmune diseases, like systemic lupus erythematosus (SLE), in which the immune system attacks own tissue”, says Nisha Limaye. Starting from patient samples, her lab focuses on the genetic causes of these diseases.

Nisha Limaye started to work on autoimmune diseases during her PhD in Dallas (USA). There she met her future husband, who she then followed to Belgium. She got a post-doc position at de Duve Institute in 2005, in the group of Miiikka Vikkula. Her talent for research was recognized in 2010 when she was appointed as FNRS qualified researcher. Since 2018 she runs her own lab. She has built a diverse group that is characterized by a passion for science and a strong team spirit. In just three years, they have achieved remarkable results.

One of the diseases the team investigates is lupus nephritis (LN), a severe and frequent complication of the autoimmune disease SLE. In LN, the immune system attacks the kidney tissue, which leads to functional impairment or even complete failure.

Nisha Limaye’s team hypothesized that the kidney cells participate in the pathological process, instead of being just passive victims. “We therefore aimed our studies at the tissue of patients, rather than only the blood.”

Gaëlle Tilman, a researcher in the group who according to Nisha Limaye “does not stop until she gets to the bottom of things”, recently made a promising discovery on the disease. She found that a phenomenon called cellular senescence occurs in the kidneys of LN patients. “When cells go into senescence, they stop proliferating, but still produce molecules that act on the environment around them. Senescence occurs in normal tissue remodeling processes, such as embryogenesis and wound healing. After such processes, the senescent cells are cleared. But here, they persist in the tissue”, explains Gaëlle Tilman.

The team showed that senescence in the LN kidney is related to the severity of the disease, she continues: “Patients with high levels of senescent cells had a bad outcome after five years. We also saw that CD8-positive T cells (a type of lymphocyte with a major role in immune defense) are located near the senescent cells, in regions that show significant fibrosis. This suggests that there may be some interaction between the senescent kidney cells and these immune cells, with a functional role in the development of LN.” It is not yet clear what that role entails,

“We always find thousands of ‘genetic variants,’ the challenge is to identify which ones cause the disease.”



adds Nisha Limaye: “We now want to work out how the senescent cells participate in the disease.”

The discovery could be a lead for a treatment. “There are drugs, used in cancer treatment, that eliminate senescent cells. We want to test whether these would work for LN. Besides that, the results may provide us with a prognostic marker. Biopsies taken to make a diagnosis of LN can be analyzed for markers of senescent cells, to see if they have the power to predict how the disease will develop in the coming years.”

Collaboration is an indispensable aspect of the team’s work. They work together with immunologists within the Institute and have strong links with the rheumatology department at University Hospital Saint-Luc. PhD student Cécile Boulanger works half her time in the lab and the other half as physician in the pediatric hematology and oncology department of the hospital. “For some of the children that I see in the clinic, I try to identify the genetic cause of their disease.”

Sometimes the research has directly led to a better treatment. This was the case for a 9-year-old boy with Aicardi-Goutières syndrome, a rare brain disease. Cécile Boulanger noticed that he had a sign not usually associated with this syndrome: the virtual absence of B cells in his blood. Through analysis of his genetic data, she discovered that

the boy had a second disorder called Bruton’s disease. He is now treated with immunoglobulins, antibodies that are normally produced by B cells, which help him to fight infections. In another case, she identified a genetic variant that modifies a major regulator of the immune system, in DNA from a 10-year-old girl who was chronically and severely ill. The same variant was present in archived DNA from her mother, who had passed away from a similar condition. The girl now receives a treatment that targets this specific molecule.

These rewarding results motivate Cécile Boulanger to combine the two intensive jobs, though it is often difficult to divide her time. “I feel that the research I do also makes me a better doctor.”

The genetic research that the team performs is laborious work. “We always find thousands of ‘genetic variants,’ that is, nucleotides that differ between people. Most of them are harmless, the challenge is to identify which ones cause the disease. In around 30 percent of the persons with immune diseases, we can find a genetic cause. In others, the cause may lie in the other, non-coding part of the genome or in epigenetic factors.” Results are thus not guaranteed, but this cannot temper Nisha Limaye’s enthusiasm. “I love to do research, to be free to follow my curiosity. Sometimes it feels like I’m paid to play.”

WHEN THE CELLULAR COMMUNICATION FAILS

Receptors are the cells' antennas that receive messages from other cells. Jean-Baptiste Demoulin studies one type of them, the PDGF receptor. Errors in the genetic code of the receptor can lead to a variety of diseases. For one of these diseases, his team found a treatment.

PDGF (Platelet-derived growth factor) is an important messenger molecule in our body. It plays a role in embryonic development, but also in later life, for example in wound healing. PDGF instructs its target cell by binding to a molecule on the cell surface, the PDGF receptor. Jean-Baptiste Demoulin got acquainted with the PDGF receptor during his post-doc study at the Ludwig Institute in Sweden and has been studying it since then. "There are so many things about the receptor that we don't know yet."

He especially looks at the roles of the receptor in human diseases. These are many and diverse. The receptor is involved in certain types of leukemia and tumors, and in non-cancerous diseases such as atherosclerosis, fibrosis and neurological disorders. His team studies these in collaboration with clinicians. To obtain data and samples, but also to share knowledge. "We have expertise in biochemistry and molecular biology. Physicians who treat the patients have a better feeling of what is really happening in the disease", Jean-Baptiste Demoulin says.

His team is working together with Dr. Gaël Nicolas of the university of Rouen on a rare neurodegenerative disease called primary familial brain calcification. The disease, characterized by the deposit of calcium salts in the brain, can lead to a range of motor, cognitive and psychiatric symptoms. Some ten years ago, Dr. Nicolas found that a patient had a mutation in the PDGF receptor, which was

characterized by Jean-Baptiste Demoulin. It was the first time that the receptor was linked to brain calcification, but since then, many more patients with a mutated receptor were found.

Recently, the team has performed an in-depth analysis of how these mutations affect the PDGF receptor, again in collaboration with Dr. Nicolas. They also included the mutation of a girl whose mother contacted the team directly to obtain information about her uncertain diagnosis. Using cultured cells and biochemical assays, they found that all pathogenic mutations lead to an inactive receptor, however this happens in different ways. Some mutations hinder the expression on the cell surface, others make the receptor unable to bind to PDGF and a third mechanism induces the loss of enzymatic activity. Some mutations, which were initially thought to be pathogenic, were found to have very little effect on the receptor.

The new knowledge makes a better diagnosis possible. "If a patient has one of these mutations in the PDGF gene, a diagnosis can immediately be made. We also corrected mistakes made in the diagnoses of some patients. But unfortunately it does not give leads for a treatment. If a receptor works too much, we can block it. But if it does not work, it's not easy to restore its function", says Jean-Baptiste Demoulin.

“There are so many things about the PDGF receptor that we don’t know yet.”



It’s the other way around in infantile myofibromatosis (IM), a disease the team has been studying for about seven years now. IM are rare tumors that can grow in various places of the body. They mostly occur in children under 2 years. “The tumors are benign, but if they grow large, they may cause serious injury. If they are in the head, they can damage the brain, and in the abdomen they may harm organs. It can lead to permanent damage and some children die of the disease.”

The team of Jean-Baptiste Demoulin found that in children with the disease, the PDGF receptor is overactive. “Normally, when PDGF binds to the receptor, a brief signal is triggered inside the cell. In infantile myofibromatosis, the receptor signals continuously, also without PDGF.”

Based on this finding, the team had an idea for a treatment. “A drug named imatinib, which is used in some leukemias, is a potent inhibitor of the signaling activity of PDGF receptors. We first tested it on cultured cells of one patient and this worked well. Because it was already approved, it could then be used in the patient. This was a 10-year-old American boy who had myofibromatosis and skin problems that caused contraction of the hands. I remember well that the MD of the boy called me after the treatment had started, and said that the boy could lace his shoes! The drug has greatly improved the quality of his life, even though it limits his growth as a side-effect.” This

was 7 years ago. Since then, some other children have also been treated successfully with the drug.

Having studied the receptor for many years, Jean-Baptiste Demoulin has become the world expert in the field. Clinicians from across the world ask him for advice. A few years ago, he was contacted by a London clinician who had a patient with histiocytosis, a rare disease affecting immune cells. The cause of the disease was unknown, but genetic analyses showed a mutation in the PDGF receptor gene. “We analyzed the mutation and found that it was activating the receptor. Recently, we found a second patient with this mutation, confirming a true relationship between the histiocytosis and the receptor.”

Still as eager to study ‘his’ receptor as he was 20 years ago during his post-doc, Jean-Baptiste Demoulin has many more questions he wants to answer. “Why does the activated receptor lead to myofibromatosis in one patient and to histiocytosis in another? That really puzzles me. We also try to find another inhibitor of the PDGF receptor, with fewer side effects. And we continue to work on brain calcification. If we understand the receptor better, we might at some point find a treatment.”

REINFORCE THE DEFENSE

Cancer immunotherapy has emerged as a new treatment for various cancers. Its development started with discoveries by the team of Thierry Boon, with Pierre Coulie as one of the members. Today, he explores the immunological activity in early stage tumors. Immunotherapy will remain a key treatment of cancer, he expects.

The immune system can specifically detect and eliminate pathogens, without touching normal cells. Stimulating this ability, by vaccines, has long been a common practice to fight bacteria and viruses. That the immune system could also eliminate cancer was proposed, back in the '50s, but never proven. "It was a nice dream", says Pierre Coulie.

The first step from dream to reality was set at de Duve Institute (called ICP at the time). In the mid-'80s, Thierry Boon demonstrated for the first time that the human immune system can indeed detect and specifically eliminate cancer cells. Young MD Pierre Coulie joined the team of Thierry Boon in this exciting time. Having worked at the Institute since 1976, first as a medical student, then as PhD student and researcher in the group of Jacques Van Snick, he was attracted to the unconventional research style of Thierry Boon. "Most researchers were following the same tracks. Thierry Boon's approach was completely out of the classical pathway. He attacked problems that could not be answered at the time."

The novelty of the team's approach was to look into the genetic make-up of the cancer cells. While designing new ways to experiment, they succeeded to identify the molecules on the cancer cells' surfaces (antigens) that immune cells recognize and the genes that code for them. The discoveries they made are now textbook material.

The work of the team led to a large, worldwide interest in cancer immunology. Pierre Coulie: "Once it became clear that immune cells can recognize tumor cells, we knew there would be ways to stimulate the anti-cancer activity." At the Institute, an enormous effort was undertaken to develop therapeutic cancer vaccines. With support of the Ludwig Institute, scientists from the Institute collaborated with University Hospital Saint-Luc and other hospitals in Belgium and abroad, as well as several pharmaceutical companies, to set up clinical trials. But the outcome was disappointing. "Sometimes the results were exciting, but never good enough to be developed further. Some patients responded, but they were too few. As the results accumulated, people lost interest", says Pierre Coulie.

Then there was an unexpected turn, when other labs made a breakthrough with immune-stimulating drugs. These drugs boosted the complete immune system, not only the tumor-specific response as Thierry Boon's team envisioned. "It was transformative. Many more patients responded, sometimes tumors were rejected and metastases prevented. The success came as a surprise. Almost nobody had anticipated that the anti-tumor response could be boosted like that to have a clinical impact. It was also expected to trigger enormous problems with autoimmunity. Which it also did, but over the years clinicians devised ways to circumvent these effects, which are nevertheless still present."

“Once it became clear that immune cells can recognize tumor cells, we knew there would be ways to stimulate the anti-cancer activity.”



The drugs showed some miraculous results. Pierre Coulie: “Patients with melanoma and lung cancer, who had no treatment options left, recovered after treatment. Even some patients with brain metastases are still alive ten years later. This has never happened before.”

Despite the fantastic clinical results, the number of patients responding to the treatment remains low. Since he started his own group, the charismatic scientist investigates why immunotherapy works in some patients and not in others. “Our objective is to understand the status of the immune system in these tumors. Is it active? If not, are tumor cells ignored by the system because they are not recognized? Or has the immune response been active before, but has the tumor become resistant? In the first case, we should look for ways to make tumor cells seen by the immune system. In the second, the question is how we can circumvent the resistance.” Pierre Coulie’s team tries to answer these questions by studying samples from patients with breast and bladder cancer. “We are looking at the very early stages of breast cancer, called in situ carcinoma. At this stage, there are very small tumors that may grow and cause cancer, but can also disappear. In some patients, we observed immunological activity in these early stages. Bladder carcinoma”, he continues, “is superficial and often detected early. Interesting is that certain types are treated with BCG, a vaccine for tuberculosis consisting of living bacteria. In a significant proportion of the patients it helps

to shrink the tumor. This is probably immune-mediated, but nobody knows how it works. Our hypothesis is that inflammation stimulates the immune response.”

Understanding the immune responses in early stages of a tumor can widen the applicability of immunotherapy, believes Pierre Coulie. “The future of cancer treatment is early detection followed by immunotherapy combined with other treatments, there is little doubt about that. Many promising new modalities of immunotherapy are explored. Like the genetic manipulation of immune cells: cells are taken from a patient, endowed with anti-tumor specificity and then re-injected. Or mRNA vaccines, which are now used for COVID, but were actually being developed for cancer. These can be combined with new techniques for early detection, such as sequencing tumor DNA in the blood. Detecting tumor cells before they are too many, makes treatment much more effective.”

Cancer immunology has been a thriving field since he entered it, finds Pierre Coulie, who has become a highly regarded professor in and outside the Institute. Next to being a gifted immunologist, he is a beloved teacher and holds various social positions, such as president of the Foundation against Cancer. But humbleness stays one of his virtues. “I landed in this fantastic field by chance and feel extremely privileged to work in this interesting environment, surrounded by smart and enthusiastic people.”

IN A NUTSHELL

SPAGHETTI-LIKE PROTEIN ESSENTIAL FOR BACTERIUM'S DEFENSE

Bacteria are increasingly resistant to antibiotics, which is a major global health problem. Under the motto "To fight your enemy, you have to know his strengths and weaknesses", the laboratory of Jean-François Collet tries to understand how bacteria defend themselves.

Bacteria have one or two boundary walls (membranes) to protect themselves from invaders such as antibiotics. The walls are made up of proteins with specific structures that determine their function. In the outer protective wall, in particular lipoproteins are found, which are proteins attached to the wall via a lipid (fatty) anchor. These lipoproteins participate in the construction of the wall, in its maintenance and in its defense, thus allowing the bacteria to live and to conquer.

Jessica El Rayes, researcher in Jean-François Collet's team, observed that between the active part of the lipoprotein

and the lipid part, there is a sequence without structure, which resembles cooked spaghetti: all soft and able to adapt its shape as it desires. Though little research has been done on these unstructured sequences, they are present in many bacteria such as *E. coli* or *Borrelia* (Lyme disease).

The researcher found that the bacterium was weakened when the 'soft spaghetti' was transformed into spirelli or when it was shortened into angel's hair. This demonstrates the essential role of the disordered sequence: without it, the lipoproteins no longer reach the surrounding wall and the bacterium is weakened. This finding also shows that there are still many regions within proteins that we know nothing about.

Reference

El Rayes J, Szewczyk J, Deghelt M, Csoma N, Matagne A, Iorga BI, Cho SH, Collet J-F. Disorder is a critical component of lipoprotein sorting in Gram-negative bacteria. *Nat Chem Biol.* 2021;17:1093-100.

A NEW NEUROLOGICAL DISEASE CAUSED BY GLUCOSE-1,6-BISPHOSPHATE DEFICIENCY

It has long been known that the brain contains a lot of a molecule called glucose-1,6-bisphosphate (because it contains glucose and two phosphates), but it was unclear why we have so much of it in the brain (and we think particularly in neurons) and whether it plays an important role or not. About ten years ago, Maria Veiga-da-Cunha and Emile Van Schaftingen identified the gene that codes for the enzyme that makes this molecule. Recently, this has led to the discovery of four patients in whom the enzyme in question does not function and who have therefore a glucose-1,6-bisphosphate deficiency. The researchers have described the clinical and biochemical characterization of this new neurological disease in *The American Journal of Human Genetics*.

The patients were discovered 'by chance'. At present, when faced with patients, especially very young ones, whose disease is not understood, clinicians often ask geneticists to sequence their genome to see if they can find mutated

gene(s) that could explain the disease. Geneticists share their findings concerning mutated genes in databases. By searching these databases, Maria Veiga-da-Cunha and her team were able to get in touch with clinicians who care for the four patients (two in the USA, one in Austria and one in Denmark). This allowed them to obtain cells from the patients to study them in their laboratory.

These young patients have serious neurological problems, including motor and language development. Following the discovery of this new disease, they now know that it is important to have glucose-1,6-bisphosphate in the brain. They continue their work to try to understand why, with the serious hope of making a scientific breakthrough that will be useful for patients.

Reference

Morava E, Schatz UA, Topping PM, Abbott MA, Baumann M, Brasch-Andersen C, Chevalier N, Dunkhase-Heinl U, Flegler M, Haack TB, Nelson S, Potelle S, Radenkovic S, Bommer GT, Van Schaftingen E, Veiga-da-Cunha M. Impaired glucose-1,6-bisphosphate production due to bi-allelic PGM2L1 mutations is associated with a neurodevelopmental disorder. *Am J Hum Genet.* 2021;108:1151-60.

NEW INSIGHTS IN HOW CANCER CELLS CAN KEEP ON DIVIDING

Telomeres are specialized structures found at the ends of our chromosomes. These 'protective caps' are important in the aging process. Every time a cell divides, the telomeres get shorter. When the telomere length becomes too short, the cell can no longer replicate and goes into senescence.

Cancer cells circumvent entry into senescence and attain immortality by maintaining their telomere length. They can do so in two ways. Most cancer cells reactivate the enzyme telomerase that restores telomere length. An estimated 10% of cancers (and up to 20% of pediatric cancers) hijacks cellular DNA replication and repair factors in a mechanism called alternative lengthening of telomeres (ALT).

The group of Anabelle Decottignies has previously found indications that these two mechanisms mutually exclude each other and cannot coexist in one cell. In recent

research they further explored the interplay between the telomerase and ALT pathways. In their studies they used hybrid cells, made by hybridization of a telomerase-expressing cell and an ALT-positive cell, as well as various cultured cancer cells.

They found more evidence that the two mechanisms indeed cannot coexist and obtained new insight in the complex interference between them. They also unravelled that, in ALT cancer cells, the RNA molecule hTR and the protein NHP2 have a crucial role in regulating the DNA damage response that leads to senescence. The results suggest that hyper-activation of the DNA damage response, through the modulation of hTR signaling, may be a valid option for future therapies targeting cancer cells with the ALT mechanism.

Reference

Raghunandan M, Geelen D, Majerova E, Decottignies A. NHP2 downregulation counteracts hTR-mediated activation of the DNA damage response at ALT telomeres. *EMBO J.* 2021;40:e106336

MECHANISM UNCOVERED FOR THE SYSTEMIC CONTROL OF AN IMMUNE- AND MOOD-REGULATING AMINO ACID

Tryptophan is an important amino acid in our body. It is the precursor of neuro-active compounds that regulate our mood and also a potent regulator of immune responses. We get tryptophan from our food and the intake thus varies largely. However, the levels in the blood are remarkably constant. The group of Benoit Van den Eynde recently uncovered the mechanisms that ensure this homeostasis.

Tryptophan is degraded in the liver by an enzyme called tryptophan 2,3-dioxygenase (TDO). The group discovered how tryptophan itself regulates the stability of the enzyme complex. The enzyme contains two types of tryptophan-binding sites: catalytic sites, which are responsible for tryptophan degradation, and noncatalytic sites, which regulate the enzyme's stability. Simon Klaessens, researcher in the group, showed that binding of tryptophan to the noncatalytic sites stabilizes the enzyme

complex by reducing its destruction by the proteasome. So, when tryptophan is abundant, it induces its own degradation. When tryptophan is scarce, it detaches from the noncatalytic sites. This leads to dissociation of the enzyme complex and the unmasking of a site, called degron, that triggers its degradation by the ubiquitin-proteasome system. The degradation of tryptophan is thus interrupted and the blood level maintained. The group also identified the location of the degron as well as the protein complex that mediates the destruction of the enzyme.

The results provide a framework to manipulate the tryptophan blood levels, using TDO inhibitors to increase it and TDO stabilizers to reduce it. This could be of medical interest for the management of mood disorders, autoimmune disorders, and cancer.

Reference

Klaessens S, Stroobant V, Hoffmann D, Gyrd-Hansen M, Pilotte L, Vigneron N, De Plaen E, Van den Eynde BJ. Tryptophanemia is controlled by a tryptophan-sensing mechanism ubiquitinating tryptophan 2,3-dioxygenase. *Proc Natl Acad Sci USA.* 2021;118:e2022447118.

IN A NUTSHELL

INCREASED KRAS EXPRESSION INITIATES PANCREATIC CANCER

Pancreatic cancer is one of the most aggressive and deadly cancers, with only an 8% survival rate after 5 years. A gene called KRAS, a so-called oncogene, appears to play an important role in this cancer. Although KRAS is mutated in about 30% of cancers, this mutation is particularly common in pancreatic cancer, with almost 95% of patients affected.

Patrick Jacquemin and his team developed a tool to visualize the expression of KRAS protein in pancreatic tissue. They developed two new mouse models in which the protein (the normal version or the mutated version) has been fused to a fluorescent protein. This made it possible to visualize, for the very first time, the expression pattern of KRAS in the pancreas and the cancer that derives from it.

Using these models, Mohamad Assi, post-doc in the team, found that KRAS expression, contrary to common

belief, is not present in all cells of the pancreas, but only in a small number of these cells. When the pancreas is inflamed, a condition that is a precursor event of pancreatic cancer, the majority of these pancreatic cells start to express KRAS. He also discovered that the same is true for a whole series of proteins essential for KRAS activity, called effectors. In collaboration with Prof. Mariano Barbacid's team in Madrid, it was shown that one of these effectors, called C-RAF, plays a determining role in this tumorigenic process. The results suggest the interest of targeting the expression of oncogenes as a therapeutic option.

Reference

Assi M, Achouri Y, Lorient A, Dauguet N, Dahou H, Baldan J, Libert M, Fain JS, Guerra C, Bouwens L, Barbacid M, Lemaigre FP, Jacquemin P. Dynamic regulation of the expression of KRAS and its effectors determines the ability of pancreatic acinar cells to initiate tumorigenesis. *Cancer Res.* 2021;81:2679-89.

NEW MODEL GIVES INSIGHT IN PROGRESSION OF CHOLANGIOCARCINOMA

Cholangiocarcinoma (CCA) is a cancer that begins in cholangiocytes, the cells that line the bile ducts and gallbladder. The prognosis of CCA is dismal. Surgery is the only curative treatment, but is often not possible due to a late diagnosis. Numerous studies investigated the molecular mechanisms operating in full-blown CCA, but little is known about mechanisms that initiate CCA and promote progression toward malignancy. The group of Frédéric Lemaigre aims to fill this knowledge gap.

To study the initiation of CCA, the group developed a mouse model that mimics the development of iCCA (intrahepatic CCA). In this model they introduced a mutation in the oncogene KRAS, a gene that is often mutated in this type of cancer. They succeeded to express the gene only in cholangiocytes, and not in other liver cells, which makes it possible to specifically study iCCA. They then induced inflammation of the liver through a diet to mimic chronic

cholangitis, a risk factor for the development of iCCA. The model developed iCCA-tumors in a way that recapitulates the tumorigenesis in humans very well.

With this model and in vitro studies, the researchers investigated which signaling pathways drive the development of iCCA. They identified a gene-regulatory pathway, involving a protein called Tensin-4, that is activated during tumorigenesis and which promotes cell proliferation and migration. While it is too early to translate this research into improved diagnosis or treatment, the results contribute to our fundamental understanding of the disease mechanisms. The researchers will continue their research by investigating how the cancer cells interact with their local environment to proliferate and migrate.

Reference

Di-Luoffo M, Pirenne S, Saandi T, Lorient A, Gérard C, Dauguet N, Manzano-Núñez F, Alves Souza Carvalhais N, Lamoline F, Konobrocka K, De Greef V, Komuta M, Halder G, Jacquemin P, Lemaigre FP. A novel mouse model of cholangiocarcinoma uncovers a role for Tensin-4 in tumor progression. *Hepatology.* 2021;74:1445-60.

RESEARCH GROUPS





© CUSL / Hugues Depasse

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.



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 or interleukins. 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 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 mutant-specific inhibitors. 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. 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). Since this region is not required for physiologic function of TpoR, it

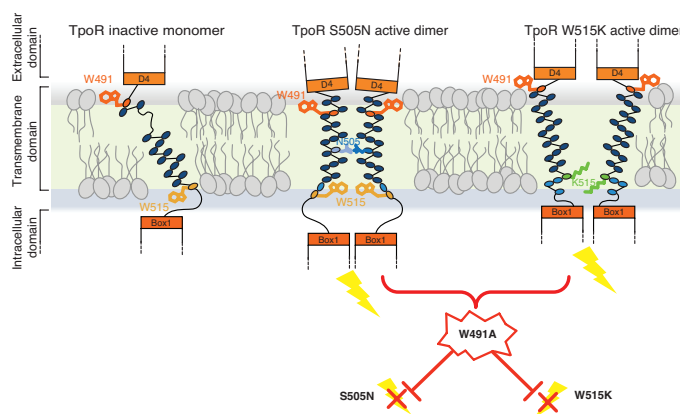
can become a target for therapy given its accessibility to protein therapeutics.

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 read-outs for structural determinants, biophysical approaches, as well as in vivo transgenesis, microscopy and fractionation, mouse bone marrow transplantation, as well as investigation of primary patient cells.



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).

Staff members

Clinical Investigator: Jean-Philippe Defour • **Senior Investigators:** Didier Colau, Christian Pecquet • **Guest Investigator:** Pierre De Meyts • **Postdoctoral Fellow:** Audrey Nedelec • **PhD Students:** Alina Alexandru, Sarah Bailly, Harsh Goyal, Gabriel Levy, Nicolas Papadopoulos, Elise Sepulchre, Gaëlle Vertenoil • **Research Assistants:** Lidvine Genet, Céline Mouton, Yacine Rahmani, Madeleine Swinarska • **Technical Assistant:** Ouadih Nechar



Nick van Gastel

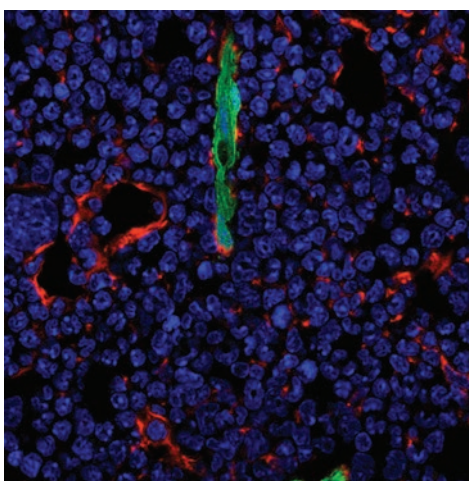
CELLULAR METABOLISM & MICROENVIRONMENT

We aim to understand how metabolic interactions between cells in the bone marrow control blood cell production, how these pathways become dysregulated in leukemia, and how we can leverage this information for therapeutic purposes.

Converting nutrients from the environment into energy and biomass is a fundamental challenge of life. Unicellular organisms, like bacteria or yeasts, face this challenge in each cell individually. However, they can release certain metabolites as communication signals to indicate changes in nutrient availability, the presence of environmental stress or to coordinate growth. An important advantage of multi-cellularity is the ability of cells to metabolically diversify and work together, with metabolites produced in one cell type used as nutrients by another. In complex organisms such as mammals, metabolites are still used for cellular communication, but the extent and importance of these interactions is not well understood.

One example of a tissue in which many different cell types work together is the bone marrow, where daily 200 billion red blood cells, 10 billion white blood cells, and 400 billion platelets are made. The correct functioning of this process relies not only on blood stem cells, but also on their interactions with other cell types in the bone marrow microenvironment such as bone cells, blood vessel cells, immune cells and connective tissue cells, collectively referred to as the bone marrow niche. The bone marrow niche is also involved in the development and progression of blood malignancies such as leukemia, in which blood stem cells start to grow uncontrollably and no longer form normal blood cells.

Our laboratory explores how metabolic communication between different cells in the bone marrow regulates blood stem cell function, blood cell production and leukemia growth. We use state-of-the-art metabolic analysis techniques in combination with cell and animal models to investigate how metabolites produced by one cell type influence the behavior of the other cells in its environ-



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.

ment. The goal of our research is to identify niche-derived metabolic signals important for the maintenance of blood stem cells and the production of red blood cells, white blood cells and platelets. This information can then be used to improve bone marrow transplantation or help in the treatment of blood diseases. By comparing normal and leukemic blood cell production, we further 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.

Staff members

PhD Students: Céline Nielsen, Hernan Tirado Cardenas
Undergraduate Student: Lofti Laaouimir • **Research Assistant:** Fleur Leguay



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.

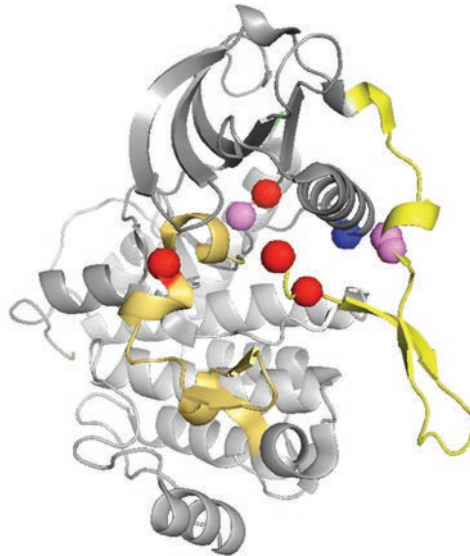
CANCER SIGNALING

We have a long-standing interest in platelet-derived growth factors (PDGF), which act via two receptor-tyrosine kinases, namely PDGFRA and PDGFRB. These proteins play important roles in the development of the embryo, as well as in cancer and 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 pre-clinical 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 different human diseases. Our promising results suggest that

some patients may benefit from PDGF receptor inhibitors. We now aim to understand these diseases in more detail and validate treatments.

Staff members

Clinical Investigator: Violaine Havelange • **Postdoctoral Fellows:** Chrysanthi Alexandri, Pierre Autin • **PhD Students:** Boutaina Boulouadnine, Joanne Péters, Ariane Sablon • **Undergraduate Student:** Laurence de Villenfagne de Vogelsanck • **Research Assistant:** Sandrine Lenglez • **Administrative Support:** Geneviève Schoonheydt



Pierre Coulie

HUMAN TUMOR IMMUNOLOGY

Cancer immunotherapy is a breakthrough but only for a minority of cancer patients. We explore early stage tumors for signs of anti-tumor T cell immune responses, such as antigenicity and inflammation.

Our immune system protects us by detecting and destroying foreign bodies like bacteria and viruses. Key effectors in this process are T cells, a type of white blood cells. T cells can also recognize tumor cells, as demonstrated by T. Boon and colleagues at de Duve Institute when they discovered the specific markers recognized on tumor 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.

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-1 β . 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-1 β by monocytes, another type of white blood cells and an important source of IL-1 β . Monocytes can secrete IL-1 β while they die, thus releasing their intracellular content.

However we have observed that under certain conditions monocytes secrete IL-1 β but do not die. We try to understand the mechanism of this secretion. Using CRISPR-Cas9 libraries we identified genes involved in this secretion. Specifically blocking or increasing IL-1 β secretion could have important medical applications in chronic inflammatory diseases or cancer.

“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.”

Staff members

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



The immune system defends us against cancer and infections, but requires tight control to avoid allergy or auto-immunity. We study how Tregs and TGF- β control immune responses, hoping to design immunotherapeutic approaches for cancer or auto-immunity.

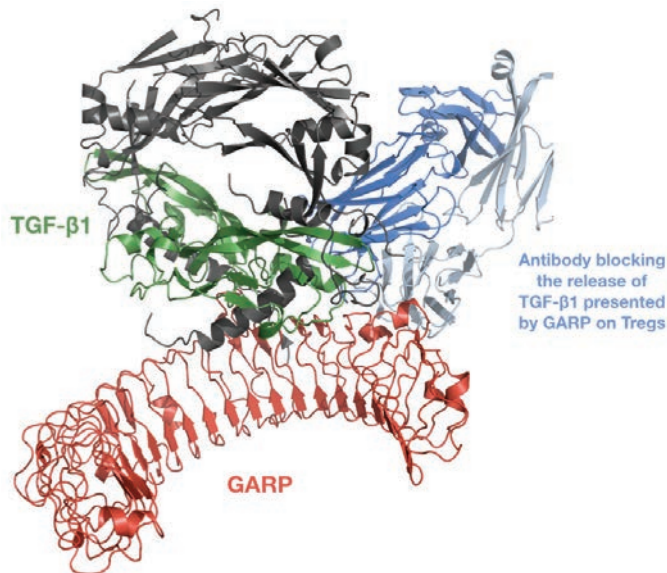
REGULATORY T CELLS & TGF- β

Immune cells protect us against infections and cancer because they can kill 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 contributes to cancer progression and chronic infections.

We try to identify the mechanisms by which Tregs suppress immune responses. We found that Tregs produce a protein called TGF- β 1, which acts as an inhibitory messenger on immune cells. We also found that production of the immunosuppressive TGF- β 1 requires another Treg protein called GARP. We developed tools (e.g. monoclonal antibodies) that bind GARP and block TGF- β 1 production by Tregs. We used x-ray crystallography to solve the 3D structure of a protein assembly comprising GARP, TGF- β 1 and a blocking antibody (Figure). This allowed us to understand how GARP presents TGF- β 1 for activation on Tregs, and how our antibody actually blocks this process. We explored in mouse models whether anti-GARP antibodies could be used as drugs to block Treg immunosuppression in patients suffering from cancer. We observed in several mouse models

of cancer 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 also reported that anti-GARP antibodies act in the mouse tumor microenvironment by modifying the function and abundance not only of immune cells such as T cells and Tregs, but also that of other non-immune and non-cancerous cells such as endothelial cells. 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



3D structure of TGF- β 1 presented by GARP on Tregs, blocked by an anti-GARP antibody which could serve for the immunotherapy of cancer.

University Hospital Saint-Luc. 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: Grégoire de Streel, Emilie Dupré, Camille Michiels, David Schröder • **PhD Students:** Julien Devreux, Mathieu Jamez, Ananyashree Kathotia, Fanny Lambert, Pierre Van Meerbeeck, Séverine Wautier • **Undergraduate Student:** Noémie Dupuis • **Research Assistants:** Fatima Benhaddi, Nicolas Chalou, Noora Vaherto-Bleecx • **Administrative Support:** Emmanuelle Hemelrike



Benoit Van den Eynde

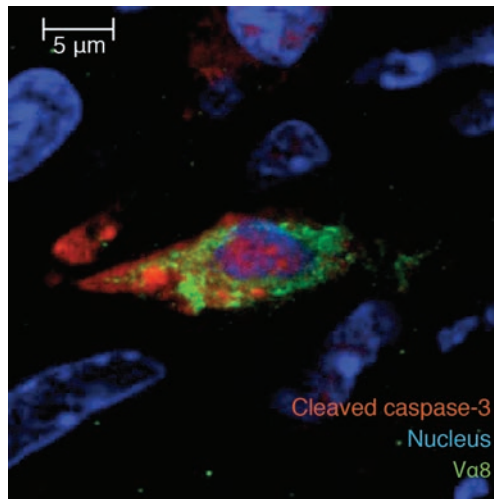
IMPROVING CANCER IMMUNOTHERAPY

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.

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.



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

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 (TGF β). 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, Jingjing Zhu • **Postdoctoral Fellows:** Joanna Abi Habib, Veronica Finisguerra, Wenbin Ma • **PhD Students:** Raphaële Bombart, Florence Boon, Pierre-Hubert Desimpel, Tereza Dvorakova, Simon Klaessens, Dorian Lapaille, Julie Lesenfants, Pierre-Florent Petit, Marie Solvay • **Undergraduate Student:** Amale Refla • **Research Assistants:** Giuseppe Attardo, Loubna Boudhan, Andja Carciu, Martin Doyen, Matteo Formenti, Minh Phuong Le, Luc Pilotte, Bénédicte Tollet • **Administrative Support:** Isabelle Grisse



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.

T LYMPHOCYTE DYSFUNCTION

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.

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 either ovarian or lung cancer. Ovarian cancer

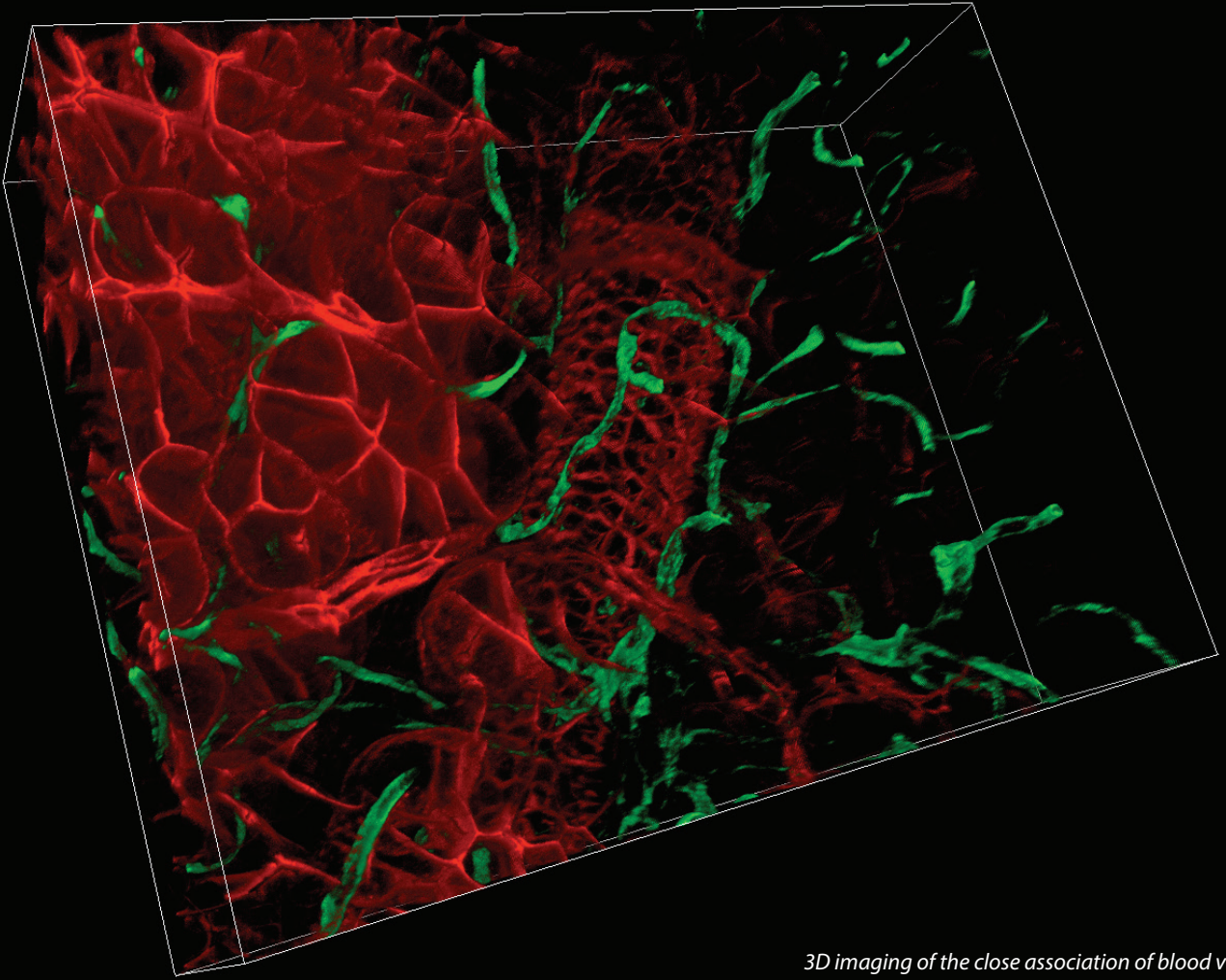
is often diagnosed at an advanced stage and patients receive chemotherapy before surgery. However, today it is still impossible to predict if and how a patient will respond to chemotherapy. To explain the heterogeneous responses to chemotherapy, we collect samples before and after treatment, and we study the immune cells, the tumor micro-

environment and the genetics of the tumors. For lung cancer, chemotherapy and immune checkpoint inhibitors are the standard of care. To achieve the best outcomes for patients and to minimize side effects, it is important to predict how patients will respond to treatment. We examine if high level of MDSCs in the blood before treatment correlates to poor clinical response rates. We dream of identifying factors that could predict therapeutic outcomes or that could be targeted to improve the clinical management of future patients.

“There is a need to understand how myeloid-derived suppressor cells, which are present in most cancer patients, participate in immune suppression.”

Staff members

Clinical Investigator: Frank Aboubakar Nana • **Postdoctoral Fellow:** Annika Bruger • **PhD Students:** Thibault Hirsch, Svetlana Ivanoff, Mathieu Luyckx, Damien Neyens, Christophe Vanhaver, Shiqiang Xu • **Undergraduate Student:** Jeremy Van Laethem • **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.



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 sinusoids, stretching of muscle cells during contraction or pressure exerted by tumors on surrounding cells. We aim at elucidating how plasma membrane lipid composition and biophysical properties contribute to cell deformation, as a prerequisite towards understanding diseases.

We mainly use RBCs, as the simplest and best-characterized human cell model with remarkable deformability. Using high-resolution confocal imaging and atomic force microscopy (coll. D. Alsteens, UCLouvain), we discovered the existence of stable submicrometric lipid domains at the living RBC plasma membrane. Three types of domains coexist, showing differential composition, membrane curvature association, lipid order and role in RBC deformation. Cholesterol-enriched domains contribute to RBC deformation through their gathering in highly curved membrane areas. The two other domains, coenriched in cholesterol and sphingolipids, 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.

At the end of their lifetime, RBCs become less deformable and lose part of their membrane by extracellular vesicle (EV) release. EV release is also relevant to blood tubes stored at 4°C and accompanied by the loss of cholesterol-enriched domains, suggesting they could represent

sites susceptible to vesiculation. Despite a lower extent of vesiculation, this relationship is also relevant to RBC concentrates at the end of the conservation period (coll. Croix-Rouge de Belgique), opening the possibility of targeting cholesterol to limit EV release in RBC concentrates before transfusion.

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

Membrane lipid domains and biophysical properties are deregulated in RBC-related diseases, including spherocytosis, elliptocytosis (coll. B. Brichard & C. Lambert, University Hospital Saint-Luc) and hypobetalipoproteinemia. Extension to erythroleukemia, a rare type of acute myeloid leukemia with poor prognosis is ongoing (coll. V. Havelange).

We recently started to explore the contribution of plasma membrane lipids for myoblast migration and fusion into myotubes and for breast cancer cell invasion. Both myoblasts and mammary cells exhibit different types of lipid domains with distinct roles in cell migration. Moreover, the comparison of malignant with pre- and non-malignant cells reveals that cholesterol-enriched domains and plasma membrane biophysical properties are deregulated in breast cancer (coll. D. Alsteens) and that the decrease of cholesterol content specifically inhibits invasion of the malignant cells. Our data open the possibility to target cholesterol by a pharmaceutical approach in breast cancer.

Staff members

Senior Investigator: Patrick Van Der Smissen (Platform Manager) • **PhD Students:** Anne-Sophie Cloos, Marine Ghodsi, Mauriane Maja, Amaury Stommen, Juliette Vanderroost • **Undergraduate Student:** Jawad Tarfouss • **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.

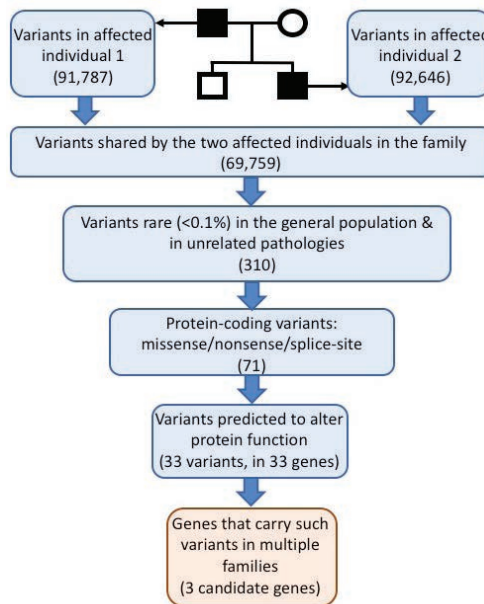
Our immune system, responsible for defending us against harmful pathogens such as certain bacteria and viruses, can sometimes turn on us. It may mistake components of our own cells for foreign invaders, or react too zealously against perceived threats, causing significant collateral damage to our own 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 dysfunction, in rheumatic (auto-immune, 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. 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.

Another important focus of our research is the organs that are damaged by systemic immune dysfunction. More specifically, we study the interaction between immune and non-immune cells in the kidney in lupus nephritis, a frequent and severe complication of systemic lupus erythematosus. Our goal is to understand why some patients go on to have chronic or even end-stage renal disease despite therapy, while others respond well. Ultimately, by understanding the genetic and molecular bases of these rare diseases, we seek to better predict, prevent, and treat them.



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.

Staff members

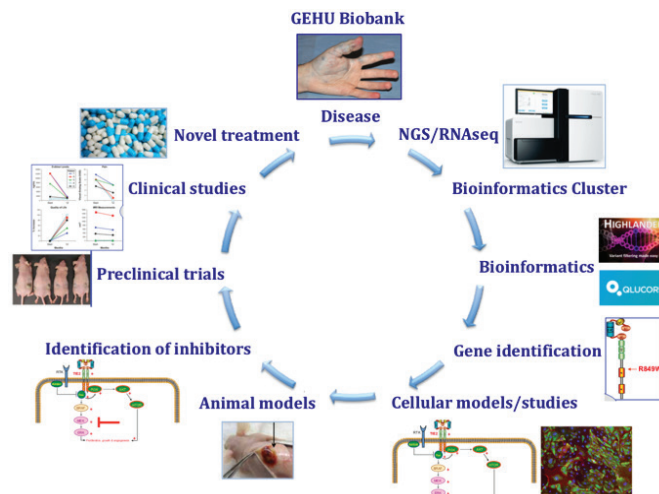
Postdoctoral Fellow: Gaëlle Tilman • PhD Students: Charlotte Baert, Cécile Boulanger, Elsa Khoury, Hiba Maalouf, Pierre Maus • Undergraduate Student: Laura Watteyne • Research Assistant: Delphine Nolf



We aim to understand the mechanisms underlying cardiovascular and skeletal disorders, and some cancers. We evaluate the contribution of genetic variation to human disease by using bioinformatics and artificial intelligence. We also generate models to test novel molecular therapies.

HUMAN GENETICS

The bases of many disorders remain unknown, and treatments are often aimed at alleviating symptoms. We try to identify the causes of vascular tumors and malformations, lymphedema, and cleft lip and palate. 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 bioinformatic tool Highlander or QluCore/R, respectively (Figure). We manage the UCLouvain Genomics Platform and an important computational cluster.



Workflow from bedside to bench back to patients

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 due to somatic mutations. Due to these mutations, the PI3K/AKT or the RAS/MAPK signaling pathway is abnormally activated, which we could show in cellular models (Figure). Using mouse models, 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, coordinated

by Prof. L. Boon at University Hospital Saint-Luc (Figure). More recently, we have generated a model for arteriovenous malformation, and it is being tested for efficiency of medical treatments. Similarly, we provided insight to the pathogenesis of Gorham-Stout disease, a complex lymphatic anomaly, and discovered a novel treatment option for these patients.

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%.

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 • **PhD Students:** Murat Alpaslan, Mirta Basha, Simon Boutry, Julien Coulie, Martina De Bortoli, Nassim Homayun Sepehr, Eleonore Pairet, Peyman Ranji, Stanislas Smadja • **Undergraduate Students:** Guillaume Navette, Giordamée N'kakou, Lucas Potier • **Research Assistants:** Bill Brancart, Fabrice Cahay, Audrey Debue, Anaïs Dupuis, Séverine Gonze, Mickaël Nguyen • **Technical Assistants:** Bruno Maricq, Danny Plessiet • **Administrative Support:** Patricia Dresse, Liliana Niculescu



Charles De Smet

EPIGENETICS IN CANCER

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

Maintenance of gene expression programs is essential to ensure proper functioning of the various cell types that make up the body. To this end, cells have evolved “epigenetic” regulatory mechanisms, based on the addition of chemical modifications on defined genes. Among such modifications, DNA methylation has an essential role in the long-term inactivation of tissue-specific genes. Importantly, the distribution of DNA methylation marks is profoundly altered in most tumors, and there is evidence that this contributes to cancer progression. The causes and consequences of this epigenetic disruption in tumor cells remain however unclear.

“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). Bioinformatics analyses are being conducted to better define the group of CG genes, and to explore possible mechanisms underlying their epigenetic de-repression in tumor cells (in collaboration with the team of Laurent Gatto).

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 somatic tissues: one in the lower digestive tract, and the other in stratified epithelia. In lung tumors, activation of several of these genes was associated with poor patient outcome.

Staff members

PhD Students: Anna Diacofotaki, Jean Fain • Undergraduate Students: Claudia Denoue, Camille Wangermez



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.

Although we 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, most cancer cells avoid telomere shortening. In 80% 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 hTR subunit of telomerase in the regulation of DNA damage response at telomeres. Last year, we developed new assays for ALT diagnosis on tumor sections and established the first ALT⁺ mouse xenograft model.

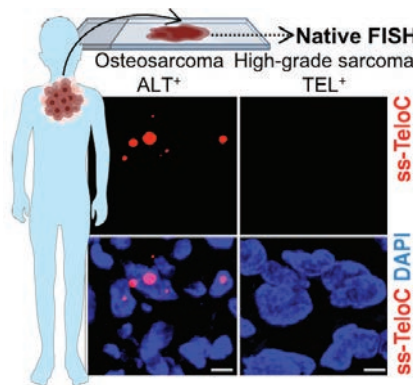
Another part of our research focuses on Telomeric Repeat-containing RNA species, dubbed TERRA, which

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 in 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 and evaluated telomeres and senescence in lungs from IPF patients. Telomeropathy diagnosis is achieved through telomere length measurement in blood cells using a

technique called Flow-FISH, which was not available in Belgium. Recently, 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. Over the last year, we also investigated the link between mitochondrial genome sequence and telomere length.



The native FISH assay to detect the ALT mechanism in solid paediatric and adult tumors: a red FISH probe containing the G-rich telomeric sequence is used to detect single-stranded C-rich telomeric DNA, a hallmark of ALT⁺ cells.

Staff members

Postdoctoral Fellow: Gabriel Le Berre • **PhD Students:** Kamar Bouchoucha, Eloïse Claude, Céline Coquette, Dan Geelen • **Undergraduate Student:** Maxence Casier • **Research Assistant:** Manon Mahieu



Frédéric Lemaigre &
Patrick Jacquemin

CELL DIFFERENTIATION

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

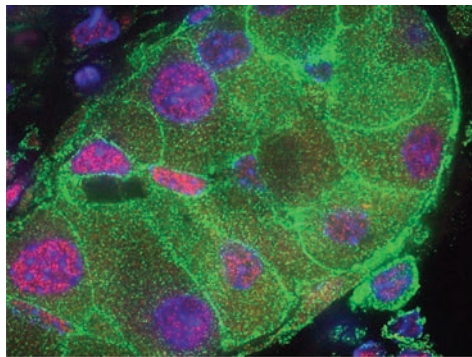
To develop into a complex organism cells in the embryo need to proliferate, differentiate and organize in three-dimensional tissues. While focusing on liver and pancreas, our group aims at identifying the mechanisms that promote cell differentiation and tissue morphogenesis in the embryo, and those that perturb differentiation in adults and induce liver or pancreatic cancer. We share our findings on normal differentiation with collaborators who transpose the information in cell culture protocols to produce hepatic or pancreatic cells for cell therapy. Our observations on disease mechanisms aim at promoting early cancer diagnosis and identifying targets for therapy.

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.

Cholangiocytes also form the epithelial lining of the gallbladder. 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 TGF β signaling. Parallel to our research on liver development, we investigate how cells transit from normal to precancerous and eventually invasive cancer states in gallbladder cancer and intrahepatic cholangiocarcinoma. For the latter, we developed an original mouse model that faithfully reproduces the sequential steps of tumorigenesis in humans, and identified a gene network promoting tumor progression.

In pancreas, the most abundant cells are the exocrine cells. These comprise acinar cells that produce digestive enzymes, and ductal cells that delineate pancreatic ducts through which acinar enzymes flow to the gut. Implementing our expertise in cell differentiation, we identified ductal cells as a cell type of origin of pancreatic

ductal adenocarcinoma (PDAC), as well as signaling cascades promoting formation of precancerous lesions and their evolution to cancer. We found how primary cilia, EGF signaling and peroxiredoxin control inflammation, a main driver of tumorigenesis. Importantly, we also uncovered a novel post-translational mechanism regulating the activity of KRAS – the most frequently mutated oncogene in PDAC.



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.

Staff members

Senior Investigator: Younes Achouri (Platform Manager) • **Postdoctoral Fellows:** Mohamad Assi, Malak Haidar, Fátima Manzano Núñez, Alejandra Vargas Valderama, Ilianna Zoi • **PhD Students:** Catalina De Schrevel, Angeline Fages, Lila Gannoun, Maxime Libert, Marie-Albane Minati, Sophie Pirenne, Memoona Rajput Bhatti, Margaux Wulleman • **Research Assistants:** Sabine Cordi, Hajar Dahou, Marine Fellmann • **Technical Assistants:** Freddy Abrassart, Roméo Delemazure, Bruno Maricq • **Administrative Support:** Marjorie Decroly, Julie Klein



The goal of our research is to understand how Wnt signaling pathways regulate skin stem cell maintenance and skin 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.

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.

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

Staff members

Postdoctoral Fellow: Chim Kei Chan • **PhD Students:** Gaia Cangiotti, Juliette de Lhoneux • **Research Assistant:** Ivan Carrillo Ordonez • **Administrative Support:** Aimée-Lys Rusesabagina



Christophe Pierreux

EPITHELIAL DIFFERENTIATION

Our group studies paracrine communications between epithelial cells and their endothelial environment that govern epithelial differentiation during thyroid and pancreas organogenesis, and in diseases.

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 form particular tridimensional structures, like closed spheres in the thyroid. They also gradually specialize by acquiring specific function(s), e.g. production of digestive enzymes in the pancreas. These happen during embryonic development through timely and tightly controlled epithelial differentiation programs. Loss or impairment of the tridimensional organization and specialization of these cells are frequently observed in pathological conditions.

Our group aims at understanding how thyroid and pancreatic epithelial cells 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, the thyroid follicles, 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. Recently, we have deciphered the precise 3D topological relationships between embryonic pancreatic epithelial cells and cells in their microenvironment, a prerequisite for organ 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 shaping the thyroid follicles. We are now investigating the messages contained in extracellular vesicles released by thyroid cells during cancer development.

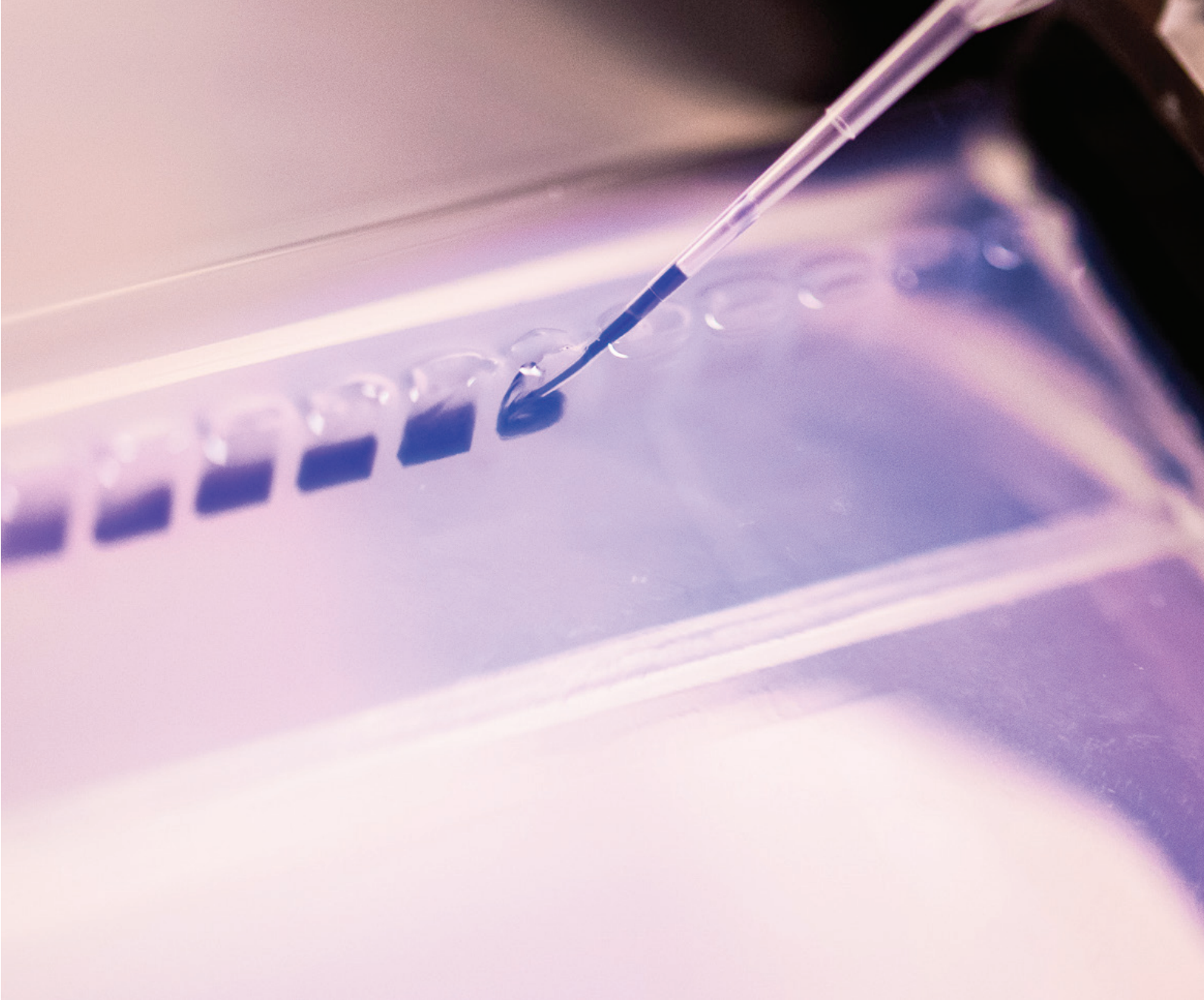
“In-depth characterization of tissular, cellular and molecular mechanisms during embryonic development and disease paves the way towards organ bioprinting and therapeutic testing.”

We are also investigating epithelial homeostasis in adult organs. On the one hand, we study blood vessels remodeling during pancreatitis, a condition mainly affecting our western countries, and investigate 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, cystinosis. 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 in mouse and rat models of the disease.

Staff members

Emeritus: Pierre J. Courtoy • **Postdoctoral Fellows:** Virginie Janssens, Manon Moulis • **PhD Students:** Elias Aajja Maazoubi, Ophélie Delcorte, Laura Glorieux, Hélène Lefort, Catherine Spourquet • **Undergraduate Students:** Fairouz Chahinez Djaaba, Laura Vandooren • **Research Assistant:** Pascale Lemoine • **Technical Assistants:** Freddy Abrassart, Roméo Delemazure • **Administrative Support:** Aimée-Lys Rusesabagina



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

INFECTIONS AND INFLAMMATION



Jean-François Collet

BACTERIAL STRESS RESPONSES

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

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

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. 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.

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

Staff members

Senior Investigators: Seung Hyun Cho, Pauline Leverrier • **Guest Investigators:** Bogdan Iorga, Kojiro Ishiguro, Hiroyuki Kanamaru, Raika Yamagiwa • **Postdoctoral Fellows:** Michaël Deghelt, Jessica El Rayes, Alexandra Gennaris, Alexandre Marbaix, Chi Nguyen, Laurie Thouvenel • **PhD Students:** Naemi Csoma, Kilian Dekoninck, Emile Dupuy, Reeda Harb, Elisa Pierre, Alexandre Thurman • **Undergraduate Student:** Alix Dachsbeck • **Research Assistants:** Carla Aspite, Asma Boujdat



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.

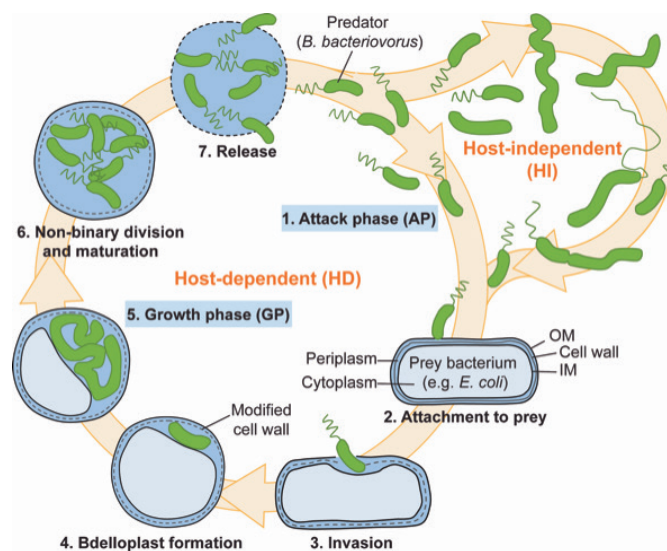
Acquiring fundamental knowledge on the cell biology of bacteria is a prerequisite for many clinical applications, including the fight against pathogenic strains, the development of solutions to the problem of antibiotic resistance, and the appropriate use of bacteria with beneficial roles in the human 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.

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.

Recently, 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). This year, we also started to investigate the impact of the prey morphology and physiology on the predation cycle. 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

Postdoctoral Fellows: Sander Govers, Yoann Santin, Renske van Raaphorst • **PhD Students:** Jovana Kaljević, Thomas Lamot, Ophélie Remy • **Research Assistant:** Charles de Pierpont



Jean-Paul Coutelier

INFECTIONS & IMMUNITY

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

The possibility for evolved 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. A dysbalance between proinflammatory and regulatory immune responses may be related to such distinct clinical forms of infectious diseases.

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 mimic 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 an enhanced risk to develop cancer after *Schistosoma* infection.

“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).”

Staff members

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



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 notably 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, which promote antiviral resistance in neighboring cells and alert the immune cells in a systemic fashion. Our research focuses on topics related to the interplay between viral infections and the immune response of the host and in particular the IFN response.

Theiler's virus is a mouse picornavirus that has a striking ability to persist in the central nervous system despite a strong and specific immune response. We study how the leader (L) protein encoded by this virus and by related cardioviruses interfere with innate immunity. Our recent data show that L can hijack cellular kinases of the RSK family to interfere with the activation of PKR, a key effector of the IFN response. Our data suggest the 'model of the clamp' whereby L recruits and activates cellular kinases of the RSK family and promotes the phosphorylation of specific targets by activated RSKs. Phosphorylated targets would then act as second messengers to trigger the effects of the L protein (Figure).

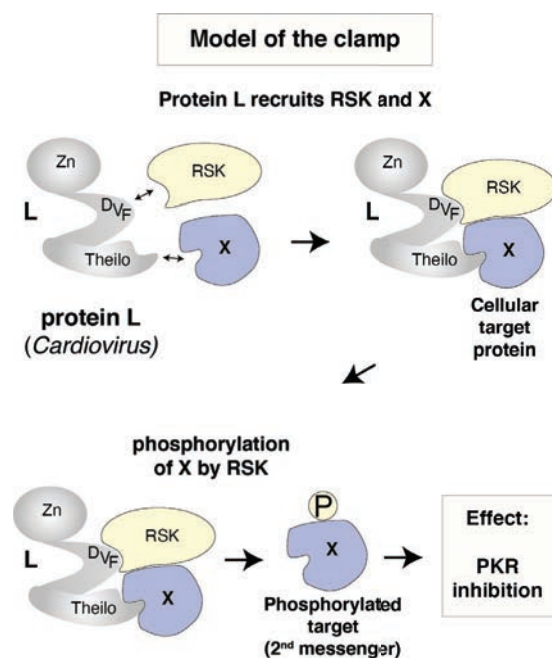
Ongoing research:

- We currently test the model of the clamp and analyze the involvement of individual kinases of the RSK family in the virulence of micro-organisms as well as in cell physiology.

- We analyze the mechanisms by which RSK recruitment by cardiovirus L proteins triggers PKR inhibition as well as perturbation of nucleo-cytoplasmic trafficking in the infected cell. We further analyze the involvement of phosphorylation in the fine-tuning of PKR activity since a deficient PKR activity can lead to increased sensitivity to viral infections whereas a too high PKR activity was associated with crippling autoimmune diseases such as Aicardi-Goutières syndrome or systemic lupus erythematosus.

- In view of the COVID-19 emergency, we also embarked in basic researches related to the SARS-CoV-2 coronavirus, the COVID-19 agent. We 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.



'Model of the clamp': the L protein binds RSK and recruits targets, which, once phosphorylated by RSK, act as second messengers to trigger the effects of L.

Staff members

Postdoctoral Fellows: Nicolas Capelli, Frédéric Sorgeloos
PhD Students: Camille Duflos, Belén Lizcano-Perret
Undergraduate Student: Romane Milcamp
Research Assistants: Stéphane Messe, Fanny Wavreil
Technical Assistant: Danny Plessiet



Jean-Christophe Renauld &
Laure Dumoutier

INFLAMMATORY DISORDERS & CYTOKINES

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

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

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

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.

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

Staff members

Emeritus: Jacques Van Snick • **PhD Students:** Ornella Cala, Mathilde Choteau, Christel Courtain, Léna Puigdevall • **Undergraduate Student:** Clara Stewardson • **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 destroyed 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. Another metabolite repair enzyme is a highly conserved protein called Nit1, which degrades a damaged form of glutathione, deaminated glutathione, resulting from side activities of transaminases.

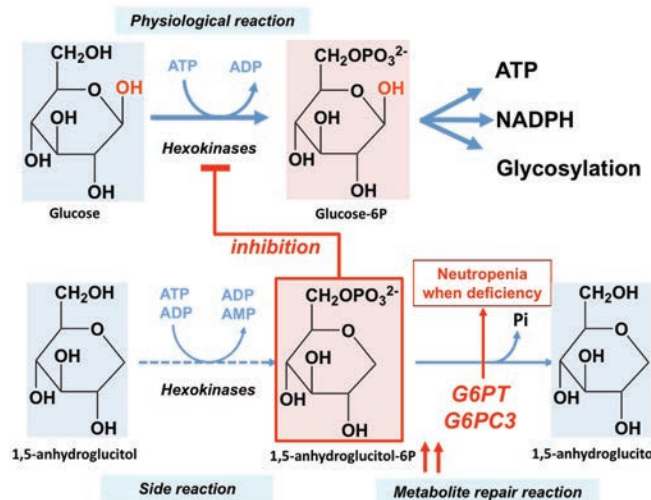
The metabolite repair concept led us to understand the cause of the congenital neutropenia found in patients

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.

In collaboration with clinicians, we recently identified a new neurological disease due to deficiency in an enzyme that serves to make high concentrations of glucose-1,6-bisP in the brain. Our data indicate that this deficiency does not lead to a glycosylation defect and that glucose-1,6-bisP plays an important role in the brain.



Staff members

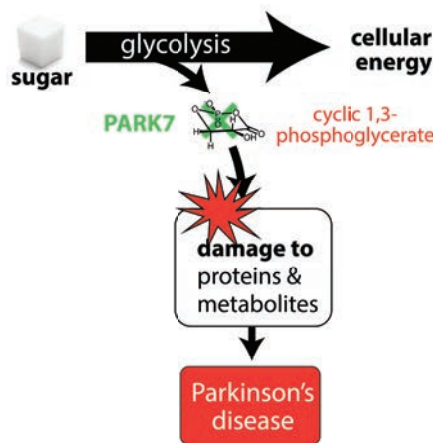
Postdoctoral Fellows: Takfarinas Kentache, Pierre Mounkoro
 • Undergraduate Student: Jennifer Diederich • Research Assistant: Nathalie Chevalier • Technical Assistant: Karim Acherki • Administrative Support: Pauline Leverrier, Marie-Victoire Uwimana



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

METABOLISM IN CANCER & OTHER DISEASES

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 bio-synthetic building blocks and for ATP synthesis.



Degradation of glucose in glycolysis leads to a newly discovered reactive metabolite that causes cellular damage, unless it is eliminated by the Parkinson's disease protein PARK7.

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.

In this context, we have been interested in a protein called PARK7, which is inactivated by mutations in some hereditary cases of Parkinson's disease. We discovered that this enzyme serves as a guardian to prevent damage of metabolites and proteins caused by glucose metab-

olism. In fact, we found that a metabolite in glycolysis spontaneously converts into the reactive compound cyclic 1,3-phosphoglycerate that can attack amino groups in both proteins and metabolites. PARK7 eliminates this compound and thereby prevents damage. In contrast, deficiency of PARK7 leads to Parkinson's disease and the accumulation of damaged proteins and metabolites (which carry glycerate or phosphoglycerate modifications).

olism. In fact, we found that a metabolite in glycolysis spontaneously converts into the reactive compound cyclic 1,3-phosphoglycerate that can attack amino groups in both proteins and metabolites. PARK7 eliminates this compound and thereby prevents damage. In contrast, deficiency of PARK7 leads to Parkinson's disease and the accumulation of damaged proteins and metabolites (which carry glycerate or phosphoglycerate modifications).

Staff members

Senior Investigator: Isabelle Gerin • **Postdoctoral Fellows:** Marina Bury, Joseph Dewulf, Sven Potelle • **PhD Students:** Francesco Caligiore, Isaac Heremans, Jean Jacobs, Stéphanie Paquay • **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.

“Drug targeting AMPK with novel compounds will be beneficial for the treatment of type 2 diabetes.”

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. We also showed that pharmacological AMPK activation by compound ‘SC4’ in WAT inhibits insulin-stimulated lipogenesis and glucose uptake to prevent lipid accumulation, a major cause of insulin resistance, but without affecting insulin-stimulated fatty acid esterification. AMPK activation by SC4 also inhibited noradrenaline-induced lipolysis, which could also be beneficial for treating T2D. In the liver, a panel of small-molecule AMPK activators was shown to inhibit glucagon-stimulated glucose production, pertinent for treating T2D, although one compound (991) had off targets effects by interfering with pyruvate uptake and redox state.

In addition to our work on AMPK, we run the mass spectrometry 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 Prof. E. Van Schaftingen, we described a new syndrome, caused by genetic NAA80 variants, leading to decreased actin acetylation and disrupted associated molecular functions, reflecting the importance of controlled actin dynamics for inner ear, brain and muscle. With the group of Prof. S. Constantinescu we showed that cleavage by β -secretase of the amyloid precursor protein (APP)

to produce the C99 transmembrane protein is regulated by dimeric C99 transmembrane orientation.

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:** Pauline Chateau, Marion Hardy • **Research Assistants:** Gaëtan Herinckx, Nusrat Hussain, Roxane Jacobs • **Technical Assistant:** Freddy Abrassart • **Administrative Support:** Aimée-Lys Rusesabagina

Etienne Marbaix &
Patrick Henriot



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-1 α , TGF- β s and Lefty2, in the control of MMP expression. We recently turned to PGRMC1, a potential modulator of progesterone response involved in control of cell survival and proliferation. 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: Lucie Samain • 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.



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?

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.

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

Staff members

Senior Investigator: Axelle Lorient • **PhD Students:** Philippe Hauchamps, Manoj Selvaraju, Chong Tang, Christophe Vanderaa • **Undergraduate Students:** Julie Devis, Samuel Grégoire • **Research Assistant:** Manon Martin • **Administrative Support:** Marjorie Decroly

SELECTED PUBLICATIONS

Stefan Constantinescu

1. Jia R, Balligand T, Atamanyuk V, Nivarthi H, Xu E, Kutzner L, Weinzierl J, Nedelec A, Kubicek S, Lesyk R, Zagrijtschuk O, Constantinescu SN, Kralovics R. Hematoxylin binds to mutant calreticulin and disrupts its abnormal interaction with thrombopoietin receptor. *Blood*. 2021;137:1920-31.
2. 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.
3. Balligand T, Achouri Y, Pecquet C, Gaudray G, Colau D, Hug E, Rahmani Y, Stroobant V, Plo I, Vainchenker W, Kralovics R, Van den Eynde B, Defour JP, Constantinescu SN. Knock-in of murine Calr del52 induces essential thrombocythemia with slow-rising dominance in mice and reveals key role of Calr Exon9 in cardiac development. *Leukemia*. 2020;34:510-21.
4. Pecquet C, Chachoua I, Roy A, Balligand T, Vertenoil G, Leroy E, Albu RI, Defour J-P, Nivarthi H, Hug E, Xu E, Ould-Amer Y, Mouton C, Colau D, Vertommen D, Marlar SM, Marty C, Plo I, Vainchenker W, Kralovics R, Constantinescu SN. Calreticulin mutants as oncogenic rogue chaperones for TpoR and traffic-defective pathogenic TpoR mutants. *Blood*. 2019;133:2669-81.
5. Labuhn M, Perkins K, Papaemmanuil E, Matzk S, Varghese L, Metzner M, Kennedy A, Amstislavskiy V, Risch T, Bhayadia R, Samulowski D, Garnett C, Cruz Hernandez D, Stoilova B, Iotchkova V, Scheer C, Yoshida K, Schwarzer A, Taub J, Crispino JD, Weiss MJ, Hayashi A, Taga T, Ito E, Ogawa S, Reinhardt D, Yaspo ML, Campbell PJ, Roberts I, Constantinescu SN, Vyas P, Heckl D, Klusmann JH. Mechanisms of progression of myeloid preleukemia to transformed myeloid leukemia in children with Down syndrome. *Cancer Cell*. 2019;36:123-38.e10.
6. Leroy E, Balligand T, Pecquet C, Mouton C, Colau D, Shiao AK, Dusa A, Constantinescu SN. Differential effect of inhibitory strategies of the V617 mutant of JAK2 on cytokine receptor signaling. *J Allergy Clin Immunol*. 2019;144:224-35.
7. Varghese LN, Defour JP, Pecquet C, Constantinescu SN. The thrombopoietin receptor: Structural basis of traffic and activation by ligand, mutations, agonists, and mutated Calreticulin. *Front Endocrinol (Lausanne)* 2017;8:59.
8. Chachoua I, Pecquet C, El-Khoury M, Nivarthi H, Albu RI, Marty C, Gryshkova V, Defour JP, Vertenoil G, Ngo A, Raslova H, Courtoy PJ, Choong ML, Plo I, Vainchenker W, Kralovics R, Constantinescu SN. Thrombopoietin receptor activation by myeloproliferative neoplasm associated calreticulin mutants. *Blood*. 2016;127:1325-35.
9. Staerk J, Kallin A, Demoulin J-B, Vainchenker W, Constantinescu SN. JAK1 and Tyk2 activation by the homologous polycythemia vera JAK2 V617F mutation: cross talk with IGF1 receptor. *J Biol Chem*. 2005;280:41893-9.
10. James C, Ugo V, Le Couedic JP, Staerk J, Delhommeau F, Lacout C, Garcon L, Raslova H, Berger R, Bennaceur-Griscelli A, Villeval JL, Constantinescu SN, Casadevall N, Vainchenker W. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005;434:1144-8.

Nick van Gastel

1. van Gastel N, Spinelli JB, Haigis MC, Scadden DT. Analysis of leukemia cell metabolism through stable isotope tracing in mice. *Bio Protoc*. 2021;11:e4171.
 2. Daniels VW, Zoeller JJ, van Gastel N, McQueeney KE, Parvin S, Potter DS, Fell GG, Ferreira VG, Yilma B, Gupta R, Spetz J, Bhola PD, Endress JE, Harris IS, Carrilho E, Sarosiek KA, Scadden DT, Brugge JS, Letai A. Metabolic perturbations sensitize triple-negative breast cancers to apoptosis induced by BH3 mimetics. *Sci Signal*. 2021;14:eabc7405.
 3. Wang YP, Sharda A, Xu SN, van Gastel N, Man CH, Choi U, Leong WZ, Li X, Scadden DT. Malic enzyme 2 connects the Krebs cycle intermediate fumarate to mitochondrial biogenesis. *Cell Metab*. 2021;33:1027-41.
 4. van Gastel N, Scadden DT. Young haematopoietic stem cells are picky eaters. *Cell Res*. 2021;31:377-8.
 5. Oki T, Mercier F, Kato H, Jung Y, McDonald TO, Spencer JA, Mazzola MC, van Gastel N, Lin CP, Michor F, Kitamura T, Scadden DT. Imaging dynamic mTORC1 pathway activity in vivo reveals marked shifts that support time-specific inhibitor therapy in AML. *Nat Commun*. 2021;12:245.
 6. van Gastel N, Carmeliet G. Metabolic regulation of skeletal cell fate and function in physiology and disease. *Nat Metab*. 2021;3:11-20.
 7. van Gastel N, Spinelli JB, Sharda A, Schajnovitz A, Baryawno N, Rhee C, Oki T, Grace E, Soled HJ, Milosevic J, Sykes DB, Hsu PP, Vander Heiden MG, Vidoudez C, Trauger SA, Haigis MC, Scadden DT. Induction of a timed metabolic collapse to overcome cancer chemoresistance. *Cell Metab*. 2020;32:391-403.
 8. Burberry A, Wells MF, Limone F, Couto A, Smith KS, Keane J, Gillet G, van Gastel N, Wang JY, Pietilainen O, Qian M, Eggen P, Cantrell C, Mok J, Kadiu I, Scadden DT, Eggen K. C9orf72 suppresses systemic and neural inflammation induced by gut bacteria. *Nature*. 2020;582:89-94.
 9. Yusuf RZ, Saez B, Sharda A, van Gastel N, Yu VWC, Baryawno N, Scadden DT, Acharya S, Chattopadhyay S, Huang C, Viswanathan V, S'aulis D, Covert J, Sykes DB, Keibler MA, Das S, Hutchinson JN, Churchill M, Mukherjee S, Lee D, Mercier F, Doench J, Bullinger L, Logan DJ, Schreiber S, Stephanopoulos G, Rizzo WB, Scadden DT. Aldehyde dehydrogenase 3a2 protects AML cells from oxidative death and the synthetic lethality of ferroptosis inducers. *Blood*. 2020;136:1303-16.
 10. van Gastel N, Stegen S, Eelen G, Schoors S, Carlier A, Daniëls VW, Baryawno N, Przybylski D, Depypere M, Stiers PJ, Lambrechts D, Van Looveren R, Torrekens S, Sharda A, Agostinis P, Lambrechts D, Maes F, Swinnen JV, Geris L, Van Oosterwyck H, Thienpont B, Carmeliet P, Scadden DT, Carmeliet G. Lipid availability determines fate of skeletal progenitor cells via SOX9. *Nature*. 2020;579:111-7.
- ## Jean-Baptiste Demoulin
1. Lenglez S, Sablon A, Fénelon G, Boland A, Deleuze JF, Boutoleau-Bretonnière C, Nicolas G, Demoulin J-B. Distinct functional classes of PDGFRB pathogenic variants in primary familial brain calcification. *Hum Mol Genet*. 2022;31:399-409.
 2. Guérit E, Arts F, Dachy G, Boulouadnine B, Demoulin J-B. PDGF receptor mutations in human diseases. *Cell Mol Life Sci*. 2021;78:3867-81.

3. Dachy G, de Krijger RR, Fraitag S, Théate I, Brichard B, Hoffman SB, Libbrecht L, Arts FA, Brouillard P, Vikkula M, Limaye N, Demoulin J-B. Association of PDGFRB mutations with pediatric myofibroma and myofibromatosis. *JAMA Dermatol.* 2019;155:946-50.
4. Pond D*, Arts FA*, Mendelsohn NJ, Demoulin J-B, Scharer G, Messinger Y. A patient with germ-line gain-of-function PDGFRB p.N666H mutation and marked clinical response to imatinib. *Genet Med.* 2018;20:142-50. (*equal contribution)
5. Arts FA, Sciôt R, Brichard B, Renard M, de Rocca Serra A, Dachy G, Noël LA, Velghe AI, Galant C, Debiec-Rychter M, Van Damme A, Vikkula M, Helaers R, Limaye N, Poirel HA, Demoulin J-B. PDGFRB gain-of-function mutations in sporadic infantile myofibromatosis. *Hum Mol Genet.* 2017; 26:1801-10.
6. Coomans de Brachène A, Demoulin J-B. FOXO transcription factors in cancer development and therapy. *Cell Mol Life Sci.* 2016;73:1159-72.
7. Arts FA, Chand D, Pecquet C, Velghe AI, Constantinescu S, Hallberg B, Demoulin J-B. PDGFRB mutants found in patients with familial infantile myofibromatosis or overgrowth syndrome are oncogenic and sensitive to imatinib. *Oncogene.* 2016; 35:3239-48.
8. Demoulin J-B, Essaghir A. PDGF receptor signaling networks in normal and cancer cells. *Cytokine Growth Factor Rev.* 2014; 25:273-83.
9. Toffalini F, Demoulin J-B. New insights into the mechanisms of hematopoietic cell transformation by activated receptor tyrosine kinases. *Blood.* 2010;116:2429-37.
10. Medves S, Duhoux FP, Ferrant A, Toffalini F, Ameye G, Libouton JM, Poirel HA, Demoulin J-B. KANK1, a candidate tumor suppressor gene, is fused to PDGFRB in an imatinib-responsive myeloid neoplasm with severe thrombocytopenia. *Leukemia.* 2010; 24:1052-5.
5. Dheur M-S, Poirel HA, Ameye G, Tilman G, Saussoy P, Defour J-P, Camboni A, Van Den Neste E, Coulie PG, van Baren N. Characterization of two new high-grade B-cell lymphoma cell lines with MYC and BCL2 rearrangements that are suitable for in vitro drug sensitivity studies. *Leuk Lymphoma.* 2019;60:1043-52.
6. Liénart S, Merceron R, Vanderaa C, Lambert F, Colau D, Stockis J, van der Woning B, De Haard H, Saunders M, Coulie PG, Savvides SN, Lucas S. Structural basis of latent TGF- β 1 presentation and activation by GARP on human regulatory T cells. *Science.* 2018;362:952-6.
7. Gross S, Erdmann M, Haendle I, Volland S, Berger T, Schultz E, Strasser E, Dankerl P, Janka R, Schliep S, Heinzerling L, Sotlar K, Coulie P, Schuler G, Schuler-Thurner B. Twelve-year survival and immune correlates in dendritic cell-vaccinated melanoma patients. *JCI Insight.* 2017;2:e91438.
8. Lethé B, Snauwaert S, Bricard O, Schroder D, Gomard T, Hames G, Muller C, Lurquin C, Gauthy E, Essaghir A, Vandekerckhove B, Coulie PG. A new transcript in the TCRB locus unveils the human ortholog of the mouse pre-Dss1 promoter. *Immun Inflamm Dis.* 2017;5:346-54.
9. Coulie PG, Van den Eynde BJ, van der Bruggen P, Boon T. Tumour antigens recognized by T lymphocytes: at the core of cancer immunotherapy. *Nat Rev Cancer.* 2014;14:135-46.
10. Corbière V, Chapiro J, Stroobant V, Ma W, Lurquin C, Lethé B, van Baren N, Van den Eynde BJ, Boon T, Coulie PG. Antigen spreading contributes to MAGE Vaccination-induced regression of melanoma metastases. *Cancer Res.* 2011;71:1253-62.

Sophie Lucas

1. Gaignage M, Zhang X, Stockis J, Dedobbeleer O, Michiels C, Cochez P, Dumoutier L, Coulie PG, Lucas S. Blocking GARP-mediated activation of TGF- β 1 did not alter innate or adaptive immune responses to bacterial infection or protein immunization in mice. *Cancer Immunol Immunother.* 2022; epub Jan 1.
2. Georgery H, Devresse A, Saad Albichr I, Lucas S, Yombi J-C, Belkhir L, De Greef J, Scohy A, Kabamba B, Goffin E, Kanaan N. Delayed humoral response after two doses of the BNT162b2 vaccine in a Belgian kidney transplant cohort. *Transplantation.* 2022;106:e192-3.
3. Bertrand C, Van Meerbeeck P, de Streeel G, Vaherto-Bleeckx N, Benhaddi F, Rouaud L, Noel A, Coulie PG, van Baren N, Lucas S. Combined blockade of GARP:TGF- β 1 and PD-1 increases infiltration of T cells and density of pericyte-covered GARP⁺ blood vessels in mouse MC38 tumors. *Front Immunol.* 2021;12:704050.
4. Noël G, Langouo Fontsa M, Garaud S, De Silva P, de Wind A, Van den Eynden GG, Salgado R, Boisson A, Locy H, Thomas N, Solinas C, Migliori E, Naveaux C, Duvillier H, Lucas S, Craciun L, Thielemans K, Larsimont D, Willard-Gallo K. Functional Th1-oriented T follicular helper cells that infiltrate human breast cancer promote effective adaptive immunity. *J Clin Invest.* 2021;131:e139905.
5. Slattery K, Woods E, Zaiatz-Bittencourt V, Marks S, Chew S, Conroy M, Goggin C, MacEochagain C, Kennedy J, Lucas S, Finlay DK, Gardiner CM. TGF β drives NK cell metabolic dysfunction in human metastatic breast cancer. *J Immunother Cancer.* 2021;9:e002044.
6. de Streeel G, Bertrand C, Chalon N, Liénart S, Bricard O, Lecomte S, Devreux J, Gaignage M, De Boeck G, Marien L, Van De Walle I, van der Woning B, Saunders M, de Haard H, Vermeersch E, Maes W, Deckmyn H, Coulie PG, van Baren N, Lucas S. Selective inhibition of TGF- β 1

Pierre Coulie

1. Lenogue K, Walencik A, Laulagnier K, Molens JP, Benlalam H, Dreno B, Coulie P, Pule M, Chaperot L, Plumas J. Engineering a human plasmacytoid dendritic cell-based vaccine to prime and expand multispecific viral and tumor antigen-specific T-cells. *Vaccines (Basel).* 2021;9:141.
2. Triaille C, Vansteenkiste L, Constant M, Ambroise J, Méric de Bellefon L, Nzeusseu Toukap A, Sokolova T, Galant C, Coulie P, Carrasco J, Durez P, Lauwerys BR. Paired rheumatoid arthritis synovial biopsies from small and large joints show similar global transcriptomic patterns with enrichment of private specificity *TCRB* and TCR signaling pathways. *Front Immunol.* 2020;11:593083.
3. de Streeel G, Bertrand C, Chalon N, Liénart S, Bricard O, Lecomte S, Devreux J, Gaignage M, De Boeck G, Mariën L, Van De Walle I, van der Woning B, Saunders M, de Haard H, Vermeersch E, Maes W, Deckmyn H, Coulie PG, van Baren N, Lucas S. Selective inhibition of TGF- β 1 produced by GARP-expressing Tregs overcomes resistance to PD-1/PD-L1 blockade in cancer. *Nat Commun.* 2020;11:4545.
4. Narasimhaiah D, Legrand C, Damotte D, Remark R, Munda M, De Potter P, Coulie PG, Vikkula M, Godfraind C. DNA alteration-based classification of uveal melanoma gives better prognostic stratification than immune infiltration, which has a neutral effect in high-risk group. *Cancer Med.* 2019;8:3036-46.

produced by GARP-expressing Tregs overcomes resistance to PD-1/PD-L1 blockade in cancer. *Nat Commun.* 2020;11:4545.

7. Liénart S, Merceron R, Vanderaa C, Lambert F, Colau D, Stockis J, van der Woning B, De Haard H, Saunders M, Coulie PG, Savvides SN, Lucas S. Structural basis of latent TGF- β 1 presentation and activation by GARP on human regulatory T cells. *Science.* 2018;362:952-6.

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

9. Dedobbeleer O, Stockis J, van der Woning B, Coulie PG, Lucas S. Cutting Edge: Active TGF- β 1 Released from GARP/TGF- β 1 complexes on the surface of stimulated human B lymphocytes increases class-switch recombination and production of IgA. *J Immunol.* 2017;199:391-6.

10. Cuende J, Liénart S, Dedobbeleer O, van der Woning B, De Boeck G, Stockis J, Huygens C, Colau D, Somja J, Delvenne P, Hannon M, Baron F, Dumoutier L, Renauld J-C, De Haard H, Saunders M, Coulie PG, Lucas S. Monoclonal antibodies against GARP/TGF- β 1 complexes inhibit the immunosuppressive activity of human regulatory T cells in vivo. *Sci Transl Med.* 2015;7:284ra56.

Benoit Van den Eynde

1. Klaessens S, Stroobant V, Hoffmann D, Gyrd-Hansen M, Pilotte L, Vigneron N, De Plaen E, Van den Eynde BJ. Tryptophanemia is controlled by a tryptophan-sensing mechanism ubiquitinating tryptophan 2,3-dioxygenase. *Proc Natl Acad Sci USA.* 2021;118:e2022447118.

2. Canè S, Van Snick J, Uyttenhove C, Pilotte L, Van den Eynde BJ. TGF β 1 neutralization displays therapeutic efficacy through both an immunomodulatory and a non-immune tumor-intrinsic mechanism. *J Immunother Cancer.* 2021;9:e001798.

3. McAuliffe J, Chan HF, Noblecourt L, Ramirez-Valdez RA, Pereira-Almeida V, Zhou Y, Pollock E, Cappuccini F, Redchenko I, Hill AV, Leung CSK, Van den Eynde BJ. Heterologous prime-boost vaccination targeting MAGE-type antigens promotes tumor T-cell infiltration and improves checkpoint blockade therapy. *J Immunother Cancer.* 2021;9:e003218.

4. Van den Eynde BJ. Arid5a: A Missing Link between EMT and Tumoral Immune Resistance. *Cancer Immunol Res.* 2021;9:854.

5. Abi Habib J, De Plaen E, Stroobant V, Zivkovic D, Bousquet M-P, Guillaume B, Wahni K, Messens J, Busse A, Vigneron N, Van den Eynde BJ. Efficiency of the four proteasome subtypes to degrade ubiquitinated or oxidized proteins. *Sci Rep.* 2020;10:15765.

6. Van den Eynde BJ, van Baren N, Baurain J-F. Is there a clinical future for IDO1 inhibitors after the failure of epacadostat in melanoma? *Annu Rev Cancer Biol.* 2020;4:241-56.

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

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

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

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

Pierre van der Bruggen

1. Vanhaver C, van der Bruggen P, Bruger AM. MDSC in mice and men: mechanisms of immunosuppression in cancer. *J Clin Med.* 2021;10:2872.

2. Renard HF, Tyckaert F, Lo Giudice C, Hirsch T, Valades-Cruz CA, Lemaigre C, Shafaq-Zadah M, Wunder C, Wattiez R, Johannes L, van der Bruggen P, Alsteens D, Morsomme P. Endophilin-A3 and Galectin-8 control the clathrin-independent endocytosis of CD166. *Nat Commun.* 2020;11:1457.

3. Bruger AM, Vanhaver C, Bruderek K, Amodio G, Tavukcuoglu E, Esendagli G, Gregori S, Brandau S, van der Bruggen P. Protocol to assess the suppression of T-cell proliferation by human MDSC. *Methods Enzymol.* 2020;632:155-92.

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

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

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

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

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

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

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

Donatienne Tyteca

1. Dumitru AC, Stommen A, Koehler M, Cloos A-S, Yang J, Leclercq A, Tyteca D*, Alsteens D*. Probing PIEZO1 Localization upon Activation Using High-Resolution Atomic Force and Confocal Microscopy. *Nano Letters*. 2021; 21, 4950-4958. (*equal contribution).
2. Dumitru AC, Mohammed D, Maja M, Yang J, Verstraeten S, del Campo A, Mingeot-Leclercq M-P, Tyteca D, Alsteens D. Label-free imaging of cholesterol assemblies reveals hidden nanomechanics of breast cancer cells. *Adv Sci*. 2020;7:2002643.
3. Pollet H*, Cloos A-S*, Stommen A*, Vanderroost J, Conrard L, Paquot A, Ghodsi M, Carquin M, Léonard C, Guthmann M, Lingurski M, Vermeylen C, Killian T, Gatto L, Rider M, Pyr dit Ruys S, Vertommen D, Vikkula M, Brouillard P, Van Der Smissen P, Muccioli G, Tyteca D. Aberrant membrane composition and biophysical properties impair erythrocyte morphology and functionality in elliptocytosis. *Biomolecules*. 2020;10:E1120. (*equal contribution)
4. Cloos A-S, Ghodsi M, Stommen A, Vanderroost J, Dauguet N, Pollet H, D'Auria L, Mignolet E, Larondelle Y, Terrasi R, Muccioli G, Van Der Smissen P, Tyteca D. Interplay between plasma membrane lipid alteration, oxidative stress and calcium-based mechanism for extracellular vesicle biogenesis from erythrocytes during blood storage. *Front Physiol*. 2020;11:712.
5. Conrard L, Stommen A, Cloos A-S, Steinkühler J, Dimova R, Pollet H, Tyteca D. Spatial relationship and functional relevance of three lipid domain populations at the erythrocyte surface. *Cell Physiol Biochem*. 2018;51:1544–65.
6. Léonard C, Pollet H, Vermeylen C, Gov N, Tyteca D*, Mingeot-Leclercq M-P*. Tuning of differential lipid order between submicrometric domains and surrounding membrane upon erythrocyte reshaping. *Cell Physiol Biochem*. 2018;48:2563–82. (*equal contribution)
7. Dumitru AC, Conrard L, Lo Giudice C, Henriët P, Veiga-da-Cunha M, Derclaye S, Tyteca D, Alsteens D. High-resolution mapping and recognition of lipid domains using AFM with toxin-derivatized probes. *Chem Commun (Camb)*. 2018;54:6903-6.
8. Gournas C, Gkionis S, Carquin M, Twyffels L, Tyteca D, André B. Conformation-dependent partitioning of yeast nutrient transporters into starvation-protective membrane domains. *Proc Natl Acad Sci USA*. 2018;115:E3145-54.
9. Léonard C, Alsteens D, Dumitru AC, Mingeot-Leclercq M-P, Tyteca D. Lipid domains and membrane (re)shaping: from biophysics to biology. In: Epanand RM and Ruysschaert J-M, eds. *The biophysics of cell membranes* (Springer Series in Biophysics 19), Chapter 5. Springer Nature (Singapore). 2017 pp.121-75.
10. Léonard C, Conrard L, Guthmann M, Pollet H, Carquin M, Vermeylen C, Gailly P, Van Der Smissen P, Mingeot-Leclercq M-P, Tyteca D. Contribution of plasma membrane lipid domains to red blood cell (re)shaping. *Sci Rep*. 2017;7:4264.

Nisha Limaye

1. Tilman G, Bouzin C, Aydin S, Tamirou F, Galant C, Coulié PG, Houssiau F, Lauwerys B, Limaye N. High p16^{INK4a}, a marker of cellular senescence, is associated with renal injury, impairment and outcome in lupus nephritis. *RMD Open*. 2021;7:e001844.

2. Boulanger C, Chatzis O, Nolf D, Brichard B, Lauwerys B, Nassogne M-C, Limaye N. Atypical phenotype? The answer's in the genotype: AGS caused by a novel *RNASEH2C* variant combined with XLA caused by a *BTK* deficiency. *Rheumatology (Oxford)*. 2021;60:e240-2.
3. Dachy G, de Krijger RR, Freitag S, Théate I, Brichard B, Hoffman SB, Libbrecht L, Arts FA, Brouillard P, Vikkula M, Limaye N, Demoulin J-B. Association of PDGFRB mutations with pediatric myofibroma and myofibromatosis. *JAMA Dermatol*. 2019;155:946-50.
4. Nätyнки M, Kangas J, Miinalainen I, Sormunen R, Pietilä R, Soblet J, Boon LM, Vikkula M, Limaye N, Eklund L. Common and specific effects of TIE2 mutations causing venous malformations. *Hum Mol Genet*. 2015;24:6374-89.
5. Limaye N, Kangas J, Mendola A, Godfraind C, Schlögel MJ, Helaers R, Eklund L, Boon LM, Vikkula M. Somatic activating PIK3CA mutations cause venous malformation. *Am J Hum Genet*. 2015;97: 914-21.
6. Boscolo E, Limaye N, Huang L, Kang KT, Soblet J, Uebelhoer M, Mendola A, Natynki M, Seront E, Dupont S, Hammer J, Legrand C, Brugnara C, Eklund L, Vikkula M, Bischoff J, Boon LM. Rapamycin improves TIE2-mutated venous malformation in murine model and human subjects. *J Clin Invest*. 2015;125:3491-504.
7. Uebelhoer M, Nätyнки M, Kangas J, Mendola A, Nguyen H, Soblet J, Godfraind C, Boon LM, Eklund L, Limaye N*, Vikkula M*. Venous malformation-causative TIE2 mutations mediate an AKT-dependent decrease in PDGFB. *Hum Mol Genet*. 2013;22:3438-48. (*equal contribution)
8. Limaye N*, Wouters V*, Uebelhoer M, Tuominen M, Wirkkala R, Mulliken JB, Eklund L, Boon LM, Vikkula M. Somatic mutations in the angiopoietin receptor gene TIE2 cause solitary and multiple sporadic venous malformations. *Nat Genet*. 2009;41:118-24. (*equal contribution)
9. Limaye N, Belobrajdic K, Wandstrat AE, Bonhomme F, Edwards SV, Wakeland EK. Prevalence and evolutionary origins of autoimmune susceptibility alleles in natural mouse populations. *Genes Immun*. 2008;9:61-8.
10. Wandstrat AE*, Nguyen C*, Limaye N*, Chan AY, Subramanian S, Tian X-H, Yim Y-S, Pertsemliadis A, Gardner, HR Jr, Morel L, Wakeland EK. Association of extensive polymorphisms in the SLAM/CD2 gene cluster with murine lupus. *Immunity*. 2004;21:769-80. (*equal contribution)

Miikka Vikkula

1. Brouillard P, Witte MH, Erickson RP, Damstra RJ, Becker C, Quéré I, Vikkula M. Primary lymphoedema. *Nat Rev Dis Primers*. 2021;7:77.
2. Queisser A, Seront E, Boon LM, Vikkula M. Genetic basis and therapies for vascular anomalies. *Circ Res*. 2021;129:155-73.
3. Mäkinen T, Boon LM, Vikkula M, Alitalo K. Lymphatic malformations: genetics, mechanisms and therapeutic strategies. *Circ Res*. 2021;129:136-54.
4. Canaud G, Hammill AM, Adams D, Vikkula M, Keppler-Noreuil KM. A review of mechanisms of disease across PIK3CA-related disorders with vascular manifestations. *Orphanet J Rare Dis*. 2021;16:306.

5. Greene AK, Brouillard P, Sudduth CL, Smits PJ, Konczyk DJ, Vikkula M. EPHB4 mutation causes adult and adolescent-onset primary lymphedema. *Am J Med Genet A*. 2021;185:3810-3.
6. Homayun-Sepehr N, McCarter AL, Helaers R, Galant C, Boon LM, Brouillard P, Vikkula M, Dellinger MT. KRAS-driven model of Gorham-Stout disease effectively treated with trametinib. *JCI Insight*. 2021;6:e149831.
7. Brouillard P, Schlögel MJ, Homayun Sepehr N, Helaers R, Queisser A, Fastré E, Boutry S, Schmitz S, Clapuyt P, Hammer F, DompMartin A, Weitz-Tuoretmaa A, Laranne J, Pasquesoone L, Vilain C, Boon LM, Vikkula M. Non-hotspot PIK3CA mutations are more frequent in CLOVES than in common or combined lymphatic malformations. *Orphanet J Rare Dis*. 2021;16:267.
8. Coulie R, Niyazov DM, Gambello MJ, Fastré E, Brouillard P, Vikkula M. Hypotrichosis-lymphedema-telangiectasia syndrome: Report of ileal atresia associated with a SOX18 de novo pathogenic variant and review of the phenotypic spectrum. *Am J Med Genet A*. 2021;185:2153-9.
9. Smeland MF, Brouillard P, Prescott T, Boon LM, Hvingel B, Nordbakken CV, Nystad M, Holla ØL, Vikkula M. Biallelic ANGPT2 loss-of-function causes severe early-onset non-immune hydrops fetalis. *J Med Genet*. 2021; epub Dec 7.
10. Georges A, Yang ML, Berrandou TE, Bakker MK, Dikilitas O, Kiando SR, Ma L, Satterfield BA, Sengupta S, Yu M, Deleuze JF, Dupré D, Hunker KL, Kyryachenko S, Liu L, Sayoud-Sadeg I, Amar L, Brummett CM, Coleman DM, d'Escamard V, de Leeuw P, Fendrikova-Mahlay N, Kadian-Dodov D, Li JZ, Lorthioir A, Pappaccogli M, Prejbsiz A, Smigielski W, Stanley JC, Zawistowski M, Zhou X, Zöllner S; FEIRI investigators; International Stroke Genetics Consortium (ISGC) Intracranial Aneurysm Working Group; MEGASTROKE, Amouyel P, De Buyzere ML, Debette S, Dobrowolski P, Drygas W, Gornik HL, Olin JW, Piwonski J, Rietzschel ER, Ruigrok YM, Vikkula M, Warchol Celinska E, Januszewicz A, Kullo IJ, Azizi M, Jeunemaitre X, Persu A, Kovacic JC, Ganesh SK, Bouatia-Naji N. Genetic investigation of fibromuscular dysplasia identifies risk loci and shared genetics with common cardiovascular diseases. *Nat Commun*. 2021;12:6031.

Charles De Smet

1. Vander Linden C, Corbet C, Bastien E, Martherus R, Guilbaud C, Petit L, Wauthier L, Lorient A, De Smet C, Feron O. Therapy-induced DNA methylation inactivates MCT1 and renders tumor cells vulnerable for MCT4 inhibition. *Cell Rep*. 2021;35:109202.
2. Fain JS, Lorient A, Diacofotaki A, Van Tongelen A, De Smet C. Transcriptional overlap links DNA hypomethylation with DNA hypermethylation at adjacent promoters in cancer. *Sci Rep*. 2021;11:17346.
3. Viceconte N*, Lorient A*, Lona Abreu P, Scheibe M, Fradera Sola A, Butter F, De Smet C, Azzalin CM, Arnoult N, Decottignies A. PAR-TERRA is the main contributor to telomeric repeat-containing RNA transcripts in normal and cancer mouse cells. *RNA*. 2021;27:106-21. (*equal contribution)
4. Fain JS, Van Tongelen A, Lorient A, De Smet C. Epigenetic coactivation of MAGEA6 and CT-GABRA3 defines orientation of a segmental duplication in the human X chromosome. *Cytogenet Genome Res*. 2019;159:12-8.

5. De Pauw A, Andre E, Sekkali B, Bouzin C, Esfahani H, Barbier N, Lorient A, De Smet C, Vanhoutte L, Moniotte S, Gerber B, di Mauro V, Catalucci D, Feron O, Hilfiker-Kleiner D, Balligand J-L. Dnmt3a-mediated inhibition of Wnt in cardiac progenitor cells improves differentiation and remote remodeling after infarction. *JCI Insight*. 2017;2:e91810.
6. Van Tongelen A, Lorient A, De Smet C. Oncogenic role of DNA hypomethylation through the activation of cancer-germline genes. *Cancer Lett*. 2017;396:130-7.
7. Cannuyer J, Van Tongelen A, Lorient A, De Smet C. A gene expression signature identifying transient DNMT1 depletion as a causal factor of cancer-germline gene activation in melanoma. *Clin Epigenetics*. 2015;7:114.
8. Lorient A*, Van Tongelen A*, Blanco J, Klaessens S, Cannuyer J, van Baren N, Decottignies A, De Smet C. A novel cancer-germline gene carrying pro-metastatic miR-105 and TET-targeting miR-767 induced by DNA hypomethylation in tumors. *Epigenetics*. 2014;9:1163-71. (*equal contribution)
9. De Smet C, Lorient A. DNA hypomethylation and activation of germline-specific genes in cancer. In: Karpf AR, ed. *Epigenetic alterations in oncogenesis (Adv Exp Med Biol 754)*, Chapter 7. Springer (NY). 2013 pp.149-66.
10. De Smet C, Lorient A, Boon T. Promoter-dependent mechanism leading to selective hypomethylation within the 5' region of gene MAGE-A1 in tumors cells. *Mol Cell Biol*. 2004;24:4781-90.

Anabelle Decottignies

1. Claude E*, de Lhoneux G*, Pierreux CE, Marbaix E, de Ville de Goyet M, Boulanger C, Van Damme A, Brichard B, Decottignies A. Detection of alternative lengthening of telomeres mechanism on tumor sections. *Mol Biomed*. 2021;2:32. (*equal contribution)
2. Raghunandan M, Geelen D, Majerova E, Decottignies A. NHP2 downregulation counteracts hTR-mediated activation of the DNA damage response at ALT telomeres. *EMBO J*. 2021;40:e106336.
3. Viceconte N*, Lorient A*, Lona Abreu P, Scheibe M, Fradera Sola A, Butter F, De Smet C, Azzalin CM, Arnoult N, Decottignies A. PAR-TERRA is the main contributor to telomeric repeat-containing RNA transcripts in normal and cancer mouse cells. *RNA*. 2021;27:106-21. (*equal contribution)
4. Claude E, Decottignies A. Telomere maintenance mechanisms in cancer: telomerase, ALT or lack thereof. *Curr Opin Genet Dev*. 2020;60:1-8.
5. Froidure A*, Mahieu M*, Hoton D, Laterre PF, Yombi JC, Koenig S, Ghaye B, Defour JP, Decottignies A. Short telomeres increase the risk of severe COVID-19. *Aging*. 2020;12:19911-22. (*equal contribution)
6. Episkopou H*, Diman A*, Claude E, Viceconte N, Decottignies A. TSPYL5 depletion induces specific death of ALT cells through USP7-dependent proteasomal degradation of POT1. *Mol Cell*. 2019;75:469-82. (*equal contribution)
7. Benyelles M, Episkopou H, O'Donohue MF, Kermasson L, Frange P, Poulain F, Burcu Belen F, Polat M, Bole-Feysoot C, Langa-Vives F, Gleizes PE, de Villartay JP, Callebaut I, Decottignies A*, Revy P*. Impaired telomere integrity and rRNA biogenesis in PARN-deficient patients and knock-out models. *EMBO Mol Med*. 2019;11:e10201. (*equal contribution)

8. Viceconte N, Dheur M-S, Majerova E, Pierreux CE, Baurain J-F, van Baren N, Decottignies A. Highly aggressive metastatic melanoma cells unable to maintain telomere length. *Cell Rep.* 2017;19:2529-43.
9. Diman A*, Boros J*, Poulain F, Rodriguez J, Purnelle M, Episkopou H, Bertrand L, Francaux M, Deldicque L, Decottignies A. Nuclear respiratory factor 1 and endurance exercise promote human telomere transcription. *Sci Adv.* 2016;2:e1600031. (*equal contribution)
10. Arnoult N*, Van Beneden A*, Decottignies A. Telomere length regulates TERRA levels through increased trimethylation of telomeric H3K9 and HP1alpha. *Nat Struct Mol Biol.* 2012;19:948-56. (*equal contribution)

Frédéric Lemaigre & Patrick Jacquemin

1. Assi M, Achouri Y, Lorient A, Dauguet N, Dahou H, Baldan J, Libert M, Fain JS, Guerra C, Bouwens L, Barbacid M, Lemaigre FP, Jacquemin P. Dynamic regulation of the expression of KRAS and its effectors determines the ability of pancreatic acinar cells to initiate tumorigenesis. *Cancer Res.* 2021;81:2679-89.
2. Di-Luoffo M, Pirenne S, Saandi T, Lorient A, Gérard C, Dauguet N, Manzano-Núñez F, Alves Souza Carvalhais N, Lamoline F, Konobrocka K, De Greef V, Komuta M, Halder G, Jacquemin P, Lemaigre FP. A novel mouse model of cholangiocarcinoma uncovers a role for Tensin-4 in tumor progression. *Hepatology.* 2021;74:1445-60.
3. Buckens H, Pirenne S, Achouri Y, Dauguet N, Dahou H, Baldan J, Bouwens L, Lemaigre F, Jacquemin P, Assi M. Peroxiredoxin-I sustains inflammation during pancreatitis. *Cell Mol Gastroenterol Hepatol.* 2021;12:741-3.
4. Verboven E, Moya IM, Sansores-García L, Xie J, Hillen H, Kowalczyk W, Vella G, Verhulst S, Castaldo SA, Algueró-Nadal A, Romanelli L, Mercader-Celma C, Souza NA, Soheily S, van Huffel L, Van Brussel T, Lambrechts D, Roskams T, Lemaigre FP, Bergers G, van Grunsven L, Halder G. Regeneration defects in Yap and Taz mutant mouse livers are caused by bile duct disruption and cholestasis. *Gastroenterology.* 2021;160:847-62.
5. Marsee A, Roos F, Verstegen MMA, HPB Organoid Consortium, Gehart H, de Koning E, Lemaigre F, Forbes SJ, Peng WC, Huch M, Takebe T, Vallier L, Clevers H, van der Laan LJW, Spee B. Building a consensus on definition and nomenclature of human hepatic, biliary and pancreatic organoids. *Cell Stem Cell.* 2021;28:816-32.
6. Minnis-Lyons SE, Ferreira-González S, Aleksieva N, Man TY, Gadd VL, Williams MJ, Guest RV, Lu W-Y, Dwyer BJ, Jamieson T, Nixon C, Hul N, Lemaigre FP, McCafferty J, Leclercq I, Sansom OJ, Boulter L, Forbes SJ. Notch-IGF1 signaling during liver regeneration drives biliary epithelial cell expansion and inhibits hepatocyte differentiation. *Sci Signal.* 2021;14:eaay9185.
7. Gérard C, De Mot L, Cordi S, van Eyll J, Lemaigre F. Temporal dynamics of a CSF1R signaling gene regulatory network involved in epilepsy. *PLoS Comp. Biol.* 2021;17:e1008854.
8. Meyers N, Gérard C, Lemaigre FP, Jacquemin P. Differential impact of the ERBB receptors EGFR and ERBB2 on the initiation of precursor lesions of pancreatic ductal adenocarcinoma. *Sci Rep.* 2020;10:5241.
9. Lemaigre FP. Development of the intrahepatic and extrahepatic biliary tract: a framework for understanding congenital diseases. *Annu Rev Pathol.* 2020;15:1-22.

10. Collet L, Ghurburrun E, Meyers N, Assi M, Pirlot B, Leclercq IA, Couvelard A, Komuta M, Cros J, Demetter P, Lemaigre FP, Borbath I, Jacquemin P. Kras and Lkb1 mutations synergistically induce intraductal papillary mucinous neoplasm derived from pancreatic duct cells. *Gut.* 2020;69:704-14.

Wen-Hui Lien

1. Lang CMR, Chan CK, Veltri A, Lien WH. Wnt signaling pathways in keratinocyte carcinomas. *Cancers.* 2019;11:1216.
2. Adam RC, Yang H, Ge Y, Lien WH, Wang P, Zhao Y, Polak L, Levorse J, Baksh SC, Zheng D, Fuchs E. Temporal layering of signaling effectors drives chromatin remodeling during hair follicle stem cell lineage progression. *Cell Stem Cell.* 2018;22:398-413.
3. Veltri A, Lang C, Lien WH. Concise Review: Wnt signaling pathways in skin development and epidermal stem cells. *Stem Cells.* 2018;36:22-35.
4. Jossin Y, Lee M, Klezovitch O, Kon E, Alexia C, Lien WH, Fernandez TE, Cooper JA, Vasioukhin V. Lgl1 connects cell polarity with cell-cell adhesion in embryonic neural stem cells. *Dev Cell.* 2017;41:481-95.
5. Lien WH, Fuchs E. Wnt some lose some: transcriptional governance of stem cells by Wnt/ β -catenin signaling. *Genes Dev.* 2014;28:1517-32.
6. Lien WH, Polak L, Lin M, Lay K, Zheng D, Fuchs E. In vivo transcriptional governance of hair follicle stem cells by canonical Wnt regulators. *Nat Cell Biol.* 2014;16:179-90.
7. Beronja S, Janki P, Heller E, Lien WH, Keyes BE, Oshimori N, Fuchs E. RNAi screens in mice identify physiological regulators of oncogenic growth. *Nature.* 2013;501:185-90.
8. Lien WH, Guo X, Polak L, Lawton LN, Young RA, Zheng D, Fuchs E. Genome-wide maps of histone modifications unwind in vivo chromatin states of the hair follicle lineage. *Cell Stem Cell.* 2011;9:219-32.
9. Ezhkova E, Lien WH, Stokes N, Pasolli HA, Silva JM, Fuchs E. EZH1 and EZH2 cogovern histone H3K27 trimethylation and are essential for hair follicle homeostasis and wound repair. *Genes Dev.* 2011;25:485-98.
10. Lien WH, Klezovitch O, Fernandez TE, Delrow J, Vasioukhin V. α -Catenin controls cerebral cortical size by regulating the hedgehog signaling pathway. *Science.* 2006;311:1609-12.

Christophe Pierreux

1. Heymans C, Spourquet C, Delcorte O, Villacorte-Tabelin M, Dupasquier S, Achouri Y, Mahibullah S, Lemoine P, Balda MS, Matter K, Pierreux CE. Spatio-temporal expression pattern and role of the tight junction protein MarvelD3 in pancreas development and function. *Sci Rep.* 2021;11:14519.
2. Pierreux CE. Shaping the thyroid: from peninsula to de novo lumen formation. *Mol Cell Endocrinol.* 2021;531:111313.
3. Gonay L, Spourquet C, Baudoin M, Lepers L, Lemoine P, Fletcher AG, Hanert E, Pierreux CE. Modelling of epithelial growth, fission and lumen formation during embryonic thyroid development: a combination of computational and experimental approaches. *Front Endocrinol.* 2021;12:655862.

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

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

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

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

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

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

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

Jean-François Collet

1. El Rayes J, Rodríguez-Alonso R, Collet J-F. Lipoproteins in Gram-negative bacteria: new insights into their biogenesis, subcellular targeting and functional roles. *Curr Opin Microbiol*. 2021;61:25-34.

2. El Rayes J, Szewczyk J, Deghelt M, Csoma N, Matagne A, Iorga BI, Cho SH, Collet J-F. Disorder is a critical component of lipoprotein sorting in Gram-negative bacteria. *Nat Chem Biol*. 2021;17:1093-100.

3. Godessart P, Lannoy A, Dieu M, Van der Verren SE, Soumillion P, Collet J-F, Remaut H, Renard P, De Bolle X. β -Barrels covalently link peptidoglycan and the outer membrane in the α -proteobacterium *Brucella abortus*. *Nat Microbiol*. 2021;6:27-33.

4. Dekoninck K, Létouquart J, Laguri C, Demange P, Bevernaegie R, Simorre JP, Dehu O, Iorga BI, Elias B, Cho SH, Collet J-F. Defining the function of OmpA in the Rcs stress response. *Elife*. 2020;9:e60861.

5. Rodríguez-Alonso R, Létouquart J, Nguyen VS, Louis G, Calabrese AN, Iorga BI, Radford SE, Cho SH, Remaut H, Collet J-F. Structural insight into the formation of lipoprotein- β -barrel complexes. *Nat Chem Biol*. 2020;16:1019-25.

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

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

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

9. Gennaris A, Ezraty B, Henry C, Agrebi R, Vergnes A, Oheix E, Bos J, Leverrier P, Espinosa L, Szewczyk J, Vertommen D, Iranzo O, Collet J-F, Barras F. Repairing oxidized proteins in the bacterial envelope using respiratory chain electrons. *Nature*. 2015;528:409-12.

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

Géraldine Laloux

1. Kaljević J, Saaki TNV, Govers SK, Remy O, van Raaphorst R, Lamot T, Laloux G. Chromosome choreography during the non-binary cell cycle of a predatory bacterium. *Curr Biol*. 2021;31:3707-20.

2. Laloux G. Shedding light on the cell biology of the predatory bacterium *Bdellovibrio bacteriovorus*. *Front Microbiol*. 2020;10:3136.

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

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

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

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

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

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

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

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

Jean-Paul Coutelier

1. Legrain S, Su D, Gaignage M, Breukel C, Claassens J, Brouwers C, Linssen MM, Izui S, Verbeek SJ, Coutelier J-P. Involvement of virus-induced interferon production in IgG autoantibody-mediated anemia. *Int J Mol Sci.* 2021;22:9027.

2. Gaignage M, Uyttenhove C, Jones LL, Bourdeaux C, Chéou P, Mandour MF, Coutelier J-P, Vignali DAA, Van Snick J. Novel antibodies that selectively block mouse IL-12 enable the re-evaluation of the role of IL-12 in immune protection and pathology. *Eur J Immunol.* 2021;51:1482-93.

3. Mandour M, Soe PP, Uyttenhove C, Van Snick J, Marbaix E, Coutelier J-P. Lactate dehydrogenase-elevating virus enhances natural killer cell-mediated immunosurveillance of mouse mesothelioma development. *Infect Agents Cancer.* 2020;15:30.

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

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

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

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

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

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

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

Thomas Michiels

1. Sorgeloos F, Peeters M, Hayashi Y, Borghese F, Capelli N, Drappier M, Cesaro T, Colau D, Stroobant V, Vertommen D, de Bodt G, Messe S, Forné I, Mueller-Planitz F, Collet JF, Michiels T. A case of convergent evolution: Several viral and bacterial pathogens hijack RSK kinases through a common linear motif. *Proc Natl Acad Sci USA.* 2022;119:e2114647119.

2. Cesaro T, Michiels T. Inhibition of PKR by viruses. *Front Microbiol.* 2021;12:757238.

3. Lizcano-Perret B, Michiels T. Nucleocytoplasmic trafficking perturbation induced by picornaviruses. *Viruses.* 2021;13:1210.

4. Cesaro T, Hayashi Y, Borghese F, Vertommen D, Wavreil F, Michiels T. PKR activity modulation by phosphomimetic mutations of serine residues located three aminoacids upstream of double-stranded RNA binding motifs. *Sci Rep.* 2021;11:9188.

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

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

7. Sayed IM, Verhoye L, Cocquere L, Abravanel F, Foquet L, Montpellier C, Debing Y, Farhoudi A, Wychowski C, Dubuisson J, Leroux-Roels G, Neyts J, Izopet J, Michiels T, Meuleman P. Study of hepatitis E virus infection of genotype 1 and 3 in mice with humanised liver. *Gut.* 2017;66: 920-9.

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

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

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

Jean-Christophe Renaud & Laure Dumoutier

1. Michiels C, Puigdevall L, Cochez P, Achouri Y, Cheou P, Hendrickx E, Dauguet N, Blanchetot C, Dumoutier L. A targetable, noncanonical signal transducer and activator of transcription 3 activation induced by the Y-less region of IL-22 receptor orchestrates imiquimod-induced psoriasis-like dermatitis in mice. *J Invest Dermatol.* 2021;141:2668-78.

2. La Sala G, Michiels C, Kükenshöner T, Brandstoetter T, Maurer B, Koide A, Lau K, Pojer F, Koide S, Sexl V, Dumoutier L, Hantschel O. Selective inhibition of STAT3 signaling using monobodies targeting the coiled-coil and N-terminal domains. *Nat Commun.* 2020;11:4115.

3. de Heusch M, Steenwinckel V, Cochez PM, Louahed J, Warnier G, Lemaire MM, Renaud J-C, Dumoutier L. IL-9 exerts biological function on antigen-experienced murine T cells and exacerbates colitis induced by adoptive transfer. *Eur J Immunol.* 2020;50:1034-43.

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

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

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

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

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

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

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

Emile Van Schaftingen & Maria Veiga-da-Cunha

1. Morava E, Schatz UA, Topping PM, Abbott MA, Baumann M, Brasch-Andersen C, Chevalier N, Dunkhase-Heinl U, Flegler M, Haack TB, Nelson S, Potelle S, Radenkovic S, Bommer GT, Van Schaftingen E, Veiga-da-Cunha M. Impaired glucose-1,6-biphosphate production due to bi-allelic PGM2L1 mutations is associated with a neurodevelopmental disorder. *Am J Hum Genet.* 2021;108:1151-60.

2. Kentache T, Thabault L, Deumer G, Haufroid V, Frédérick R, Linster CL, Peracchi A, Veiga-da-Cunha M, Bommer GT, Van Schaftingen E. The metalloprotein YhcH is an anomerase providing N-acetylneuraminate aldolase with the open form of its substrate. *J Biol Chem* 2021;296:100699.

3. Wortmann SB, Van Hove JLK, Derks TGJ, Chevalier N, Knight V, Koller A, Oussoren E, Mayr JA, van Spronsen FJ, Lagler FB, Gaughan S, Van Schaftingen E, Veiga-da-Cunha M. Treating neutropenia and neutrophil dysfunction in glycogen storage disease type Ib with an SGLT2 inhibitor. *Blood.* 2020;136:1033-43.

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

5. Bommer GT, Van Schaftingen E, Veiga-da-Cunha M. Metabolite repair enzymes control metabolic damage in glycolysis. *Trends Biochem Sci.* 2020;45:228-43.

6. Kentache T, Thabault L, Peracchi A, Frédérick R, Bommer GT, Van Schaftingen E. The putative *Escherichia coli* dehydrogenase YjhC metabolises two dehydrated forms of N-acetylneuraminate produced by some sialidases. *Biosci Rep.* 2020;40:BSR20200927.

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

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

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

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

Guido Bommer

1. Clerbaux LA, Schultz H, Roman-Holba S, Ruan DF, Yu R, Lamb AM, Bommer GT, Kennell JA. The microRNA miR-33 is a pleiotropic regulator of metabolic and developmental processes in *Drosophila melanogaster*. *Dev Dyn.* 2021;250:1634-50.

2. Dewulf JP, Paquay S, Marbaix E, Achouri Y, Van Schaftingen E, Bommer GT. ECHDC1 knockout mice accumulate ethyl-branched lipids and excrete abnormal intermediates of branched-chain fatty acid metabolism. *J Biol Chem.* 2021;297:101083.

3. Morava E, Schatz UA, Topping PM, Abbott MA, Baumann M, Brasch-Andersen C, Chevalier N, Dunkhase-Heinl U, Flegler M, Haack TB, Nelson S, Potelle S, Radenkovic S, Bommer GT, Van Schaftingen E, Veiga-da-Cunha M. Impaired glucose-1,6-biphosphate production due to bi-allelic PGM2L1 mutations is associated with a neurodevelopmental disorder. *Am J Hum Genet.* 2021;108:1151-60.

4. Ury B, Potelle S, Caligiore F, Whorton MR, Bommer GT. The promiscuous binding pocket of SLC35A1 ensures redundant transport of CDP-ribitol to the Golgi. *J Biol Chem.* 2021;296:100789.

5. Kentache T, Thabault L, Peracchi A, Frédérick R, Bommer GT, Van Schaftingen E. The putative *Escherichia coli* dehydrogenase YjhC metabolises two dehydrated forms of N-acetylneuraminate produced by some sialidases. *Biosci Rep.* 2020;40:BSR20200927.

6. Bommer GT, Van Schaftingen E, Veiga-da-Cunha M. Metabolite repair enzymes control metabolic damage in glycolysis. *Trends Biochem Sci.* 2020;45:228-43.

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

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

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

10. Gerin I, Ury B, Breloy I, Bouchet-Seraphin C, Bolsée J, Halbout M, Graff J, Vertommen D, Muccioli GG, Seta N, Cuisset JM, Dabaj I, Quijano-Roy S, Grahn A, Van Schaftingen E, Bommer GT. ISPD produces

CDP-ribitol used by FKTN and FKRP to transfer ribitol phosphate onto α -dystroglycan. *Nat Commun.* 2016;7:11534.

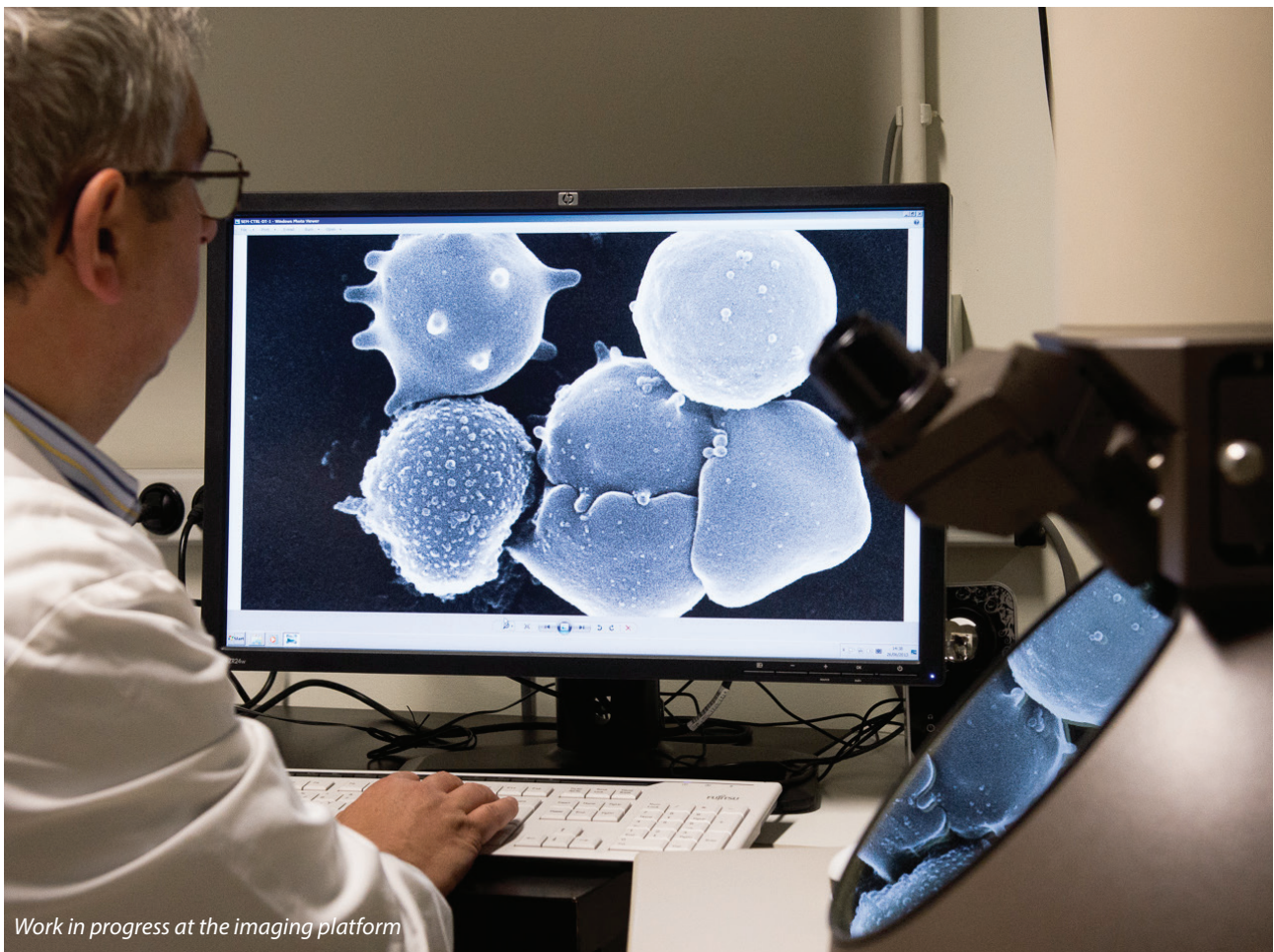
Mark Rider

1. Chuang S-J, Johanns M, Pyr dit Ruys S, Steinberg GR, Kemp BE, Viollet B, Rider MH. AMPK activation by SC4 inhibits noradrenaline-induced lipolysis and insulin-stimulated lipogenesis in white adipose tissue. *Biochem J.* 2021;478:3869-89.
2. Muffels IJJ, Wiame E, Fuchs SA, Massink MPG, Rehmann H, Musch JLI, Van Haften G, Vertommen D, van Schaftingen E, van Hasselt PM. NAA80 bi-allelic missense variants result in high-frequency hearing loss, muscle weakness and developmental delay. *Brain Commun.* 2021;3:fab256.
3. Hussain N, Chuang S-J, Johanns M, Vertommen D, Steinberg GR, Kemp BE, Rider MH. Effects of PKB/Akt inhibitors on insulin-stimulated lipogenesis and phosphorylation state of lipogenic enzymes in white adipose tissue. *Biochem J.* 2020;477:1373-89.
4. Perrin F, Papadopoulos N, Suelves N, Opsomer R, Vadukul DM, Vrancx C, Smith SO, Vertommen D, Kienlen-Campard P, Constantinescu SN. Dimeric transmembrane orientations of APP/C99 regulate γ -secretase processing line impacting signaling and oligomerization. *iScience.* 2020;23:101887.
5. Johanns M, Kviklyte S, Chuang S-J, Corbeels K, Jacobs R, Schakman O, Duparc T, Cani PD, Bouzin C, Andersén H, Bohlooly-Y M, Van der Schueren B, Oscarsson J, Rider MH. Genetic deletion of soluble 5'-nucleotidase II reduces body weight gain and insulin resistance induced by a high-fat diet. *Mol Genet Metab.* 2019;126:377-87.
6. Choumessi AT, Johanns M, Beaufoy C, Herent MF, Stroobant V, Vertommen D, Corbet C, Jacobs R, Herinckx G, Steinberg GR, Feron O, Quetin-Leclercq J, Rider MH. Two isoprenylated flavonoids from *Dorstenia psilurus* activate AMPK, stimulate glucose uptake, inhibit glucose production and lower glycemia. *Biochem J.* 2019;476:3687-704.
7. Herinckx G, Hussain N, Opperdoes FR, Storey KB, Rider MH, Vertommen D. Changes in the phosphoproteome of brown adipose tissue during hibernation in the ground squirrel, *Ictomys tridecemlineatus*. *Physiol Genomics.* 2017;49:462-72.
8. Houddane A, Bultot L, Novellasdemunt L, Johanns M, Gueuning M-A, Vertommen D, Coulie PG, Bartrons R, Hue L, Rider MH. Role of Akt/PKB and PFKFB isoenzymes in the control of glycolysis, cell proliferation and protein synthesis in mitogen-stimulated thymocytes. *Cell Signal.* 2017;34:23-37.
9. Kviklyte S, Vertommen D, Yerna X, Andersén H, Xu X, Gailly P, Bohlooly-Y M, Oscarsson J, Rider MH. Effects of genetic deletion of soluble 5'-nucleotidases NT5C1A and NT5C2 on AMPK activation and nucleotide levels in contracting mouse skeletal muscles. *Am J Physiol Endocrinol Metab.* 2017;313:E48-62.
10. Johanns M, Lai Y-C, Hsu M-F, Jacobs R, Vertommen D, Van Sande J, Dumont JE, Woods A, Carling D, Hue L, Viollet B, Foretz M, Rider MH. AMPK antagonizes hepatic glucagon-stimulated cyclic AMP signalling via phosphorylation-induced activation of cyclic nucleotide phosphodiesterase 4B. *Nat Commun.* 2016;7:10856.

Etienne Marbaix & Patrick Henriet

1. Thieffry C, Van Wynendaele M, Aynaci A, Maja M, Dupuis C, Lorient A, Marbaix E, Henriet P. AG-205 upregulates enzymes involved in cholesterol biosynthesis and steroidogenesis in human endometrial cells independently of PGRMC1 and related MAPR proteins. *Biomolecules.* 2021;11:1472.
 2. Johanns M, Lemoine P, Janssens V, Grieco G, Moestrup SK, Nielsen R, Christensen EI, Courtoy PJ, Emonard H, Marbaix E, Henriet P. Cellular uptake of proMMP-2:TIMP-2 complexes by the endocytic receptor megalin/LRP-2. *Sci Rep.* 2017;7:4328.
 3. Henriet P, Mon KS, Marbaix E. Are matrix metalloproteinases and their inhibitors reliable diagnosis biomarkers and attractive therapeutic targets in endometriosis?. *Metalloproteinases Med.* 2016;3:81-92.
 4. Coudyzer P, Lemoine P, Po C, Jordan BF, Van Der Smissen P, Courtoy PJ, Henriet P, Marbaix E. Induction of post-menstrual regeneration by ovarian steroid withdrawal in the functionalis of xenografted human endometrium. *Hum Reprod.* 2015;30:1156-68.
 5. Coudyzer P, Lemoine P, Jordan BF, Gallez B, Galant C, Nisolle M, Courtoy PJ, Henriet P, Marbaix E. Hypoxia is not required for human endometrial breakdown or repair in a xenograft model of menstruation. *FASEB J.* 2013;27:3711-9.
 6. Gaide Chevronnay HP, Selvais C, Emonard H, Galant C, Marbaix E, Henriet P. Regulation of matrix metalloproteinases activity studied in human endometrium as a paradigm of cyclic tissue breakdown and regeneration. *Biochim Biophys Acta.* 2012;1824:146-56.
 7. Selvais C, D'Auria L, Tyteca D, Perrot G, Lemoine P, Troeberg L, Dedieu S, Noël A, Nagase H, Henriet P, Courtoy PJ, Marbaix E, Emonard H. Cell cholesterol modulates metalloproteinase-dependent shedding of LRP-1 (low-density lipoprotein receptor-related protein-1) and clearance function. *FASEB J.* 2011;25:2770-81.
 8. Gaide Chevronnay HP, Galant C, Lemoine P, Courtoy PJ, Marbaix E, Henriet P. Spatio-temporal coupling of focal extracellular matrix degradation and reconstruction in the menstrual human endometrium. *Endocrinology.* 2009;150:5094-105.
 9. Galant C, Berlière M, Dubois D, Verougstraete J-C, Charles A, Lemoine P, Kokorine I, Eeckhout Y, Courtoy PJ, Marbaix E. Focal expression and final activity of matrix metalloproteinases may explain irregular dysfunctional endometrial bleeding. *Am J Pathol.* 2004;165:83-94.
 10. Marbaix E, Kokorine I, Moulin P, Donnez J, Eeckhout Y, Courtoy PJ. Menstrual breakdown of human endometrium can be mimicked in vitro and is selectively and reversibly blocked by inhibitors of matrix metalloproteinases. *Proc Natl Acad Sci USA.* 1996;93:9120-5.
- ## Laurent Gatto
1. Vanderaa C, Gatto L. Replication of single-cell proteomics data reveals important computational challenges. *Exp Rev Proteomics.* 2021;18:835-43.
 2. Mulvey CM, Breckels LM, Crook O, Sanders D, Ribeiro A, Geladaki A, Christoforou A, Britovsek NK, Hurrell T, Deery MJ, Gatto L, Smith A, Lilley KS. Spatiotemporal proteomic profiling of the pro-inflammatory response to lipopolysaccharide in the THP-1 human leukaemia cell line. *Nat Commun.* 2021;12:5773.

3. Gatto L, Gibb S, Rainer J. MSnbase, efficient and elegant R-based processing and visualisation of raw mass spectrometry data. *J Proteome Res.* 2021;20:1063–9.
4. Crook OM, Geladaki A, Nightingale DJH, Vennard O, Lilley KS, Gatto L, Kirk PDW. A semi-supervised Bayesian approach for simultaneous protein sub-cellular localisation assignment and novelty detection. *PLoS Comput Biol.* 2020;16:e1008288.
5. Pollet H, Cloos AS, Stommen A, Vanderroost J, Conrard L, Paquot A, Ghodsi M, Carquin M, Léonard C, Guthmann M, Lingurski M, Vermeylen C, Killian T, Gatto L, Rider M, Pyr Dit Ruys S, Vertommen D, Vikkula M, Brouillard P, Van Der Smissen P, Muccioli GG, Tyteca D. Aberrant membrane composition and biophysical properties impair erythrocyte morphology and functionality in elliptocytosis. *Biomolecules.* 2020;10:E1120.
6. Silverman EK, Schmidt HHHW, Anastasiadou E, Altucci L, Angelini M, Badimon L, Balligand JL, Benincasa G, Capasso G, Conte F, Di Costanzo A, Farina L, Fiscon G, Gatto L, Gentili M, Loscalzo J, Marchese C, Napoli C, Paci P, Petti M, Quackenbush J, Tieri P, Viggiano D, Vilahur G, Glass K, Baumbach J. Molecular networks in Network Medicine: Development and applications. *WIREs Syst Biol Med.* 2020;12:e1489.
7. Crook OM, Gatto L, Kirk PDW. Fast approximate inference for variable selection in Dirichlet process mixtures, with an application to pan-cancer proteomics. *Stat Appl Genet Mol Biol.* 2019;18(6).
8. Petyuk VA, Gatto L, Payne SH. Reproducibility and transparency by design. *Mol Cell Proteomics.* 2019;18:S202-4.
9. Gatto L, Breckels LM, Lilley KS. Assessing sub-cellular resolution in spatial proteomics experiments. *Curr Opin Chem Biol.* 2019;48:123-49.
10. Rainer J, Gatto L, Weichenberger CX. ensemblDb: an R package to create and use Ensembl-based annotation resources. *Bioinformatics.* 2019;35:3151-3.



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 related to Next Generation Sequencing (Massive Parallel Sequencing), including bioinformatics. These techniques facilitate and speed up data analysis, 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 fluorescence, confocal, multiphoton and super-resolution microscopy, as well as a wide range of sophisticated methods of vital confocal microscopy, immunolabeling and dynamics. It is also a source of collaborations and advices, providing users 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.
[W] <http://www.deduveinstitute.be/laboratory-animals>

MASS SPECTROMETRY

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

PRIZES, AWARDS AND HONORS

Mohamad ASSI • Perdieu-Petit Prize 2021

Awarded every three years to a UCLouvain scientist for his/her work in cancer research.

Thierry BOON • Honorary doctorate from the Vrije Universiteit Brussel

Conferred in recognition of his pioneering work in cancer immunotherapy.

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

Stefan CONSTANTINESCU • President of the Federation of European Academies of Medicine (FEAM)

Stefan CONSTANTINESCU • Tytgat Prize 2021

Awarded every three years to a Belgian researcher by the Alexandre and Gaston Tytgat Foundation as a 'reward and encouragement for his/her work and research on cancer.'

Stefan CONSTANTINESCU • Professor of Cancer Signalling at the University of Oxford, United Kingdom

Jean-Paul COUTELIER • Honorary Professor at the University of Rwanda

Laurent GATTO • Bioconductor Award 2021

Granted every year to four awardees for outstanding contributions to the Bioconductor project and community.

Patrick JACQUEMIN • Matthys-Bove Prize 2021

Awarded every four years to a UCLouvain scientist for an important contribution to the prevention, treatment or pathophysiology of serious illnesses.

Géraldine LALOUX • Member of the Board of Directors of the Belgian Society for Microbiology

Géraldine LALOUX, Wen-Hui LIEN & Sophie LUCAS • Nominated by the FNRS to the AcademiaNet network as part of 20 outstanding female researchers from the Wallonia-Brussels Federation

Selection based on outstanding scientific qualifications, remarkable academic credentials and independent leadership.

Sophie LUCAS • Francqui Chair 2020-2021 - Faculty of Medicine, University of Namur

Attributed every year by the Francqui Foundation to a Belgian professor invited by another Belgian university to give a 10-h teaching.

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

Miikka VIKKULA • Member of the Medical Scientific Advisory Committee of the Lymphangiomatosis & Gorham's Disease Alliance

Miikka VIKKULA • Member of the Board of Directors of the International Society for the Study of Vascular Anomalies

PHD THESES

Xuhao ZHANG • *Role of GARP in regulating autoimmunity and immune responses to infection or protein immunisation* • Promoter: S. Lucas

Christopher LANG • *Investigating the roles of ROR2 in mouse skin tumorigenesis and its clinical relevance with human skin tumors* • Promoter: W.-H. Lien

Alix DEVAUX • *Recherche de lymphocytes T CD8 spécifiques des cellules tumorales dans les carcinomes canauxiaux in situ du sein* • Promoter: P. Coulie, co-promoter: J. Carrasco

Raquel RODRIGUEZ ALONSO • *New insights into the β -Barrel Assembly Machinery mechanism and its interaction with the stress sensor lipoprotein RcsF in Escherichia coli* • Promoter: J.-F. Collet

Emna OUNI • *From in-depth human ovary characterization toward a biomimetic artificial ovary* • Promoter: C. Andrade Amorim, co-promoter: D. Vertommen

Teresa CESARO • *PKR regulation by phosphorylation and antiviral activity of the PKR-ADAR1 axis* • Promoter: T. Michiels

Sara LECOMTE • *GARP-dependent TGF- β 1 activation in myeloproliferative neoplasms: a new therapeutic target* • Promoter: S. Lucas

Arina KOZLOVA • *Design, synthesis and evaluation of original 1-H-indol-3-yl heterocyclic derivatives as tryptophan 2,3-dioxygenase inhibitors* • Promoter: R. Frédéric, co-promoter: B. Van den Eynde

Charlotte BERTRAND • *Multiple modes of action for antibodies targeting GARP-expressing cells in tumors* • Promoter: S. Lucas

Sheng-Ju CHUANG • *Role of AMP-activated protein kinase (AMPK) in metabolic control in white adipose tissue* • Promoter: M. Rider

Violette FERRARI • *Étude de la présentation d'antigènes de classe I : compréhension des mécanismes d'épissage peptidique sur base de l'étude de l'apprêtement d'antigènes tumoraux épissés par les 4 sous-types de protéasome* • Promoter: B. Van den Eynde, co-promoter: N. Vigneron

Benoît URY • *Function and biogenesis of ribitolphosphorylation, a novel posttranslational modification of glycoproteins* • Promoter: G. Bommer

Jessica EL-RAYES • *New insights into the journey of lipoproteins in the cell envelope of Escherichia coli: disorder matters* • Promoter: J.-F. Collet

Simon KLAESSENS • *Tryptophan 2,3-dioxygenase stability is the main checkpoint of tryptophanemia* • Promoter: B. Van den Eynde, co-promoter: E. De Plaen

Damien NEYENS • *HELIOS is a marker of HLA-E-restricted CD8 T cells with an atypical cytokine production profile* • Promoter: P. van der Bruggen

Nassim HOMAYUN SEPEHR • *Identification of genetic causes and molecular mechanisms in lymphatic anomalies* • Promoter: M. Vikkula, co-promoter: P. Brouillard

LECTURES & SCIENTIFIC EVENTS

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

Gregory FETTWEISS • *National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*
Quantitative microscopy and genomic methods synergize to reveal how transcription factors stimulate enhancer-promoter looping

Emilie DUPRE • *Centre de Recherche en Cancérologie et Immunologie Nantes Angers, University of Nantes, France*
A novel strategy to identify antigens for cancer immunotherapy: peptides from long non-coding RNAs

Marie-Pierre BOUSQUET • *Institut de Pharmacologie et de Biologie Structurale, University of Toulouse, France*
Understanding the structure-function relationships of proteasome using modern mass spectrometry approaches

François FOULQUIER • *Structural and Functional Glycobiology Unit, University of Lille, France*
Insights into the regulation of Golgi glycosylation by ions

Ward CELUS • *VIB Center for Cancer Biology, University of Leuven, Belgium*
PlexinA4 mediates cytotoxic T cell trafficking and exclusion in cancer

Denis MIGLIORINI • *Center for Translational Research in Onco-Hematology, University of Geneva, Switzerland*
Overcoming challenges in CAR-T cells for brain tumors

Etienne MEYLAN • *Jules Bordet Institute & Institute for Molecular Biology and Medicine, Université Libre de Bruxelles, Belgium*
Metabolic perturbations in lung cancer: from tumor cells to tumor-associated neutrophils

PhD Day

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

DE DUVE INSTITUTE

Directorate

Benoit Van den Eynde, Director
Jean-François Collet
Sophie Lucas
Miikka Vikkula

General Services

Administration

Pierre-Olivier Seroen (Finance & Administration Manager) • Isabelle de Duve and Andréa Soubry (External Relations) • Francisca Voermans (Research Project Coordinator) • Nathalie Krack (Administrative Coordinator) • Julie Klein and Geneviève Schoonheydt (Administrative Assistants) • Marjorie Decroly, Carine Lemoine, Francine Sakalala Ndilu, Djamila Taimount (Accounting Support)

Informatics Support

Jean-Pierre Szikora and Jacques Vanclève

Technical Support

Alain Buisseret (Manager) • Freddy Abrassart, Aurélie Boiteau, Dan Coman, Philippe Coopman, Samira Jebari, Olivier Maes, Pascale Mahieu-Gaudy, Nora Mrini, Ouadih Nechar, Danny Plessiet, Keoprasith Souvannaraj, Marcos Suarez (Technical Assistants)

Board of Directors

Luc Bertrand (Chairman) • Alexia Autenne • Vincent Blondel • Thierry Boon-Falleur • François Casier • Etienne Davignon • Frédéric Houssiau • Jean-Christophe Renault • Jacques van Rijckevorsel • Emile Van Schaftingen

Scientific Council

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

LUDWIG CANCER RESEARCH

Director

Benoit Van den Eynde

Research Groups

Stefan Constantinescu
Benoit Van den Eynde

Support

Pierre-Olivier Seroen (Administrator) • Francine Sakalala Ndilu (Accounting)



B1.74.03
Avenue Hippocrate 74
B-1200 Brussels, Belgium
[T] +32 (2) 764 74 59
[F] +32 (2) 764 75 73

SUPPORTING ORGANIZATIONS



Académie de Recherche et d'Enseignement Supérieur



Cystinosis Research Foundation, USA



European Commission



European Research Council



Fédération Wallonie-Bruxelles



Fondation contre le Cancer



Fondation Louvain



Fondation Roi Baudouin



Fondation Saint-Luc



Fondation Salus Sanguinis



Fonds Baillet Latour



Fonds de soutien Marguerite-Marie Delacroix



Fonds Jacques Goor



Fonds Joseph Maisin



Fonds National de la Recherche Scientifique



Fonds Wetenschappelijk Onderzoek



Les avions de Sébastien



Loterie Nationale



Ludwig Cancer Research



Lymphatic Malformation Institute, USA



National Institutes of Health, USA



Nederlandse Organisatie voor Wetenschappelijk Onderzoek



Région Wallonne



Télévie



Université catholique de Louvain

WELBIO Laboratories



walloon excellence in life sciences and biotechnology

Guido Bommer	41
Jean-François Collet	34
Stefan Constantinescu	17
Pierre Coulie	20
Sophie Lucas	21
Benoit Van den Eynde	22
Pierre van der Bruggen	23
Miikka Vikkula	27

PRIVATE FUNDING

M. & Mme Ch. Adriaenssen • M. & Mme M. Alloo • Association du Petit Papillon • M. & Mme B. Auxenfans • M. & Mme L. Badin • M. & Mme P. Battard • M. & Mme P. Bérend • Baron & Baronne L. Bertrand • M. & Mme J.-E. Bertrand • Mme Th.-M. Bordot • M. & Mme J.-N. Bossé • M. & Mme M. Carlier • M. F. Casier • M. & Mme J. Castillo • M. & Mme J. Coppée • M. & Mme D. Dalibot • Comte & Comtesse H. d'Ansembourg • Comte E. d'Avignon • Comte & Comtesse V. d'Avignon • M. & Mme A. De Beir • M. M. Debekker • Vicomte H. de Biolley • M. & Mme A. de Buck van Overstraeten • M. J.-M. de Buck van Overstraeten • M. & Mme Decottignies • Mme C. de Duve • M. & Mme L. de Duve • M. & Mme O. de Duve • Mme P. de Jong • Baron & Baronne J. Delen • M. & Mme M. Delloye • Pr & Mme P. De Meyts • Mme S. de Mol-Thorn • Mme A. De Plaen • M. & Mme F. De Poorter • Baron & Baronne H. de Radiguès de Chennevière • Mme M. De Ridder • M. & Mme L. De Roover • M. & Mme P. De Smet • Vicomte & Vicomtesse N. de Spoelberch • Baron & Baronne G. de Vaucleroy • M. & Mme J. de Vaucleroy • M. & Mme A. Dieryck • Mme M.-C. Donnet • Mme A. Doret • Comte & Comtesse F. du Chastel • M. & Mme J.-L. Duplat • Fondation Haas-Teichen • Fonds Maurange • M. & Mme B. Godefroid • M. & Mme L. Hayem • M. & Mme O. Homans • M. E. Hublet • M. N. Jacquemin • Mme E. Janssen • M. & Mme D. Lanckswert • M. & Mme J.-P. Lutgen • M. & Mme S. Mahieu • M. A. Mercx • Baron & Baronne D. Moorkens • Mme E. Morel de Boucle St-Denis • M. H. Mottart • M. & Mme Y. Overdick • Baron & Baronne Ch.-A. Peers de Nieuwburgh • Baronne Peterbroeck • M. & Mme M. Peterbroeck • M. & Mme J. Peters • Dr F. Robert • M. B. Rosier • M. A. Siaens • M. & Mme B. Sibille • M. D. Solvay • M. S. Sonnevile • M. & Mme

J.-C. Staquet • M. & Mme Th. Storme • M. & Mme E. Struye de Swielande • Mme C. Swenden • M. & Mme E. van Baren • Dr & Mme N. van Baren • Mme J. Van Cauwenberghe • M. & Mme L. van de Werve de Schilde • Pr & Mme B. Van den Eynde • Baron & Baronne J. van Rijckevorsel • Pr & Mme E. Van Schaftingen • M. & Mme G. Van Velthoven • M. & Mme Th. van Zuylen • M. & Mme C. Vanderhaeghe • M. B. Vanderschueren • vzw Céleste • M. & Mme P. Wailliez • M. & Mme B. Waucquez • M. & Mme P. Weerts • M. P. Willaert • M. I. Zatalovski • Mme A. Zenebergh • M. & Mme D. Zenner

CORPORATE FUNDING

ACKERMANS & VAN HAAREN • ADM • ALCOGROUP • BANQUE DEGROOF PETERCAM • BANQUE DELEN • ITEOS THERAPEUTICS • KABELWERK EUPEN • LHOIST • SAP

STEERING COMMITTEE OF THE DEVELOPMENT & EXPANSION COUNCIL

Baron Bertrand, Chairman

Members

Dorothee Cardon de Lichtbuer • Pierre Coulie • Yolande de Crayencour • Isabelle de Duve • Olivier de Duve • Vincianne Delvigne • Olivia de Schorlemer • Sophie Lammerant • Jean-Marc Legrand • Irène Mathieu • Axelle Peers de Nieuwburgh • Juliette Siaens • Andréa Soubry • Olivier Terlinden • Georges Van den Berghe • Benoit Van den Eynde • Emile Van Schaftingen • Miikka Vikkula



ACKNOWLEDGEMENTS

In 2021, de Duve Institute has attracted major donations 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. Donations 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 2021, the Institute has been able to allocate the following fellowships, entirely supported by our donors:

the 'Haas-Teichen' fellowship to Frédéric Sorgeloos (back from the United Kingdom),

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

a de Duve fellowship to Laurie Thouvenel (France),

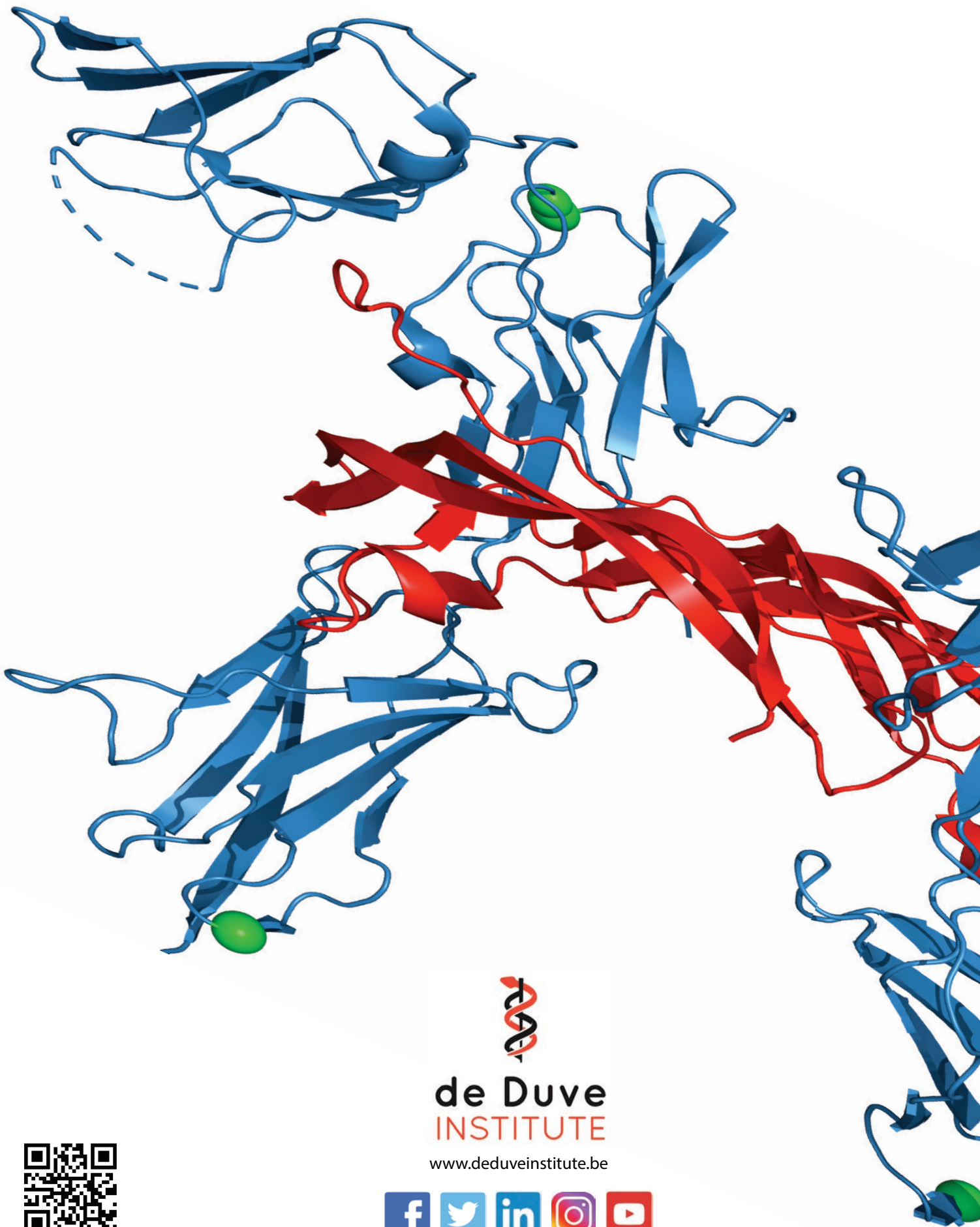
a second de Duve fellowship to Ilianna Zoi (Greece),

and a third de Duve fellowship to Sander Govers (back from the USA), followed by Emilie Dupré (France).

In addition to their support for a postdoctoral fellow, the Maurange Fund also enabled the acquisition of cutting-edge equipment for Pierre van der Bruggen'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



de Duve
INSTITUTE

www.deduveinstitute.be

