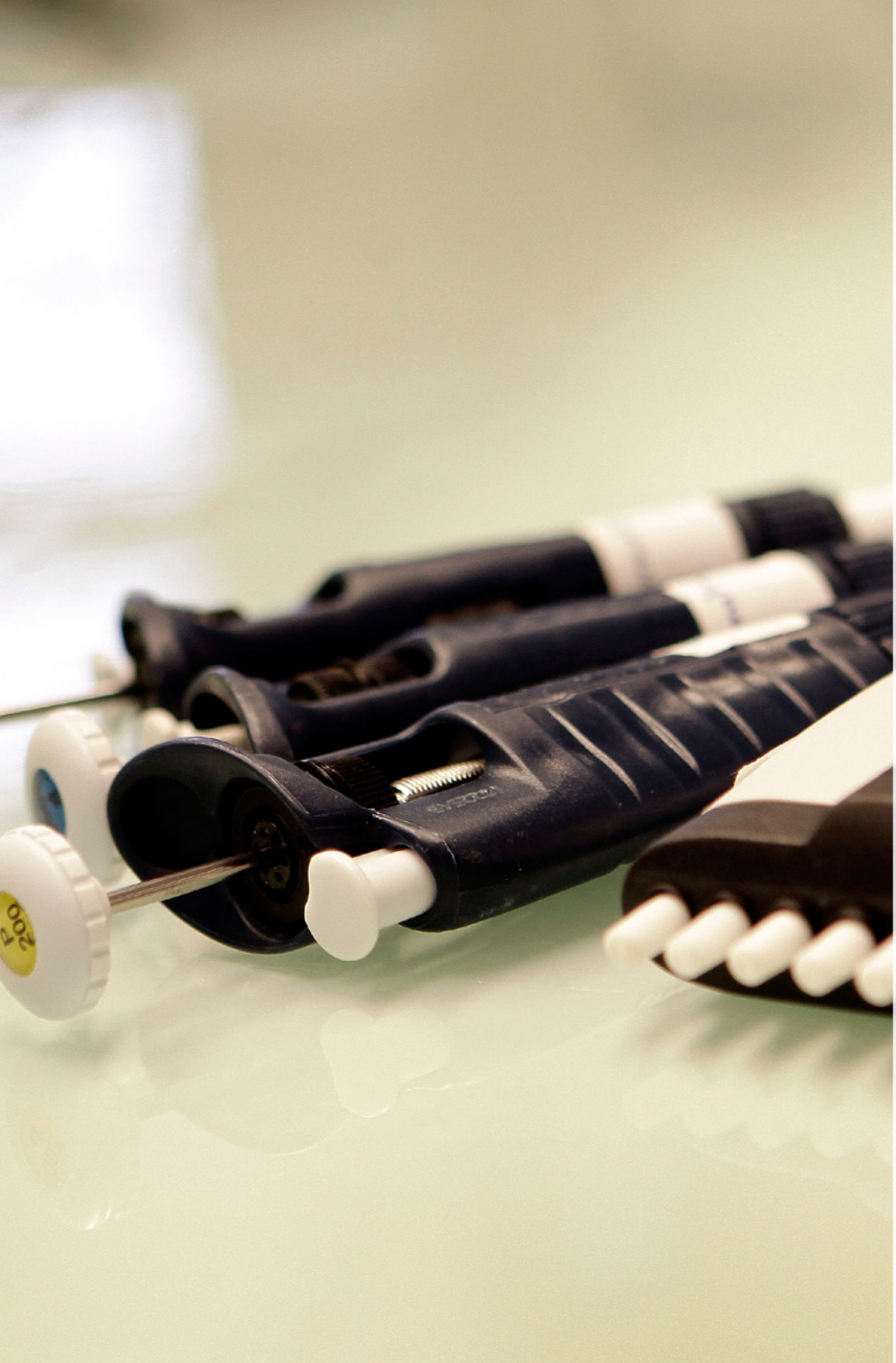


BIOPARK
CHARLEROI BRUSSELS SOUTH

# news

## The Biopark Charleroi Brussels South Newsletter

n°26 — summer 2015

## New research projects



ULB

UMONS
Université de Mons

# Mood

The fundamental research being carried out today will have a huge impact on the future. But it needs time, freedom, and funding if its creativity and excellence are to shine through.

And these resources are lacking, even if the authorities granting subsidies remain generous in these trying economic times.

The FNRS, which employs 2300 researchers, is receiving a growing number of researcher and funding applications. The international scientific commissions that assess applications are faced with difficult decisions when compiling the final rankings, so high is the quality of projects while there is only funding for 20% of them.

This means that the distribution of funding must be carefully balanced between eminent researchers and the fundamental research that will produce new fields of inquiry and cutting edge teams.

Effective applied research, which makes social and economic progress possible, must be built upon excellence in fundamental research to produce results that are tangible in the real world. Should we remain confident that funding will rise in the future?

*Véronique Halloin*
*Secretary General of the FNRS*

# New ERC project: where parasitology and nephrology meet

Etienne Pays has just secured a prestigious European Research Council (ERC) grant to fund his research into the trypanosome. The project encompasses every aspect of his 40-year career.

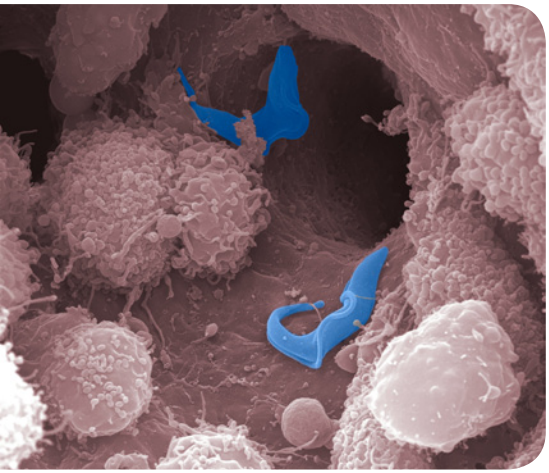
Officially retired since last October, Etienne Pays admits that he is not quite ready to leave his office: “The laboratory is overflowing with stimulating ideas, and I would be sad to leave at a time when new avenues or research are being explored”, explains the Director of the Molecular Parasitology Laboratory (IBMM). The *ERC Advanced Grant* that he has just obtained will enable him to take part in the exploration of these new fields and work on the trypanosome for a further 5 years. This blood parasite, transmitted by the bite of the tsetse fly, causes sleeping sickness in humans and has been the subject of Etienne Pays’ research for almost 40 years.

## ACCELERATED EVOLUTION

Back in 1998, the researcher and his team discovered the SRA protein that some resistant trypanosomes use to circumvent the human immune system. A few years later, in 2003, they discovered that SRA neutralises apolipoprotein-L1 (apoL1), a human protein that creates *holes* in the parasite’s membrane. They then discovered that a mutation of this protein meant that some populations in West Africa could once again fend off the trypanosome. But in resistant populations, this evolutionary advantage entailed an increased risk of renal failure caused by an autoimmune response against kidney cells on the part of the mutated

apoL1. Published in *Science* in 2010, this research established a genetic cause for kidney failure for the very first time, and to this day it is one of the most cited articles in the field of nephrology "and one of the most popular of my career", Etienne Pays adds.

Today, for his ERC project, the researcher would like to draw on all of this past research to challenge his "favourite parasite's" (as he calls it himself) capacity for adaptation. The hypothesis is ingenuous: if the trypanosome has, throughout evolution and up to the present day, managed to circumvent man's natural immune responses, it is highly likely that it will do so again. "The trypanosome is a primitive organism that adapts to its environment extremely quickly", Etienne Pays explains, "We are therefore going to subject resistant parasites to controlled and increasingly larger doses of mutated apoL1. We hope that in response to this purposefully increased pressure, some of them will manage to synthesise a new antidote to this protein".



## SEMI-RETIREMENT

If the researcher achieves his aims, the new molecule that the experiment will produce could pave the way for new treatments for kidney failure: "Currently, the SRA protein neutralises apoL1 through direct contact", he explains, "We may envisage that the new antidote will do the same against the mutated apoL1, which would impede the autoimmune response against kidney cells and therefore the disease". The idea is innovative, the project ambitious, and the sexagenarian optimistic: "I believe in the trypanosome's ability to produce something new to ensure its survival. The first results from the laboratory support this hypothesis, but it means that I will have to stay in the lab for a few years yet", he adds, smiling.

*Natacha Jordens*

## THE ROLE OF RNA POLYMERASE I

The trypanosome's ability to adapt and evolve is owed largely to the fact that certain genes whose role is to vary in order to adapt, such as those that code surface antigens or resistance proteins like SRA, are found at the end of the chromosomes, the area most likely to mutate. Curiously, it is RNA polymerase I (usually responsible for producing ribosomal RNA) that synthesises messenger RNA using these genes. This is a unique exception in nature, as this role is always performed by RNA polymerase II.

In a recent publication in *Molecular Microbiology,* the team at the Molecular Parasitology Laboratory explain the importance of this polymerase in the trypanosome's adaptation process. While parasites normally adapt in around two weeks, the process no longer works when RNA polymerase I is replaced with RNA polymerase II for the transcription of adaptive genes. Polymerase I is therefore essential to the trypanosome's rapid adaptation to its environment.

Researchers explain this with the fact that this enzyme is designed to rapidly synthesise very large quantities of RNA, making it much more efficient than RNA polymerase II. This intense activity produces major unwinding of DNA at the end of the chromosomes, providing easier access for enzymes that trigger recombination and therefore promote inventive adaptations.

*N.J.*

# Revealing the nucleolus “brick by brick”

Denis Lafontaine and Birthe Fahrenkrog are focusing on ribosomes and nuclear pore complexes as part of their nucleolus "ARC" project. Why? The nucleolus is a powerful biomarker of disease and a target for the treatment of cancers.

## WHAT IS THE FNRS?

PhD candidates, post doc students, and researchers... a great many scientists on the Biopark receive valuable support from the Fund for Scientific Research (FNRS), either directly or as part of Télévie. The FNRS also funds equipment and research projects.

Human resources and facilities that are often an extremely useful addition to projects already funded through other channels.

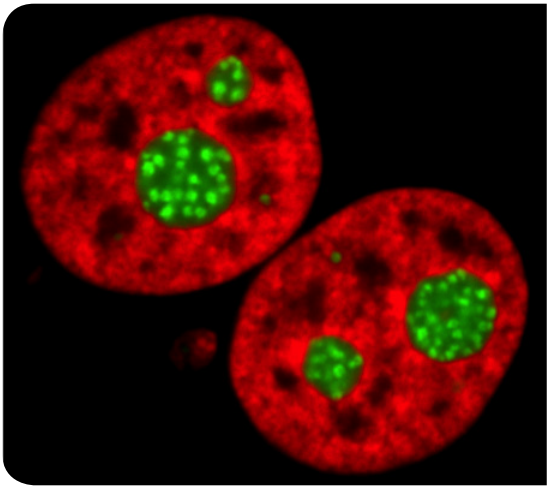
This is the case with the two “Collective Research Initiatives” (ARC) presented opposite: funded by the *Fédération Wallonie-Bruxelles,* one (Advanced) is coordinated by Denis Lafontaine, Director of Research at the FNRS, in partnership with Birthe Fahrenkrog, while the other (Consolidation), directed by Benoît Vanhollebeke, is also funded by an FNRS Incentive Grant for Scientific Research.

*N.G.*

“We can tell if a cell is healthy or not by looking at the morphology of the nucleolus, which is one of its components”, explains Denis Lafontaine (RNA Metabolism Laboratory – IBMM). “The size, shape, and even the number of nucleoli within a cell vary greatly. These three criteria are valuable indicators of the physiological state of our cells”. In practice, however, it remains difficult to use this information owing to the lack of robust clinical testing.

Researchers are now going to dismantle the nucleolus “brick by brick” to better understand the relationship between its structure and its function. “We already know what makes up the nucleolus”, Denis La Fontaine continues. “To learn more, we will use our robotic microscope to analyse the nucleolus’ morphology when each component is removed. The robotic microscope is a high bandwidth screening platform designed by our laboratory as part of an ERDF project, and illustrates my involvement in founding the CMMI”.

In parallel, Birthe Fahrenkrog (Biology of the Nucleus Laboratory – IBMM) is looking into nuclear pores, the small windows in the nucleus that manage the exchange of components within the cell. “One of the aims is to understand why some parts of the nuclear pore become diseased within the nucleolus”, the researcher explains. “Eventually, this research could help us to better understand the relationship between the structure of the nucleolus and disease, and cancer in particular”.



*Damiano Di Stazio*

From 19-23 August, Brussels will host the 10th European Molecular Biology Organization (EMBO) conference on ribosome synthesis.

Learn more: : http://events.embo.org/15-ribosomes/

# Cerebral vascular biology

Benoit Vanhollebeke's team, with support from an "ARC" funding, is investigating the blood vessels of the brain. The latest results of his research have been published in *eLife*.

Blood vessels in the brain need to solve a tricky equation: supplying billions of neurons with oxygen and nutrients, while preventing potentially toxic compounds and cells carried by the blood from entering the brain, thereby maintaining cerebral homeostasis and reliable synaptic communications.

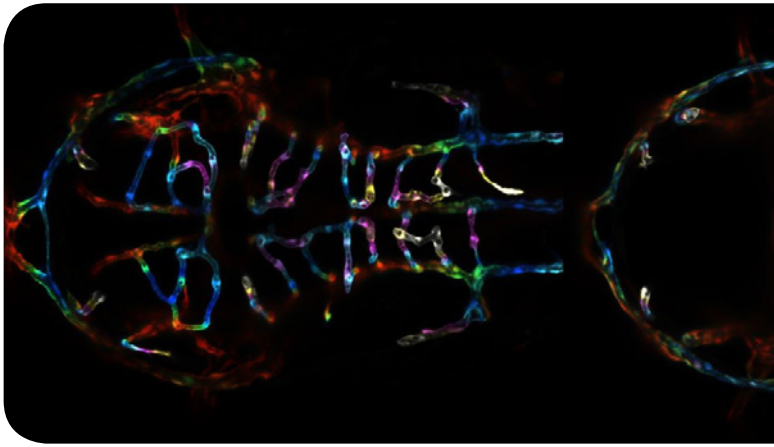
The evolutionary solution that succeeded in vertebrates is to provide endothelial cells with an array of protective characteristics known as the blood-brain barrier. This barrier represents a major clinical challenge: many neurological diseases (such as neurodegenerative diseases, strokes, and some cancers) have neurovascular components.

The key to cerebral vascular homeostasis is based on a functional bond between the signal pathways that control blood vessels in the brain and those that govern the acquisition of blood-brain barrier properties. In the earliest stages of embryonic development, only blood vessels that have begun to mature properly can enter the brain.

"And it is the very nature of these inducing signals, as well as the way that they are identified and interpreted by endothelial cells, that we are studying in my laboratory" explains the IBMM researcher, Benoit Vanhollebeke.

## ARC PROJECT – FNRS – ULB FOUNDATION

Supported by the Fondation ULB, an FNRS Incentive Grant for Scientific Research, and a "Consolidation ARC", Benoit Vanhollebeke's laboratory stands out from other research teams in the field. "Angiogenesis is a highly dynamic process, and our studies have just revealed that the implantation of blood vessels in the brain is controlled on a cellular level", the researcher continues.



The laboratory's original approach is based on the model of the zebrafish, a transparent vertebrate that allows the cerebral angiogenic processes to be observed with unparalleled spatial and temporal resolution.

"Our research has revealed the existence of a membrane complex on the surface of the brain's blood vessels that imposes strict quality control on endothelial cells that may potentially end up in the brain. Only those expressing this complex can provide a sufficient response to the angiogenic signals derived from the brain, and initiate the formation of new blood vessels."

This research, an international partnership with the Bad Nauheim Max Planck Institute in Germany, John Hopkins University in the USA, and a Japanese team in Osaka, opens up a number or future avenues of research for the laboratory.

*Damiano Di Stazio*

# New avenues for immunology

The Immunobiology Laboratory is launching two research projects: one looking into tumoural resistance, the other into intestinal immune response and obesity.

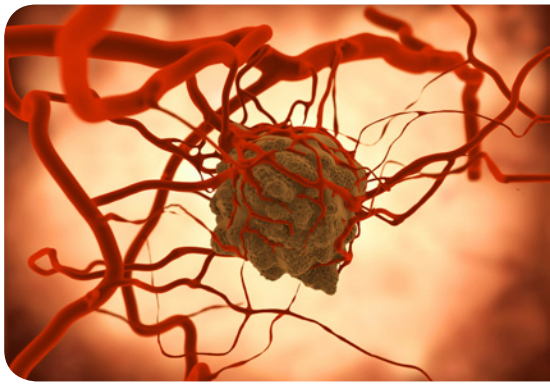

Since the first vaccination tests in the 18th century, the principles of immunology have been gradually revealing their secrets. However, there remains a lot to discover and immunology is still a field of research that presents many challenges. This is particularly true of the fight against cancer: "We know today that there is without doubt an immune response within tumours", explains Muriel Moser, Director of the Immunobiology Laboratory (IBMM), "But a number of obstacles prevent a full and effective immune response from taking place, with the result that cancer cells escape the immune system". This year the laboratory is launching a 5 year project, funded by *Fondation contre le cancer,* that will study one of these obstacles: hypoxia. "When a tumour grows quickly", Muriel Moser goes on, "there comes a point when the blood vessels are unable to reach the most distant cells. The oxygen pressure in these areas falls". The cells are then in a hypoxic state, lacking in oxygen. And yet, the tumour continues to grow. "The immune system is that most affected by hypoxia", explains the researcher, "The immune response is less effective. This prevents the tumour from being rejected. It would certainly seem to be a mechanism for escaping the immune system". In partnership with Benoît Van Den Eynde (UCL), the Immunobiology Laboratory is seeking to explore the effect of hypoxia on anti-tumoural immune responses. The aim is to discover how to block this escape mechanism and restore a fully effective immune response: "The first cancer immunotherapy tests have yielded good results, albeit less impressive than we expected", the team leader reports, "Probably due to these various obstacles. Understanding and circumventing them could be a way to improve these new treatments".

## INTESTINES AND OBESITY

Another new project launched in the last few months is *Food4Gut:* a Wallonia programme for excellence focusing on the links between the gut microbiota... and diabetes. "Type 2 diabetes is a disease often associated with obesity, and that causes insulin resistance", Muriel Moser explains, "We think that this reaction is caused by chronic inflammation, inflammation that may take place in the gut, upon contact with food". The project is run by ULB, ULg and UCL (coordinator). The general aim is to analyse the impact of certain colic nutrients on the intestinal flora and health, and to formulate a dietary strategy for reducing obesity and the associated risk of diabetes. The Immunobiology team will specifically be researching the immune response of the intestine and fat tissue in obese mice.

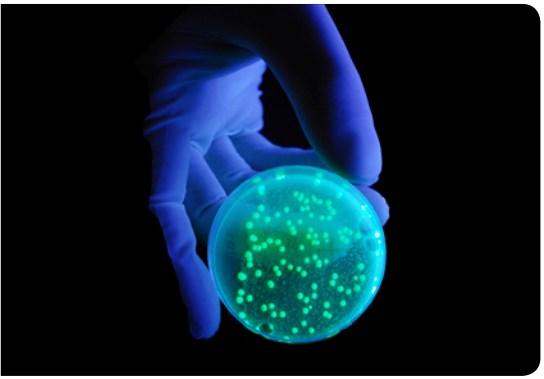
Immune cell function, cancer, diabetes, and nutrition; fundamental research today, likely to be applied tomorrow. These are new avenues for immunology, that much is sure.

*Natacha Jordens*



# Better control of bioprocesses

The Single Cells project sets out to build tools that will better control bioprocesses (for better product quality). It is backed by the Wagralim and Biowin clusters and includes a contribution from the Bacterial Genetics and Physiology Laboratory at the IBMM. The project is being run in partnership with GSK, Puratos, Delphi Genetics, and the ULg.



A number of scientific studies have shown that microbial populations, even those known as clones (genetically identical), are heterogeneous. "This heterogeneity can affect the yield and reproducibility of certain bioprocesses that use bacteria", explains Laurence Van Melderen, from the Bacterial Genetics and Physiology Laboratory at the IBMM.

To resolve this problem, GSK and Puratos, companies in the pharmaceutical and food industries, called upon the expertise Delphi Genetics and three academic research teams, including Laurence Van Melderen's laboratory. "It started with Philippe Goffin, who worked at GSK for a long time and is now part of our team", the researcher goes on. "Our role in the Single Cells project is to build and develop fluorescent biosensors that can detect 'stress' and monitor the parameters of bioprocesses in order to counteract it".

This applied research will also be of use to another academic project in the lab. "This type of project can also be of interest in fundamental research" Laurence Van Melderen specifies. "Frédéric Goormaghtigh, whose thesis is based on bacterial persistence, may also benefit from these biosensors. They will doubtless be very useful for his project, in particular for understanding the underlying physiological mechanisms of persistence".

*Damiano Di Stazio*

## "NEURON" BEWARE PROJECT

The "Neuron" BEWARE project led by Eric Bellefroid at the Developmental Genetics Laboratory (IBMM) sets out to examine neural differentiation and diversification mechanisms. The project's aim is to obtain high quality antibodies that can be used in chromatin immunopreciptation against the Myt1L, Myt1 and NZF3 transcription factors that enable non-neural cells to trans-differentiate into neurons. The research should improve our understanding of how they work, and the origins of human diseases in which these genes play a role.

*D.D.*

# Delphi Genetics & Avaxia: an international partnership

The Walloon biotechnology company Delphi Genetics and Avaxia, an American company specialising in the development of therapeutic antibodies for the treatment of intestinal inflammatory diseases, have just signed a partnership agreement. The aim? To develop effective production procedures for treating this type of disease.

"We met with Avaxia in September 2014, formulated the project in December 2014, and approved it earlier this year. It all happened very quickly!", enthuses Cédric Szpirer, Executive & Scientific Director at Delphi Genetics. Delphi Genetics and the American company Avaxia have signed a partnership agreement in a continuation of the DNAVac project, a BioWin Research & Development project intended to develop and produce antibiotic-free DNA vaccines.

"DNAVAC demonstrated that our technology can effectively remove antibiotic resistance from the DNA molecules used as a vaccine", Cédric Szpirer explains. "Thanks to this consortium, we have also gained experience of DNA immunisation procedures and antigen presentation".

## EFFICIENT PRODUCTION METHOD

The aim of the partnership? To combine the expertise of both companies in order to develop an efficient production method for a drug used to treat inflammatory intestinal diseases like Crohn's disease.

"Production begins with the immunisation of cows who then produce antibodies. These antibodies are then found in the cow's milk and boast an important property that Avaxia then exploits: when they are ingested orally, they are not digested in the patients' stomachs. Due to this, they are able to target intestinal diseases without entering the bloodstream and causing the usual side effects", explains the director of Delphi Genetics.

With its cutting edge technology, the Walloon company will work on the "immunisation" side of the project. It also hopes to increase the production of antibodies that specifically target the molecules that cause these inflammatory issues in the intestine. "What makes this project so innovative is, firstly, the immunisation of large animals like cows, and secondly the development of an original DNA production system for medium/large scale production while limiting costs", concludes Cédric Szpirer.

The aim is to demonstrate that the product (therapeutic antibodies produced in cows) works, and that there are no side effects.

*Damiano Di Stazio*

# Véronique Kiermer, *Nature* group "Publishers are partners"

Doctor of Science from the ULB, Véronique Kiermer is now Director of Author and Reviewer Services at the prestigious *Nature* group. She recently visited the Biopark, a campus that is home to many of her former colleagues.

"As I look around the room I recognise faces that I saw when defending my thesis. It's a bit intimidating", Véronique Kiermer smiles, standing at the front of an IBMM auditorium. And yet on this April afternoon, the young woman is not here to earn a degree from the Biopark, but rather to talk about her current role as Director of Author and Reviewer Services for *Nature* group.

Following her doctoral thesis in molecular biology at the ULB, Véronique Kiermer set off for America and the University of California (San Francisco), where she earned a post-doctorate certificate. She then spent two years working at an American biotechnology firm before being hired by the *Nature* group. For the past 11 years, she has been living in New York, "*Nature*'s head office is in London so I'm over there every couple of months for meetings, and with Eurostar Belgium isn't too far away so I'm often back", she reveals.

## NATURE METHODS

By the time *Nature* hired her, she was aged 32 and boasted a solid background in the lab, but knew nothing about the publishing world. "They were launching a new magazine, *Nature Methods,* and they liked my way of doing things", she recalls. Véronique likes a challenge, and the one *Nature* offered her was no mean feat: to launch a science magazine that published what was up to that point little understood: innovative "methods" and promising technology with real scientific applications, even if it was still at a stage where no scientific discovery had been made. Nine months and a few sleepless nights later, and *Nature Methods* was born. Today, the magazine has carved out its place in the scientific community, and Véronique Kiermer has been entrusted with new challenges at *Nature.*

As *Director of Author and Reviewer Services,* today her work is primarily concerned with the reproducibility of the results of experiments.

"In biomedical science, not everything is as reproducible as we would like. But we would like to improve reproducibility by being more stringent in how experiments are described: how often, for example, do we not precisely describe the stem cell we are using, which prevents us from obtaining the same result? Fraud is a very rare occurrence, but the lack of stringency we see can all too often lead to unintended biases. As a scientific publisher, we expect researchers to provide both transparent and strict descriptions of their experiments: there needs to be enough detail, enough specification so that we can interpret what has been done before we decide to publish or not", Véronique explains.

"The publisher is often seen as the judge, whereas it is really more of a partner. That's why we are always trying harder to explain why we refuse an article and suggest other journals whose editorial line may be more suitable. We are looking to turn the

researcher-publisher relationship into a partnership where each party has their own rights and responsibilities. One example of this are the online applications we are developing for use by the scientific community, such as a protocol database."

Another issue that can cause a conflict is open access. *Nature* launched *Nature Communication* (founded in 2010, 73% increase in articles published in 2014 from 2013) and *Scientific Reports* (in 2011, 62% increase) as open access journals. "No fewer than 44% of articles published by *Nature* group are published in open access", Véronique observes, "I really like the open access philosophy but as a business model it isn't suitable for everything. *Nature* uses an expensive editorial process that includes evaluations, specification deadlines, and rejections for over 90% of submitted articles. In light of these high costs, subscriptions are still the best business model".

*Nathalie Gobbe*

## WHAT DO YOU THINK OF BELGIAN RESEARCH?

### VÉRONIQUE KIERMER, YOU WERE EDUCATED AT THE ULB. WHAT DID YOU TAKE AWAY FROM THE YEARS SPENT ON YOUR PHD?

*Véronique Kiermer:* I learned strict working methods and a way of analysing situations that could be transferred to other roles and fields. Those years prepared me for the job I do today, even if I'm not working in a laboratory. I think that Doctors of Science need to continue to develop their skills and move into sectors beyond research, as do Doctors of Law, for example, who are often open to sectors beyond the Bar. A sciences doctorate gives you a lot of transferable skills that are needed in a variety of fields, as my own career shows. Today, I feel that as a publisher I am as useful to society as if I were a researcher in an academic laboratory.

### WHAT DO YOU THINK OF BELGIAN RESEARCH?

*Véronique Kiermer:* I think that for the resources allocated to them, Belgian education and research are of a very high standard. I am genuinely impressed by what is coming out of Belgian laboratories, and it is essential to invest in education and research if we are to continue producing such quality work. A lot of Belgian researches have international reputations within the scientific community, and yet when we talk about major European centres of research, Belgium isn't the first place to spring to mind.

### HOW WOULD YOU EXPLAIN THIS DIFFERENCE BETWEEN THE IMAGE AND THE REALITY?

*Véronique Kiermer:* Belgian researchers are too modest. They don't do enough to sell themselves to the general public, or maybe the Belgian media doesn't give them enough coverage and fails to promote their scientific work? In the USA or elsewhere in Europe, researchers communicate about their research, supported by media who do a good job of spreading the word, and they do well from this, it's clear to see.

*N.G.*

# In brief

## TWO SUCCESSFUL COURSES

In early April, **Biopark Training** held a symposium on "cancer immunotherapy". Organised in partnership with the *Centre de Formation Santé* at the ULB-Erasme *Pôle Santé,* the VUB and the UCL, 130 doctors and researchers came to watch 10 international experts present the most promising immunotherapy strategies, together with clinical results obtained in Belgium and surrounding countries.

A few days earlier, Biopark Training held a Master Class on European regulations and sourcing public and private partners in cell therapy. Over 15 attendees, half of whom belonged to French companies, took advantage of this opportunity to discuss these specialist subjects with the experts. Networking also proved effective and some companies are now planning to expand their businesses into Wallonia, according to Dominique Demonté, Director of the Biopark, and one of the session's attendees.

Both courses were a success, and will be repeated in the future.

*N.J.*

## TOWARDS NEW IMMUNOTHERAPIES?

Important cells for individual health, regulatory T lymphocytes nevertheless remain a mystery for immunobiologists. Maxime Dhainaut and Muriel Moser (**Immunobiology Laboratory, IBMM**) and their team have just published an article in *EMBO Journal* identifying a new control mechanism for regulatory T lymphocytes: they interact with dendritic cells via a receptor/ligand bond that is then internalised and broken down. This sequence of events is unexpected because it depends on the inter-cellular transfer of a regulatory T lymphocyte's receptor to a dendritic cell, which gradually loses its ability to induce an inflammatory response.

This is a promising discovery since the ability to control how these lymphocytes work could open up interesting new avenues for cancer immunotherapy and the treatment of autoimmune diseases, or even be used to prevent transplants being rejected. These "suppressor" lymphocytes do indeed seem to be an ideal target for "manipulating" the immune response.

*N.J.*

## CELL DEATH DIRECTED BY NAD

Programmed cell death is constantly taking place within the organism. Some die through "apoptosis", a relatively discreet natural process as it does not affect neighbouring cells nor provoke an inflammatory response. Others die by "necroptosis", a cell death process that is particularly characteristic of viral infections. In necroptosis, cells release pro-inflammatory molecules that attract blood cells and provoke a protective immune response.

In a study published recently in *Cell Death and Differentiation,* Nicolas Preyat (**Immunobiology Laboratory, IBMM**), Oberdan Leo (**IMI**) and their team showed that nicotinamide adenine dinucleotide (NAD) promotes necroptosis at the expense of apoptosis. This observation sheds light on the mechanisms that regulate the selection of cell death processes, still little understood, and enables us to envisage new treatment strategies in the fight against cancer: by promoting the accumulation of intracellular NAD, it may be possible to promote the death of tumour cells by necroptosis, thereby triggering an anti-tumour immune response.

*N.J.*

# In brief

## BONE THERAPEUTICS IN GOSSELIES AND BOSTON

Bone Therapeutics unveiled its new premises on 24 April, in a ceremony attended by Paul Magnette, Minister-President of Wallonia, and Jean-Claude Marcourt, Vice-President of the Walloon government.

The new 3000m² building will be shared with Promethera Biosciences and forms part of a larger project to create the Walloon Cell Therapy Platform. The ULB spin-off plans to gradually transfer all of its operational services to the new building: the administration and R&D departments are due to move in any day now, and will be followed by the production side in mid-2016.

Bone Therapeutics is also setting up shop in Boston as *Bone Therapeutics USA Inc.* at the Kendall Square biotechnology cluster. The world's ten largest biopharmaceutical companies are all present in Massachusetts, making it the ideal location for an initial footing across the Atlantic in terms of scientific and technological innovation. This location will enable Bone Therapeutics to accelerate its programme of clinical trials in the USA, while simultaneously bolstering its international presence.

*N.J.*

## CD8 T LYMPHOCYTES WITH INNATE MEMORY

Guardians of our good health, white blood cells have a range of different profiles with highly specific roles. This particular CD8 T lymphocyte sub-group is able to recognise and individually kill cells infected with a virus. Upon first making contact with a virus, a small piece of these lymphocytes becomes a "memory" specialist so that they can fight a second infection more effectively.

Surprisingly, CD8 T-lymphocytes can acquire the characteristics of memory cells "innately", without needing to recognise a given virus in advance. Stanislas Goriely's team at the **Institute for Medical Immunology (IMI)** has shed light on the cellular and molecular mechanisms involved in this process. Their work has enabled us to understand how infected cells may, by secreting antiviral molecules (interferons), promote the development of these innate memory cells. This study has helped us to understand how the cytotoxic role is acquired, and opens up new prospects in vaccinology.

*N.J.*

BIOPARK CHARLEROI BRUSSELS SOUTH

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