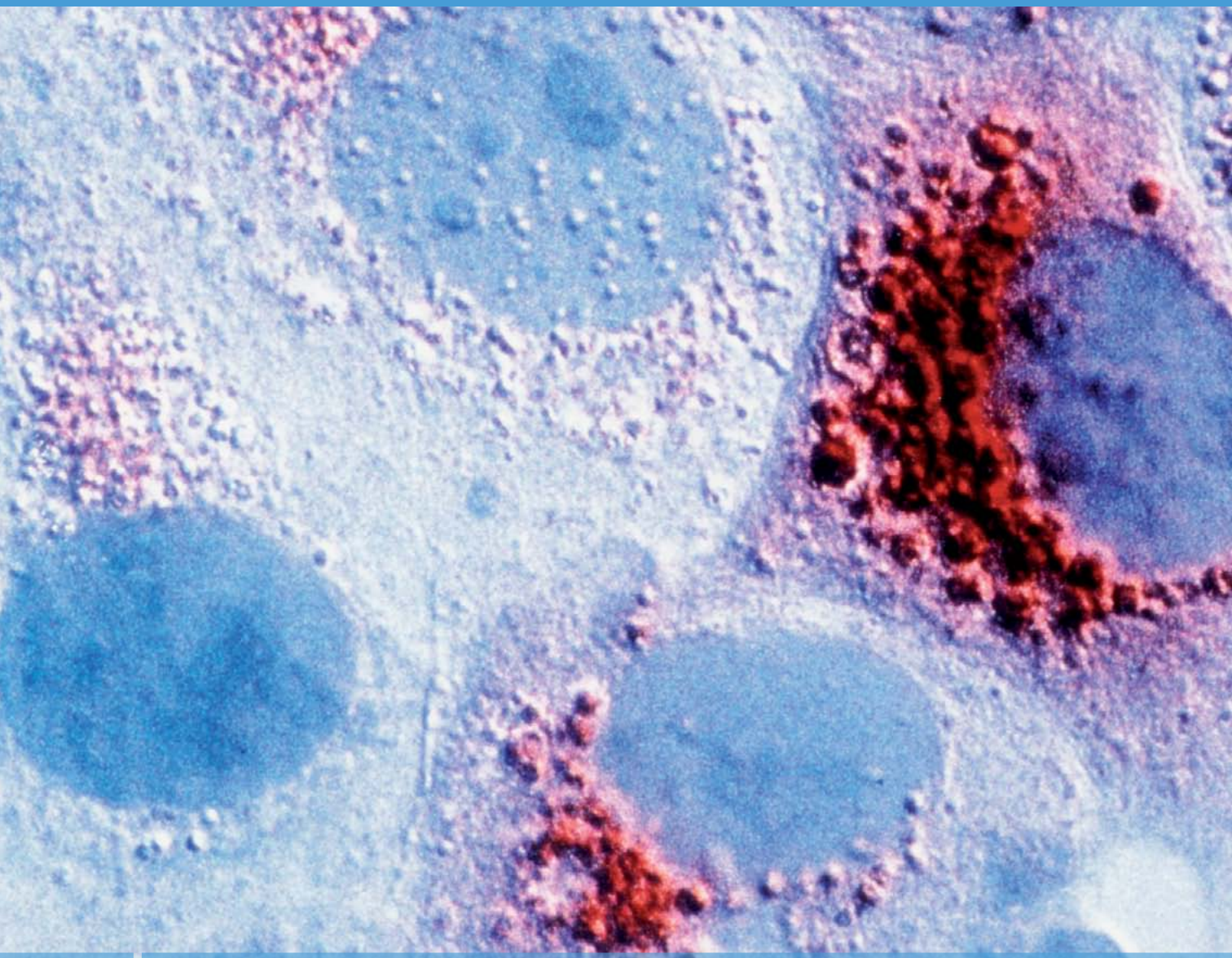
FOCUS ON ONCOLOGY | N°10 |

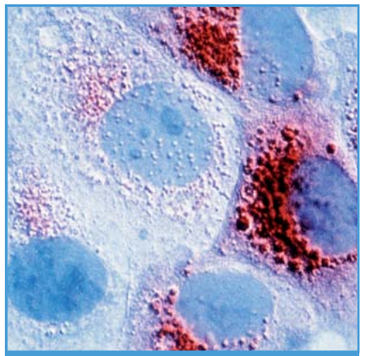
CHERCHEURS *d'Aquitaine*

The translational research magazine



ONCOSPHÈRE ›

Partnering up against cancer



COVER: Breast cancer marker
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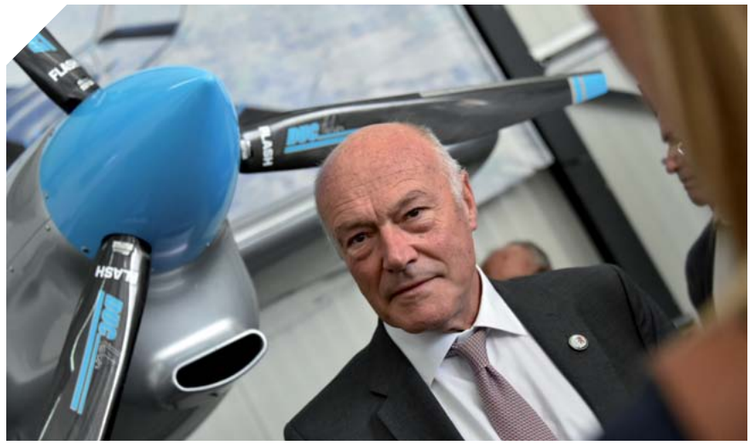


FIGHTING CANCER: A MAJOR HEALTH CHALLENGE FOR THE NOUVELLE-AQUITAINE REGION

It's a major health challenge *since the Regional Observatory of Nouvelle-Aquitaine Health (ORS) records thousands of new cases of cancer in our Region every year. The ORS is also taking a closer look at the organisation of health and society, because the burden of the treatments weighing down on patients over the long term is an additional challenge that requires rethinking the care management process.*

To meet those challenges, *oncology draws on the diversity and complementarity of the Region's fields of excellence in precision medicine, technological research, social and human sciences. Its ecosystem of scientific and economic research is extremely innovative. Some 40 regional companies currently work in the field of oncology, including 25 created or set up in the Region over the past 10 years, and 17 of them are a result of research work conducted by our Region's universities. Those figures testify to the community's substantial energy.*

The Region's ambition is to enhance that wealth and unite its strengths. Supporting scientific and technological progress will enable everyone to benefit from these innovations and position our territory as a leader in industrial, research and service sectors.

The Region has to be the crossroads – the catalyst of our territory's driving forces – to ensure the cooperation of these stakeholders.

In December 2017, the local authorities presented and voted on its health roadmap, which sets out the directions to be taken in terms of support for innovation and the competitiveness of health companies. The goal is to promote closer cooperation between so-called "hard" technologies and medicine to bring about breakthrough innovations. In 2018, the Region had already invested nearly three million euros in cancer research. The ambition is to prepare the key technologies for the challenges of tomorrow's medicine.

With that in mind, the Regional Council has boosted the creation of the regional research network named "Oncosphère" aimed at bringing together and coordinating research between the three university hospital locations in Bordeaux, Limoges and Poitiers as well as the university campuses in Pau and La Rochelle. The research can be broken down into five joint themes: tumour genesis, translational research, tumour microenvironment, technological innovations, aging and the environment.

Alain Rousset
President of the Nouvelle-Aquitaine region

UNITING FORCES FOR FASTER PROGRESS

Technological advances in recent years have ushered in a new era in cancer research. High throughput sequencing, proteomics, metabolomics, modelling, nanotechnologies and much more have opened new avenues for understanding and treating cancer better as researchers and physicians have come closer together and our information sharing capabilities have reached new levels. In this exciting context, we chose, alongside our administrative supervision and partners, to create the Oncosphère.

Our undertaking is based on strong values, those of cancerology. Collective work and daily interactions between medicine, biology, epidemiology, the social sciences and humanities are the strengths of clinical oncology. We hope to round out that interdisciplinarity based on common objectives and themes, biologists, epidemiologists, medical or technological researchers, researchers in the humanities and social sciences. In addition, we also want to be useful to patients and society in general. That is why, with hospitals, we are developing what is called translational research – research that moves the results of experimental models towards a medical application. We must go even further and rethink the relationship with patients and society by getting patients involved in our approach, particularly through the project for patients partnering up on our research themes, to help us define their orientations and interpret the findings.

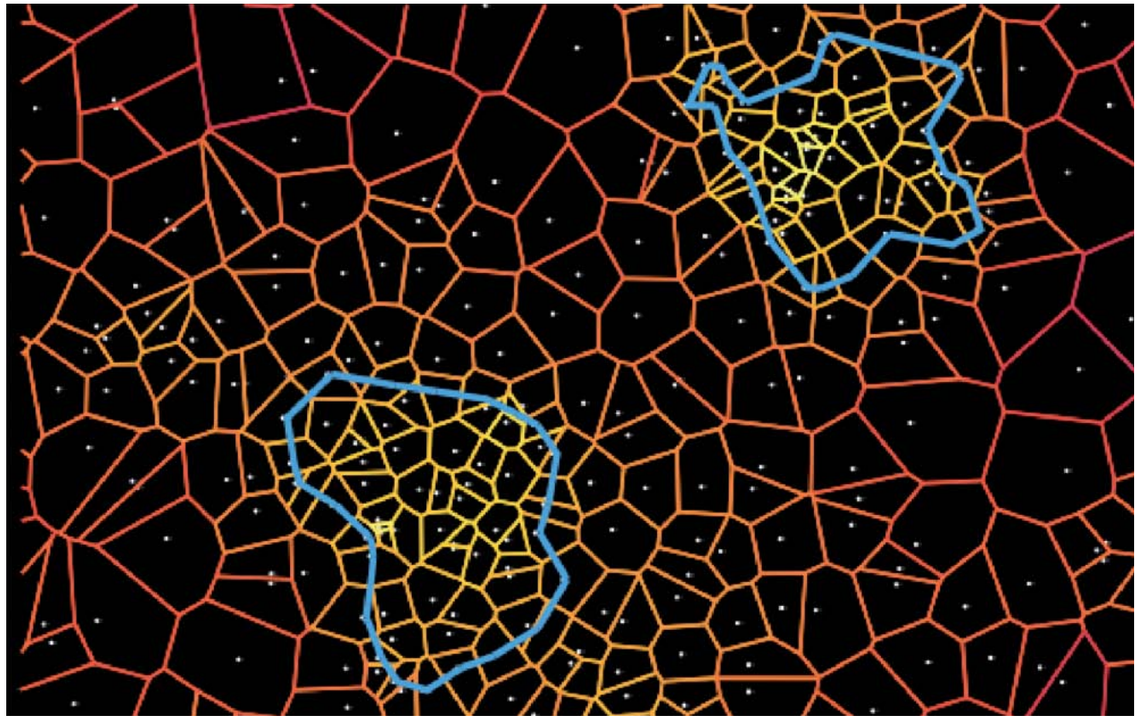
This approach and these values were initiated as early as 2013 by the BRIO SIRIC (Integrated Cancer Research Site), aimed at moving over to new, more efficient and transparent research models to bring new solutions to the fore through new perspectives.

Our project needs to be broad and call on all skills available. Nouvelle-Aquitaine offers us that opportunity with its wide range of academic research sites, research platforms and companies, whose skills are multiple and complementary, whether in Limoges, Poitiers, Bordeaux, La Rochelle or Pau.

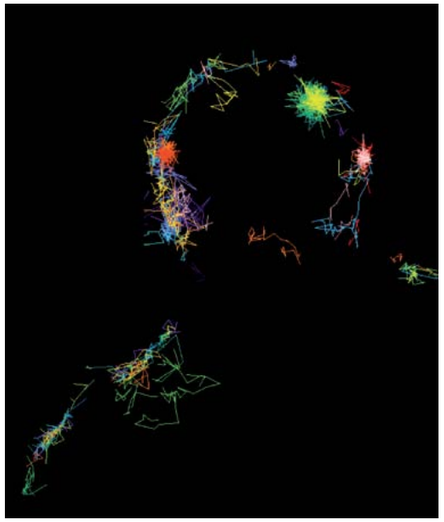
This issue of Chercheurs d'Aquitaine is aimed at sharing our enthusiasm with you. It is not meant to be exhaustive and cannot be. Through portraits and a range of topics, we hope to show you our determination and diversity, as well as introduce you to our researchers who are both passionate and humane.

Pierre Soubeyran
BRIO Director &
Nouvelle-Aquitaine Oncosphère Project Coordinator

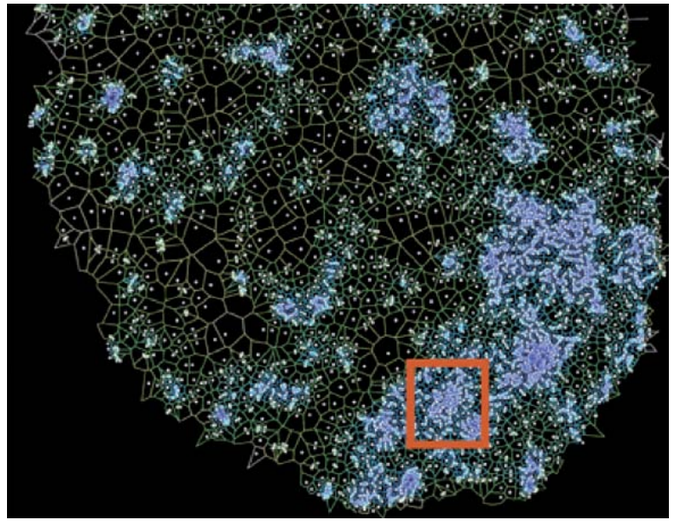
AT THE SOURCES OF LIFE



Organisation of the protein (GTPase Cdc42) on the surface of a yeast cell. It should be noted that Cdc42 (white dots) is concentrated in specific regions (inside the blue lines).



Pathways corresponding to movement of the protein (Cdc42) on the surface of a yeast cell



Cdc42 is concentrated in the half of the cell that defines the polarity axis used for cellular growth and cellular division (tips).

The study of yeast provides information about the fundamental mechanisms of cell biology, allowing better understanding of the onset of cancers.

"*The dream of every cell is to become two cells*", as Nobel Prize winner of Medicine, François Jacob liked to say. A way of emphasizing the importance of cell division. And when a cell doesn't try to become two, it gets everything ready for division to take place smoothly. All the processes dictating the life of a cell are a cycle that has been repeating itself since time immemorial: the cell cycle. It unites all the stages that make up the life of a cell. That series of events varies substantially from one cell to the next since, on one hand, it depends on the identity of the cell defined by its genetic heritage, and, on the other hand, on its ecological context, i.e. its surroundings. Still, despite its incredible diversity, the cell cycle can be divided into two major stages common to all living organisms: a growth period called the interphase and a division period called mitosis. "*Mitosis is extremely important since errors occurring during the process can be at the origin of manufacturing 'accidents' producing new cells with an abnormal number of chromosomes, called aneuploid cells*", explained Isabelle Sagot, Principal Investigator at the CNRS IBGC (Institute of Cellular Genetics and Biochemistry) UMR 5095 of Bordeaux. "*Yet we know that this type of cell can cause the formation of cancerous tumours*", she added.

That's right, the detailed study of mitosis is crucial to understanding the genesis of cancers, a consequence of chaotic cell division. To conduct their research successfully, researchers have a relatively simple model, yeast, which has mitotic phases comparable to that of human cells!!! *Saccharomyces cerevisiae*, or Baker's yeast, is precisely Derek McCusker's field of investigation, as head of the 'Dynamics of Cell Growth & Cell Division' team at the European Institute of Chemistry and Biology (IECB) in Bordeaux. He focuses his research on what he calls "*adjusting the cellular compass*". Cells have to know which direction to head in order to grow, divide and move. "How does a cell control its growth axis during mitosis so that there's an identical set of chromosomes in each daughter cell?" Derek McCusker asked. And answered: "*Well, it's by creating a stable polarity axis whose formation is defined by a specific type of protein from the family of GTPases. Those proteins are the cell compasses that allow them to differentiate their front from their back, their top from their bottom!!!*". GTPases are essential to all living beings. Without them, we die because cells can't divide normally. "*To be more precise, the formation of the cell's polarity axis during mitosis depends on the activity of the Cdc42 protein, which is a Rho-family GTPase*", Derek McCusker concluded. Research biologists and doctors are increasingly interested in the Cdc42 protein. For example, it is known that Cdc42 activators are responsible for the onset of cancers in mammals, i.e. an uncontrolled proliferation of cells. Isabelle Sagot has suggested other tracks of research: "*The majority of normal cells, and even some cancer cells, are not always in the process of dividing. So what determines whether a cell divides or not? That question is at the heart of the cancerization process. What's more, quiescent cancer cells can hide in a body for years, and suddenly start dividing again, that's the phenomenon of recurrent metastases.*" Understanding the molecular processes that control the transitions between quiescence and proliferation is therefore critical to shedding light on the fundamentals of cancerization processes. Consequently, the "yeast" model could provide answers to those questions, as it has in the past for several cellular processes. And yes, yeast has already won over 10 Nobel prizes! So stay tuned... ■

Didier Dubrana

ANNE ROYOU

THE PERFECT PAIR

In this poised, rational woman, a sort of boundless curiosity can be distinguished that seems to motivate her entire being. Anne Royou speaks about her research topics with the fascination of a child in face of a discovery, with eyes lit up by magic and a content smile. She's grateful to her parents "*who forged my thirst for knowledge and my curiosity about everything*" in the heartland of Brittany with nature as her observation ground. "*It was so stimulating*", she reminisced. Those were the days when she dreamed of being an astronaut to float in space, and she liked telling stories in comic books she wrote and drew. However, upon graduating from secondary school with a major in science, she knew she'd become a researcher. Yet the shift occurred when enrolling in the Anglo-Saxon like post-graduate programme offered by the University Paris-Sud, centred on molecular and cellular genetics, which gave preference to laboratory experience. There, she became familiar with manipulating model organisms like yeast and drosophila as well as cutting-edge techniques. It was in Dr Roger Karess' laboratory that she discovered her field of predilection: mitosis – the last stage of the cell division cycle. An "*extremely beautiful, complex division*", she said with enthusiasm. In the early 2000s, the improvement of microscopy techniques made it possible to observe proteins in the heart of cells thanks to fluorescent proteins and opened the path to new research. So improved they provided Anne Royou with the topic for her thesis on the role of a protein during the formation of a ring anchored to the cell equator at the end of mitosis and which enables a cell to split into two distinct cells. She was then given the opportunity to pursue her research using a very high-performance microscope, in Santa Cruz where she was hosted by Dr William Sullivan.

Unforeseen discoveries gave the researcher the impression she was spoiled, due to both the scientific and artistic value when certain phenomena occurred. By chance, she managed to observe the possibility of desynchronizing the different stages of cell division. At that point, she had found the topic for her future postdoc: identifying and explaining those control and coordination mechanisms.

Consequently, she later returned to California for eight years to make further observations, such as the mechanism enabling cells to transmit the right number of chromosomes when dividing…

While there, she also met a Scottish researcher, and ended up forming a couple with him in and outside of the lab. They have so much in common: their love for cycling every day, cooking, music – omnipresent in the life of the former organ player – and even the same fields of research. But in the scientific field, the

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advantage of mutual stimulation was replaced by competition when it came to job opportunities or the quest for funding!

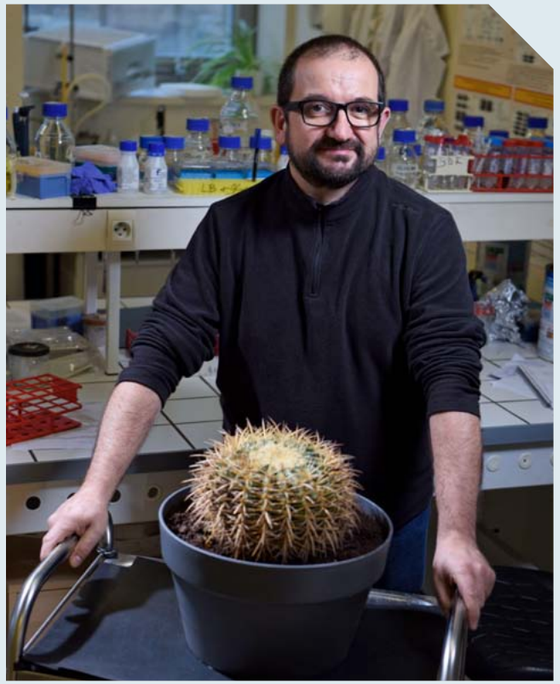
The European Institute of Chemistry and Biology gave them a dual chance upon returning to France. Although Derek McCusker set his laboratory up there in 2009, 2 years before her, they both passed the CNRS competitive exam with flying colours the same year. After "*their project's incubation*", they both joined the IBGC (Institute of Biochemistry and Cellular Genetics).

For Anne Royou, "*it's a challenge to create your own lab, starting from scratch*". Thanks to support from the Regional Council, the ATIP/Avenir programme and European funding, she created her lab in 2011, with a team united around atypical projects dealing with the control and dynamics of cell division. "*The Oncosphère is going to create bridges between researchers working on the fundamental aspects related to cancer and the ones invested in specific cancers*", she explained, foreseeing new beneficial exchanges to come. An outlook in which she hopes to do joint work on drosophila or another organoid with the researcher close to her heart… ■

Constance Deveaud

BENOÎT PINSON

THE GAME OF SPOTTING DIFFERENCES



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From his native region, the Vendée "*with the ocean at the garden gate*", Benoît Pinson has kept the taste for nature and wide-open spaces. Very early on, he was motivated by the workings of vegetal and animal life: "*I've always been obsessed by biology*" he said. So it was only natural for him to enter the faculty of biology in 1987 at the University of Bordeaux, in the end only leaving for two years during his 2nd post-doctorate in Oslo from 1998 to 2000. With a major in biochemistry, a thesis on the physicochemical mechanisms of a purine transporter in yeast, then his first postdoc on metabolism regulation and here he is, with a life commitment to metabolic reactions with the aim of unveiling the secrets of cellular energy.

Now a research director at Bordeaux's Institute of Biochemistry and Cellular Genetics, his fascination for discovery has never faded. His principle: "*play the game of spotting differences*", question, interrogate, measure, compare over the course of the analyses. His goal: find the metabolites that play a destructive or protective role for cells by regulating essential biological functions, and identify the cascades and elements… in hopes of bringing fundamental research closer to the clinical universe and the patient.

That's a challenge met alongside a group from the Necker-Enfants Malades Hospital. In 2010, Benoît Pinson's team was contacted to study the blood and urine of patients suffering from a rare disease. The study confronted the team with new constraints, much to the delight of Pinson, who "*likes a scientific challenge*". After putting their approach and technical expertise to good use, several metabolites, markers for the targeted disease, were discovered in 2015 making it possible to improve its diagnosis.

Although Benoît Pinson "*prefers the humility of small steps to the big race*", that progress nevertheless marks a crucial stage in this extraordinary CNRS team's development. Since this department makes the difference through the complementarity of its expertise centred around Bertrand Daignan-Fornier, the geneticist, who spotted Benoît Pinson, the biochemist, back in 1996, and recruited him in 2000 upon his return from Norway. That cross-disciplinarity is unique. "*We can play a role in the Oncosphère project. We're going to share our questions and our knowledge with the clinicians and increase the probabilities of better understanding their needs and expectations; and them, ours*".

The Department of Metabolic Analysis, recently christened SAM (a reference to the metabolite S-Adenosyl Methionine studied in the lab), now positions itself as a service for guidance, analysis and support for new projects.

That's one more step towards "*furthering knowledge*" and motivating Benoît Pinson who has welcomed the change as "*a great opportunity at age 50!*". But he's a man who keeps his feet firmly on the ground. The countryside where he lives is where he recharges his batteries. Concerned with separating his professional and personal life, he "*never talks about science at home!*". But apparently in his spare time, this gardening enthusiast who doesn't hide his taste for plant cuttings still lets his inquiring mind indulge in a few new seed experiments… ■

Constance Deveaud

THE METABOLIC PATHWAYS IN CANCER

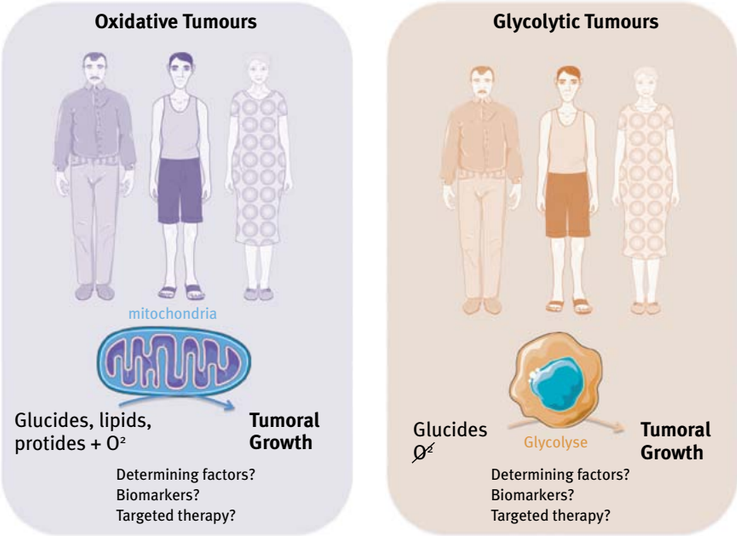
The "all genetics" days are over: scientists now look at bioenergetic dysfunctions in cells to explain pathologies.

For over sixty years, scientists believed that the metabolism of cancerous cells mainly functioned according to the *"Warburg effect"*: in other words, by feeding exclusively on glucose while consuming very little oxygen. At the time, the new metabolic pathway described by the German chemist Otto Warburg theorised that "*cancer cells drew their energy in glycolysis to meet their energy requirements but also their biomass requirements, needed for multiplying*". Moreover, the research characterising the enzyme responsible for cellular respiration, like cytochrome oxidase, earned the German chemist the Nobel Prize in Medicine in 1931 for his work. It wasn't until the early 2000s that researchers debunked the theory, thanks to in vivo experiments in humans and mice. "*In humans, for some types of cancer – like lung cancer – glucose is consumed by the mitochondria and does not use the incomplete metabolic pathway of glycolysis, which contradicts the Warburg effect. What's more, mitochondria lets cancerous cells use fats and proteins as sources of energy, which isn't possible with glycolysis*", said Rodrigue Rossignol, Inserm research Director at U1211 MRGM laboratory in Bordeaux (mrgm.fr), and CEO of the spin-off company CELLOMET (www.cellomet.com). The role of mitochondria in the bioenergetics of cancer is a major discovery that has fundamentally changed the etiology of cancer and is the subject of a european research project ITN Marie Curie TRANSMIT.

In fact, the theory of genetic anomalies is what now explains the origin of the disease. "*Targeting cancer metabolic vulnerabilities is a means of attacking or controlling the disease since the metabolic modification may occur right from the initiation of the cancer*", Rodrigue Rossignol explained. But things get complicated when you know that all tumours don't function the same way. Some tend to favour glycolysis while others use the mitochondrial pathway. In a single type of cancer, two bioenergetics groups of tumours can also be observed: glycolytic and oxidative (mitochondria)! Lastly, the two subtypes of cancer cells can even cooperate within a single tumour. The factors determining the variable metabolic profile of tumours remain unknown at present. In fact, Anne Devin, CNRS research director at the Institute of Biochemistry and Cellular Genetics (IBGC) UMR 5095, is trying to understand the modalities involved in the establishment of the Warburg effect. In the long term, that research should make it possible to thwart the Warburg effect and prevent the uncontrolled proliferation of those cells. Her cellular model: yeast! "*Thanks to that organism, we can study the kinetics of the induction of the Warburg effect and all the stages of the process leading to this bioenergetics dysfunction. Which is, to date, impossible to implement on human cells*", the biochemist explained. "*We're trying to figure out how we go from a "healthy bioenergetic" state to a "pathological bioenergetic" state*". Stay tuned... ■

Didier Dubrana

There are two subtypes of bioenergetic profiles in most types of tumours. Research is underway on the markers associated with those tumour subtypes, understanding genetic or environmental determining factors and identifying therapeutic targets.



MILOS FILIPOVIC

THERE'S POWER IN OPPOSITES

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Don't be mistaken! Behind the workaholic who relaxes only on Saturdays, is always travelling somewhere in Europe to a lecture, or a talk in the U.S., tosses aside comfort and routine in favour of new challenges, there hides a Slavic sensitivity which, whether happy or sad, needs to experience things and emotions in a sort of inalienable torment. Milos Filipovic finds balance between the two, and derives his scientific approach from the power in opposites.

His expectations are as high as his limitless ambitions, which constitute his driving force – he sets "*goals at 300%*" so he's "*never satisfied but always happy with the work achieved on a daily basis*". When he was younger, his dream was to win not one Nobel Prize, but three. At 37, he humbly aspires to play a constructive role in science, placing the emphasis on "*contribution*" rather than on "*reward*". Yet he has passed competitive exams with flying colours, won awards and obtained extensive funding.

His path as an excellent student who, as early as secondary school, knew he wanted to devote himself to science, has been marked by charismatic women of exception. Vesna Niketic, his thesis supervisor in Belgrade, "*taught me everything in the sciences, I learned everything from her*" he said. His mentor was later to become a close friend.

For his post-doctorate, he headed to Germany to study under the supervision of the chemist Ivana Ivanovic-Burmazovic, who gave him substantial freedom and free rein in his research. If in doubt, the biologist he has now become still contacts her today "*for her shrewd advice in a field sometimes worthy of science fiction! She's the best chemist I've ever met, so inspiring*" he added.

Certified to teach at the University of Nuremberg, he enjoyed the contact with students whose questions can be unsettling, and tend to keep teachers on their toes. While there, he set up a Master's degree in "*Chemistry of Life*".

He stayed in Germany nearly seven years to produce a colossal work of over 1000 pages entitled "Biological Chemistry of Gasotransmitter Signalling", receiving the university's Emmy Noether prize in November 2018. That research earned him the recognition of his peers worldwide, in particular for his work on the role of certain gases produced by cells in regulating blood pressure.

Recruited by Bertrand Daignan-Fornier, he "*took the risk of coming to France*" rather than England, sat the CNRS competitive exam (on which he ranked 1st) and received both an ATIP Avenir and the Idex Junior Chair – enough funding to create his laboratory from scratch in January 2016, and pursue his research work on the role of protein persulfidation in health and disease.

The family sphere is where he acknowledges his biggest "*scientific accomplishment*", when research is applied in a clinical situation, as close as possible to the patient. Thanks to his expertise and research, Milos Filipovic was able to help the medical team in charge of his own mother who was dying from cancer in Serbia. Their combined efforts led to her recovery seven years later.

Although professional responsibilities fill his schedule, Milos Filipovic lets the arts set the tempo in his private life. He chose to settle in the heart of 18th-century Bordeaux. A confirmed film buff, he has watched so many films for pleasure that he now reads or reviews screenplays sent to him by his most loyal Serbian friend. When he's not doing that, he re-reads (for lack of time to write more) his collection of over 100 poems written since secondary school, in Serbian of course, as well as in French, the only foreign language he learned in school, before science obliged him to learn English. Or he cultivates his taste for French culture, cuisine, wine and museums. And not a trip to Paris goes by without a visit to the Musée d'Orsay, his favourite place to experience art. ■

Constance Deveaud

THE CHALLENGES OF SKIN CANCER

Bordeaux University Hospital's oncodermatology centre has established a translational research strategy.

The number of new cases of skin cancer has more than tripled in the past 20 years. In 90% of the cases, they are carcinomas (70% basal-cell carcinomas and 20% squamous cell carcinomas). The remainder are cutaneous melanoma, less common but much more serious, Merkel-cell carcinomas, cutaneous lymphomas and rare adnexal tumours, heterogeneous groups requiring therapeutic and diagnostic expertise. Despite prevention campaigns, these cancers are a major public health problem that worsens every year as the population grows older. What's more, the number of carcinomas is underestimated, since they are not systematically recorded in cancer registers.

To meet this challenge, the dermatology department and its oncodermatology unit at the Bordeaux University Hospital – an expert centre in cutaneous lymphoma and rare cancers in two INCa-labelled networks (GFELC and CARADERM) – are at the crossroads of translational research that calls on two research teams from Inserm and the University of Bordeaux. Professor Marie Beylot-Barry cautioned: "*We're dealing with a multi-faceted medical issue. These cancers are more and more common but there are also rare cutaneous cancers requiring crucial expertise and aggressive advanced forms of the disease requiring the use of innovative therapies. Although major recent advances have improved the prognosis of melanoma, a lot remains to be done for skin cancers as a whole.*" The Bordeaux oncodermatology centre is involved in some twenty clinical trials on melanomas, carcinomas and lymphomas. The UMR 1053 (Inserm, University of Bordeaux) team working on the oncogenesis of cutaneous lymphomas with the Aquitaine platform for Cancer Molecular Genetics, plus the Biological Resource centre, the Anatomical Pathology lab and the Oncoprot team have joined forces to work together. The joint effort has made it possible to study the oncogenesis of lymphomas, do research on prognostic and diagnostic biomarkers, analyse the role of the microenvironment and open the way to therapeutic targeting with validation models on cell lines and xenografts made using patient tissues or cells. Marie Beylot-Barry added, "*For example, these approaches led to proposing a hospital programme of national clinical research focused on aggressive B-cell lymphoma, based on the Inserm U1053 research, which had identified a recurrent MyD88 mutation leading to constitutive activation of the NF-KB pathway. Several transcriptomic and proteomic studies are also underway to define predictive response markers, which may guide new therapies.*"

But oncodermatology is not limited to the so-called hard sciences! "*We call on human and social sciences to determine the factors related to delayed diagnosis, specifically in the case of basal-cell carcinoma (CBC)*", Marie Beylot-Barry explained. Caught in time, these very common skin cancers can be treated in the majority of cases. However, some patients consult for the first time with extremely advanced, destructive tumours on their face even though the cancer has been visible by the patient and/or their family for several months, or even years. Understanding the factors associated with the delay in consultation is the subject of 'PSYCHO-CBC' begun by Marie Beylot-Barry in collaboration with the health psychology team led by Bruno Quintard, professor of health psychology, at Inserm and the University of Bordeaux. "*Thanks to interviews conducted by a psychologist and a dermatologist, we're going to study the patients' and caregivers' perspective, which will make it possible to develop representative and interpretive diagrams of the disease that are an obstacle to consultation*", she continued.

The oncodermatology research also concerns rare diseases, thanks to UMR 1035 directed by Professor Alain Taieb. *Xeroderma pigmentosum*, also referred to as 'Children of the Night', is a genetic disorder that increases sensitivity to ultraviolet rays. Unprotected, the children's skin undergoes premature ageing and they develop early skin cancers. Researcher Hamid Rezvani is studying cellular metabolic pathways to understand the relationships between genomic mutation, alterations in energy metabolism and increased reactive oxygen species (ROS) levels during cancer initiation. Above and beyond these rare diseases, the research conducted by Hamid Rezvani on carcinogenesis and squamous cell carcinomas is aimed at identifying promising targets for a preventive and curative approach.

In any case, one thing is clear: the research strategy at Bordeaux oncodermatology centre is definitely well-established and ready to play a role in the Oncosphère's success. ■

Lily Bias

MAUD TOULMONDE

AN APPETITE FOR INNOVATIVE THERAPY

She was born in the vineyards of Champagne, in Reims, to two doctors: a biologist and a general practitioner. So naturally, she wanted to learn everything about the human body and saw medicine as a multiplicity of career opportunities throughout her life, as well as a terrain conducive to the expression of her feminist militancy. Yet she wasn't to become the gynaecologist as hoped during her medical training when she "*cut a lot of (umbilical) cords*" as an operating assistant or went all the way to Australia at barely age 20 for a fascinating experience dealing with alternative childbirth methods, Maud Toulmonde explained from behind her cheerful green eyes. After a change in vineyards and a detour through internal medicine and tropical diseases, Bordeaux is where she specialized in sarcoma oncology, rounded off by a Masters in Cell Biology and several interuniversity degrees, including statistics applied to clinical research (CESAM), immunology and biotherapy.

Upon arriving at the Institut Bergonié, her encounter with Dr Bui, a paediatric oncologist specialized in sarcomas, was decisive. "*Sarcomas are very rare and diverse diseases, affecting all ages and it's always a challenge for me to be able to improve the treatment and survival of my patients*", she said. That's why she didn't hesitate for a second when Professor Antoine Italiano invited her to take part in developing the unit, now a CLIPP, or certified early phase investigation centre. So there she was aboard the "*Shinkansen, that bullet train*" powered by the dynamism of the person she introduces as her mentor, "*an inexhaustible source*" in a perpetual motion of challenges to be taken up.

Since she can't imagine cancerology without clinical research, she fights on a daily basis to "*allow patients better access to innovative therapy*". Although sarcomas remain her main interest in clinical research, she also takes part in phase I/II trials on all tumours, and conducts studies on pharmacodynamic biomarkers, especially in immunotherapy.

Maud Toulmonde is especially involved in translational research work related to sensitivity mechanisms and resistance to targeted therapies and immunotherapy. She is currently pursuing a doctorate dealing with the identification of therapeutic targets in undifferentiated pleomorphic sarcomas: a project aimed at analysing those sarcomas in order to classify and target them better, in terms of therapy. The multidisciplinary aspect of cancerology motivates her "*to determine the best strategy of immediate care for the patient*". For her, "*belonging to a team is fundamental*". In preclinical and clinical research, she also makes sure to "*provide her clinician's perspective, to put issues into context*".

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On another front, she coordinates the national clinico-biological database of the French sarcoma group, which collects both treatment and follow-up data of all patients treated in the approximately 20 expert centres tasked by the French National Cancer Institute (INCa), and also biology sample references such as tumour-derived cell lines and murine models. "*Much more than a detailed clinical register, this database is a goldmine for research biologists and clinicians who are interested in sarcomas*", she added.

For this thirty-something workaholic, whose commitment can be strongly felt, a clinician's day-to-day life is a constant reminder of how important life's pleasures are. And she gives free rein to self-indulgence as soon as it's a matter of "*food, because feeding our stomachs is what allows us to feed our minds!*". As an honest-to-goodness foodie, the world's cuisines guide her travels and reading choices. But for her, French gastronomy is the one that can't be dethroned. And advised by the beloved wine négociant with whom she shares her life, the Bordeaux vineyards and its best nectars provide her with the perfect pairings... ■

Constance Deveaud

CÉLINE AUZANNEAU

TRAVELLING IN UNCHARTERED TERRITORY

Although she moved around a lot in her childhood, her hometown is the place this Poitiers native chose to study science. As far back as she can remember, she has always had a pronounced curiosity for research and discovery. "*I even did a week-long internship in a medical lab back in middle school!*" Céline Auzanneau said. Her science *baccalauréat* in hand, she quite naturally headed to the Faculty of Science where she found a sense of fulfilment all the way through to her doctorate with a thesis on the pharmacology of chloride channels in cystic fibrosis. She was interested in everything: cell biology, electrophysiology, understanding action mechanisms... and it turns out she had a genuine soft spot for new technology. But the central theme in her studies has always been to associate her fields of research with a pathology. That's why she chose to round out her academic career with training in clinical research. Yet fundamental research opened its doors first. Her 1st post-doc took her to Belgium for four years where she focused on Dent's disease and subcellular fractionation, using the procedure of isolating lysosomes. The very tool discovered by the biochemist Christian de Duve, a 1974 Nobel Prize winner, with whom she "*was lucky enough to have a conversation, when he was 80, still so starry-eyed and passionate about the tests underway and the possible findings*", she reminisced, moved. In 2009, upon returning to France and choosing the Institut Bergonié, she focused on a new pathology – cancer – including the validation and identification of new targets in oncology.

And in 2014, her series of choices unsurprisingly led her to answering a request from Professor Antoine Italiano who was putting together a dynamic team on early phase clinical trials. Hence, the young engineer in biology joined the Biopathology department and became head of several multidisciplinary projects, centred on coordinating the circuit of lab samples from volunteer patients for molecular screening.

Among her missions currently underway, Céline Auzanneau is coordinating the biology aspect of the ambitious oncology project, Multipli, within the framework of the French Genomic Medicine 2025 plan, which is aimed at integrating genome sequencing into patient care management. "*The purpose is to evaluate the feasibility and cost of high-throughput sequencing of the tumour within the context of standard care management*", Céline Auzanneau explained. "*The target for results is 7 weeks, during which we have to accompany the samples and data, create tools and traceability, exchange and communicate with all the project actors... then hope to end up with a targeted therapy.*" Multipli brings together about 2400 patients "*who we feel strongly committed to, with a genuine desire to get things moving in order to provide patients with as much chance as possible*", she insisted.

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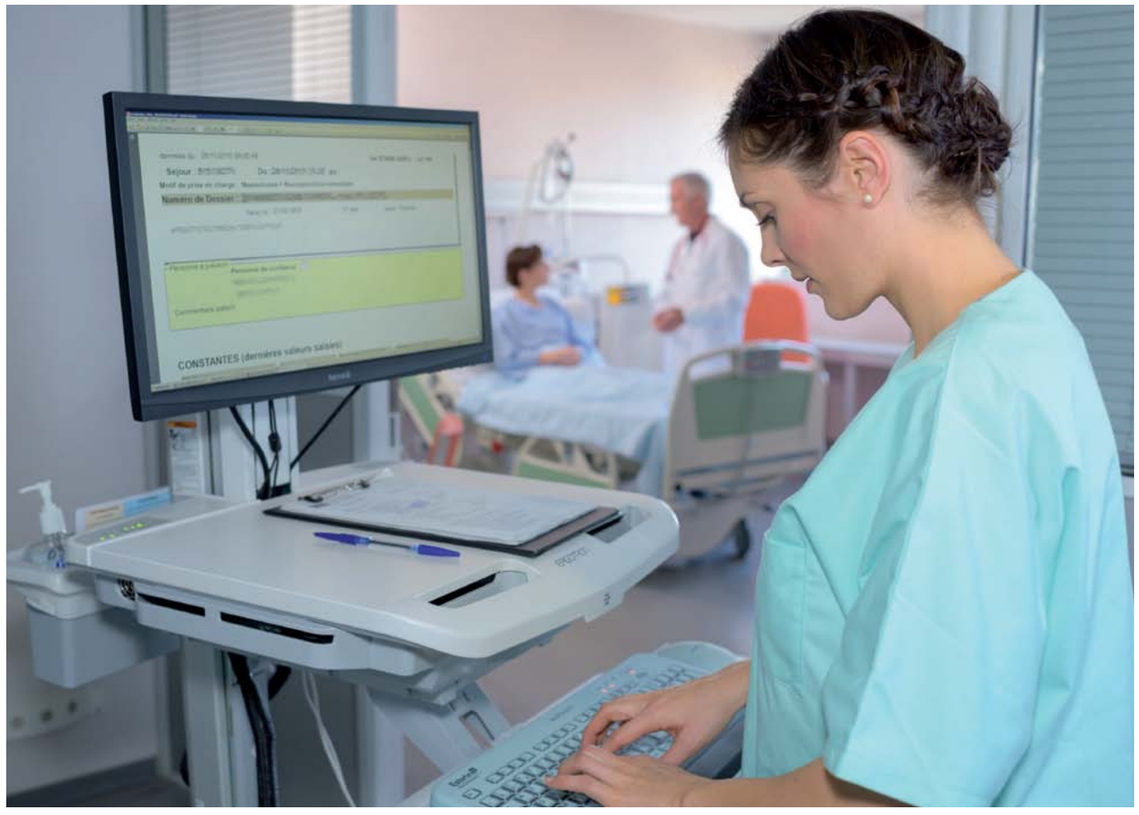
Personalised, targeted therapies have proven their effectiveness since they initially emerged. Multidisciplinary tumour boards are the opportunity to position molecular screening as early as possible in the care management process.

"*Coordinating a multidisciplinary project is like travelling in unchartered territory, you have to adapt to your environment and learn to communicate even if you don't know all the languages*", she added, before making the link with her passion for other journeys. The ones that fulfil her life and that she sometimes prepares for (or sometimes doesn't), in order to soak up new cultures, discover new horizons and make fascinating encounters. Immersion, at times total, to which she always has to adapt, like in the Himalayas, in the remote region of Ladakh that left her with very fond memories. Now her mind is already on her next adventure, when she'll take off on another trip to discover a European capital, a treat she enjoys offering her daughter for each of her birthdays. ■

Constance Deveaud

BLOCKING CANCER

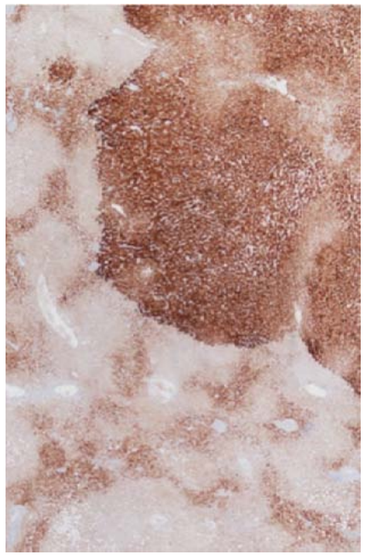


From fundamental research to the patient's bedside, a new Bordeaux consortium is giving meaning to translational research.

A group of experts including about 20 researchers and doctors has come together to find effective solutions for liver cancer.

Everyone's there: oncologists, hepatologists, anatomical pathologists, radiologists, Inserm, CNRS and University of Bordeaux researchers and emeritus professors... They've all come together to attend one of the many Bordeaux Liver Oncology Consortium (BLOC) meetings. The one-of-a-kind Bordeaux consortium "*gives meaning to translational research*", explained Frédéric Saltel, an Inserm research director. "*We've managed to connect researchers with clinicians, since the former without the latter would be pointless*". At the heart of the discussion, one of the world's most significant health problems: liver tumours. Although hepatocellular carcinoma (HCC) is the most common type of liver cancer, the vital organ can also develop many other cancer pathologies such as adenomas, cholangiocarcinomas, and hepatoblastomas. The liver is also a common site of metastasis. Liver resection (tumour ablation) and transplantation are the two most effective treatments for HCC. At an advanced stage, drug treatments, whose side effects remain major, can be administered. Progress in medical imaging accompanied by an increase in frequent clinical examinations "*make it possible to detect the little hepatic nodules earlier and earlier in a cirrhotic or non-cirrhotic liver*", explained Jean-Frédéric Blanc, professor of digestive oncology at the Bordeaux University Hospital (CHU). He also specified "*on the clinical level, two fundamental issues come up. How can these little (malignant or benign) hepatic nodules be diagnosed and how can drug treatments for advanced liver cancer be developed and optimized?*" As such, the clinician's analysis defines well-identified objectives and avenues of research. Early diagnosis and screening of liver cancer have to be improved and new therapies developed. To meet those needs, the BLOC consortium came into being in 2014 in the wake of the creation of Bordeaux's Integrated Cancer Research Site (SIRIC-BRIO). What brings fundamental research closer to clinical research is hence the study of tumours. Historically, Bordeaux is one of the cities with the highest performance as far as liver tumour classification is concerned, thanks, among other things, to research by Professors Paulette Bioulac-Sage and Charles Balabaud. Over 2500 patient tissue samples have been referenced, filling a national tissue network created over 20 years ago by Inserm. The researchers benefit from a unique data bank of malignant or benign liver tumours – that means raw material for research that now draws on the progress of Artificial Intelligence, capable of handling big data in record time. Professor Brigitte Le Bail, an anatomical pathologist at the Bordeaux University Hospital (CHU), is responsible for interpreting the hepatic tissues.

In one single location, the consortium groups together several teams and areas of research to address clinicians' needs and concerns. Prognosis and diagnosis is at the core of the Oncoprot research, a platform devoted to proteomics. (See article p. 20). Research on pre-cancer lesions is focused on the genetic causes of HCC whereas another investigative path focuses on the molecular bases of hepatic tumour cell invasion. Violaine Moreau, research director at Inserm UMR 1053 (Inserm, University of Bordeaux) explained "*abnormal cell migration and invasion is both a characteristic of malignant cancer cells and a component of metastasis – the main clinical problem in cancer. We know that the reorganisation of the actin cytoskeleton is important for cell migration, cell shape change, and interactions with other cells and the environment. Consequently, alterations in cytoskeletal signalling pathways are increasingly recognized as being important for cancer invasion and metastasis. We are striving to better understand the mechanisms of action and regulation in liver tumour cells.*" The goal is to identify the main markers and actors involved in HCC invasion. This non-exhaustive description of the research work conducted by the consortium illustrates the networking progress made by the 'hard' sciences in the field of oncology. The consortium also benefits from the expertise of radiologists, like Doctor Hervé Trillaud, hepatologist Doctor Victor de-Ledinghen, gastroenterological surgeon Dr Laurence Chiche and researchers like Dr Christophe Grosset and Dr Marion Bouchecareilh. Their range of expertise makes it possible to cover all the fields dealing with the liver in an attempt to provide an overall, collective answer to the problem of liver tumours.



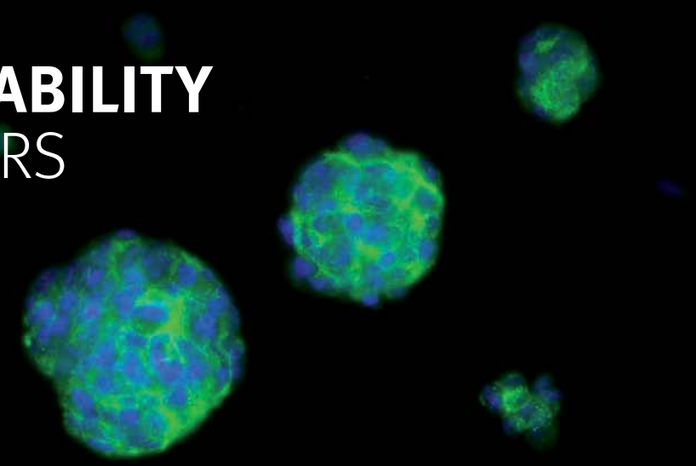
ASS1 immunostaining in hepatocellular adenoma, overexpression in tumoral part, in comparison with non Tumoral part

Yet another strong point is the cooperation with human science researchers at the University of Bordeaux, such as sociologists and economists. They are taking a special interest in cancer, innovations in genomics, and research on the impact of those innovations on the medical profession and its practices. Translational research has definitely found its full meaning with BLOC! ■

Raoul Sancy

THE UNPREDICTABILITY OF BRAIN TUMOURS

How to decipher brain tumour invasion mechanisms and predict their evolution to invent diagnostic and therapeutic tools



Glioblastoma cells cultured as neurospheres

The Angiogenesis and Tumour Microenvironment Lab UMR 1029, directed by Andreas Bikfalvi has just discovered cell signalling pathways that could serve to restrain the invasion of tumour cells in the case of glioblastoma (GBM): the deadliest brain cancer in adults. Glioblastomas are among the gliomas that can be divided into two groups: very invasive and very aggressive high-grade gliomas (glioblastomas) whose peak frequency is between the age of 50 and 60 and low-grade gliomas (LGG) that tend to affect a younger population. The survival rate for patients with a GBM is very low, around 14 months despite surgery and radiation/chemotherapy. It is known that the infiltration of the brain by tumour cells can occur at a very early stage. The origin of that invasive biological behaviour is precisely what interests the UMR 1029 team. "*We've especially worked on glioblastomas since they are aggressive tumours characterized by a high proliferation rate, abundant immature vascularisation and infiltrative areas*", Andreas Bikfalvi explained, before continuing: "*we explored two molecular pathways: chemokines and molecules of the extracellular matrix.*" Chemokines are a family of small proteins that control the cell migration and infiltration of immune cells. They are also cell signalling mediators that act both on normal and tumoral cells. *"Among the chemokine receptors, we have elucidated the role and mechanism of the CXCR3A membrane receptor in glioblastoma invasion. More specifically, targeting the CXCR3A isoform is what may constitute a promising strategy for stopping tumour cell invasion.*"

The second avenue of research concerns thrombospondins (THBS), a family of proteins belonging to the extracellular matrix. Thrombospondin-1 (THBS1) is known to have an impact on tumour cells and the microenvironment. "*We've just proved that THBS1 also plays an important role in the infiltrative process in glioblastomas, which makes it another lead to follow for therapeutic targeting*", Andreas Bikfalvi confirmed. That research provides insight into the invasion mechanisms of primary brain tumours. They make up one phase of the research conducted in the laboratory. The research was recently published in two papers in *Nature Communications* (Boyet et al, Nat Com, 2017; Daubon et al, Nat Com 2019).

Another part of the lab's research deals with low-grade gliomas (LGG). UMR 1029 has definitely surrounded itself with a multidisciplinary team (biologists, bioinformaticians, mathematicians and clinicians including two Inria teams from the Bordeaux campus) to take part in the GIOMA-PRD project aimed at understanding the still puzzling variability of how this type of cancer evolves. Thanks to the analysis of clinical, biological and molecular data gathered from patients, researchers are endeavouring to discover markers of aggressiveness in LGG and develop a predictive algorithm for tumour evolution. The scientists will work from MRI, PET and scans from a set of patients with LGG and undergoing treatment. They'll also do the molecular analysis of cancer cells and the microenvironment. Ultimately, this European research programme involving Norwegian (Bergen University) and Italian (Humanitas Neurosurgery Department, Milano) teams hopes to offer clinicians a predictive model in software form. ■

Didier Dubrana

CHRISTINE VARON

WHEN EVERYTHING FITS TOGETHER

Quite often the paths of researchers are all planned out from the start. But for the biologist Christine Varon, it was a different story altogether. It was a series of events that unexpectedly led her to stand out with her expertise in gastric cancer – the common thread in much of her research work acknowledged by numerous publications.

From childhood "*the passion for the living and the infinitely small*" was what definitely led the little 7-year old girl to having her own vivarium to raise salamanders, or entertaining herself by experimenting with crossing goldfinches with canaries!

Then came a series of false-coincidences. In high school, when too many students were enrolled in Economics, the Bordeaux native ended up in Life Science. She continued her studies at the IUT of Biology in La Rochelle where she delved into biology and microbiology enthusiastically. After some time at the Faculty of Life Science in Limoges, she returned to Bordeaux to study the biology of organisms and suddenly became passionate about the human organism and cell biology. Her DEA on the science of food and nutrition gave her the opportunity to take her first steps in cancerology. She worked on tumoral angiogenesis and specifically on a signalling pathway controlling it. She received an honorary scholarship from the French government and funding from the French Cancer League and from the French Association for Research against Cancer to fund her thesis, which she presented in 2005. Her findings and contribution to fundamental research received recognition.

Another change in direction came about when she applied for a position as an engineer at the French National Centre of Helicobacter References (CNRCH) but was offered a totally different project! Quite unexpectedly, interested in the young woman's knowledge in cell biology, the laboratory director, Professor Francis Mégraud (who was to become her mentor) offered her an incredible challenge: reproduce and extend the controversial discovery made by American researchers in 2006 demonstrating that gastric cancer, associated with the infection by *Helicobacter felis* in animals, originated in bone marrow stem cells.

Supervised by anatomical pathologist Pierre Dubus and Frédéric Mazurier, a stem cell specialist at Inserm, she embarked on an adventure as stimulating as it was innovative. For several years, the passionate young woman was active on all fronts and ended up extending the findings to *Helicobacter pylori*, the bacteria associated with gastric cancer in humans, confirming but slightly modifying the initial American findings. Hence a noteworthy publication in the international journal *Gastroenterology* in 2012. Simultaneously, a second project kept her just as busy on the new chronic inflammatory bowel diseases, such as Crohn's. The ideal investigative field for studying the cytopathogenic and pro-inflammatory properties of enterohepatic *Helicobacter* and publishing extensive results.

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The University of Bordeaux opened its doors to her in 2008 when she was given a position as a lecturer in cell biology and microbiology on Francis Mégraud's team. From then on, she built and refined her expertise in gastric cancer and centred her research on the origin of stem cells in tumours. "*Within the tumoral mass, only part of the cells is proliferative. That is the proportion we are focusing on in order to detect them in tumours and blood*", she explained. "*Knowing how to detect those cancerous stem cells means being able to isolate them to do molecular studies in order to identify their signalling pathways and contemplate adapted therapy.*"

You can sense how passionate she is, as committed to her research as to her doctoral students that she supervises and to her teaching that motivates her.

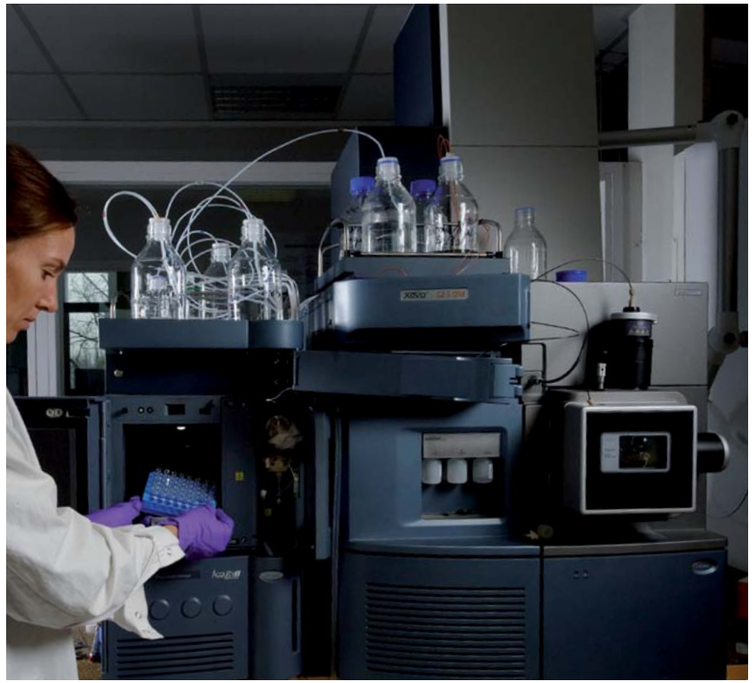
Recently appointed University Professor in cell biology and translational oncology, she plans on setting up an international course of study for a Masters in Cancer Biology.

Another brick laid by this builder at heart. But when Christine Varon leaves her microscopes behind, it's to pick up a sledgehammer and knock down walls with her husband to help out on one of the many renovation jobs they take on as a family. ■

Constance Deveaud

ONCOPROT

A tissue proteomic engineering platform - set up by the Bordeaux Research in Translational Oncology lab (U 1053 Inserm - University of Bordeaux) and housed by UMS 005 - offers its services to clinicians.



Mass spectrometry platform

The Oncoprot platform (*Onco* for oncology and *prot* for proteomics) brings together cutting-edge techniques in biological analyses to be used for analysing proteins – the proteome found in patients' tissues. The precision technology enables researchers to identify new biomarkers for diagnosis, prognosis or prediction of response to treatment by comparing tumours from different patients. "*Proteomics is the story of the caterpillar and the butterfly*", explained Frédéric Saltel, cofounder of the facility with Anne-Aurélie Raymond. "*They are very different but share the same genome. The difference comes from how the end products of their genes are expressed, in other words, their proteins.*" Consequently, although genomics has proven its worth on several types of cancer (lung, breast, etc.), proteomics could totally revolutionize personalised medicine, so long as the molecular message can be interpreted as foreseen by the Oncoprot technology. In fact, a proteome is a complex, dynamic entity because the cell protein content is constantly changing. What's more, a single gene can give rise to several proteins. A proteome contains a much higher number of proteins than a genome contains genes! The Oncoprot technology, covered by a patent, is the combination of laser microdissection and mass spectrometry for proteomic analysis. In the initial phase, the laser is used to cut cell (several cells, a single cell or part of a cell) or tissue samples. That phase is carried out by Sylvaine Di-Tommaso, who is in charge of preparing all the samples. Then, the biological sample is inserted into the mass spectrometer, which provides the identity and quality of the proteins. That phase, in addition to data analysis, is Anne-Aurélie Raymond's field of expertise. "*This technique makes it possible to analyse the proteome like an ID card for each tumour*", Frédéric Saltel added. "*The proteomes from tumours that have different clinical characteristics can then be compared, in order to identify biomarkers.*" One of those biomarkers is already routinely used by the Bordeaux University Hospital (CHU) for the diagnosis of hepatocellular adenoma of the liver. Oncoprot provides clinicians with diagnostic assistance aimed at improving patient treatment and offering increasingly personalised medical care. In the long term, Oncoprot will be applied to many types of cancer as well as to other pathologies. ■

Lily Bias

VÉRONIQUE GUYONNET-DUPÉRAT

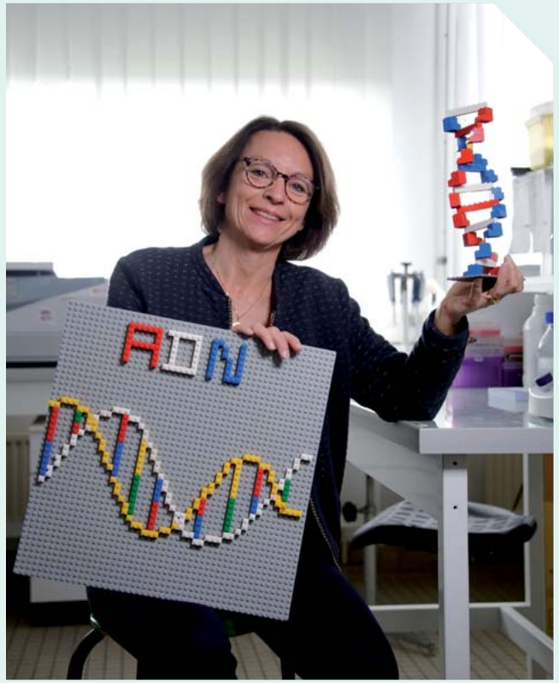
CHOOSING THE PATH TO THE JOYS OF SCIENCE

Véronique Guyonnet-Dupérat maintains very good relations with the people she works with; her enthusiasm is contagious and motivating. For her, the seriousness of a job isn't the least bit incompatible with a friendly professional atmosphere. The recognized research engineer has undertaken her career path like a human adventure that she talks about, with a smile, very much aware that her work in "*vectorology is only a very small stage before finding a therapy or before managing to understand the pathology*".

The service platform she created in 2005 produces lentiviral vectors derived from the AIDS virus. Vectors, engineered by molecular biology, are used to transport a DNA fragment and insert it into the very heart of cells kept in vitro or injected in animals. "*The viral genome is integrated into the cell genome and enables the expression of our gene of interest. Thanks to that vector, we model the disease*", she explained. The tool helps identify the genes responsible for different cancers and understand their role in the development of the disease so it can be fought. In the case of pancreatic cancer, "*we created a virus capable of targeting pancreatic tumour cells and destroying them*", she added.

As far back as high school, the Bordeaux native had already experienced "*the joys of science*". So she chose the scientific path, doing a doctorate in science with a dissertation on human mucin genes, which she presented in 1993 at the Faculty of Science in Lille. With a grant from the French Foundation for Cancer Research (ARC), she conducted a 4-year genetic study on thrombin receptors at the CNRS, then was appointed associate assistant at the University of Bordeaux where she tackled the identification of genes for susceptibility to schizophrenia. At the time, she shared an office with Professor Moreau-Gaudry, the man to begin French research on lentiviral vectors, which had originated in the USA. A close scientific bond grew between them, so close that, four years later, when she was an Inserm research engineer, with a neuroscience focus on the genetics of stress response, she was put in charge of creating a lentiviral platform. In less than 15 years, the service platform has established itself as a powerful gene transfer tool. It currently produces close to 400 virus batches a year (compared to 25 at the outset) and has built genuine partnerships with researchers in both fundamental and clinical research.

For her, the joys of science haven't run dry. As a child, she played with Legos, and she jokes about doing the same with plasmids in her lab; she continues to use them for educational purposes when she trains researchers. Because Véronique Guyonnet-Dupérat has become the ambassador for lentiviruses, now an essential tool for research. She also hosts tours of the lab for "*patient associations, including the French Muscular Dystrophy Association (AFM), to tell them about the notorious viruses. Some of the people who come, or one of their loved ones, are suffering from a genetic disease, or cancer. Every time, I'm touched to see the glimmer of hope that we can give them by explaining our research*".



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Véronique Guyonnet-Dupérat received the Inserm award for innovation in 2013, just before being distinguished as a Knight of the National Order of Merit (France). Within the Oncosphère project, she is involved in the VIP (Valorisation Innovation Platform) working group.

Focused on the infinitely small, like DNA, she "*needs to look up*" when she leaves the seclusion of her specialised lab. So she clears her mind by hiking or doing other sports. To all appearances, the friendly relations go far beyond the walls of the lab and campus, much to the delight of her tight-knit team. ■

Constance Deveaud

TREATING CANCER **IN THE ELDERLY+**

How taking into account patient age influences an oncologist's therapeutic strategy?

Nearly two-thirds of cancer cases occur in people 75 years old and older. But since we are not all equal in the face of passing time, biological age does not always reflect actual age. As such, oncologists have to adapt treatments specifically to patients who may have developed other health issues complicating their cancer management.

"*Use of standard treatment isn't always possible*", explained Professor Muriel Rainfray, geriatrician at the Bordeaux University Hospital (CHU). "*An assessment of the person's general state of health needs to be conducted in collaboration with a geriatrician, exploring several fields: medical, neuropsychology or socio-environmental, to determine whether or not the person can tolerate the anti-cancer treatments. Medical experts consider that 'Comprehensive Geriatric Assessment' (CGA) is as important as the precise analysis of the tumour to ensure effective care management*". Accordingly, in 2007, the French National Cancer Institute (INCa) launched a nationwide study making it possible to validate a new screening tool that is less time-consuming and costly than CGA: the G8 tool created based on a cohort study of 365 patients over 75 years old requiring chemotherapy, in Aquitaine, then validated in a national group (Oncodage).

The 18-month long, multicentre trial conducted by oncologist Pierre Soubeyran, Director of UMR 1218 (Inserm, University of Bordeaux), dealt with over 1500 patients over 78 years old on average. "*G8 is a geriatric screening tool including 8 items dealing with mobility, daily medications, and neuropsychological problems, etc. It can be done by an oncologist or specialised nurse in 10 minutes. At the outcome of the session, an assessment score can be established on a scale between 0 and 17*", Muriel Rainfray added. Any score under or equal to 14 reflects a geriatric frailty or vulnerability that should be taken into account by the health care team. Consequently, the treatment has to be adapted, for example, by proposing chemotherapy at lower doses, shorter periods of time, with different drugs, or even by reducing the number of sessions or trips to/from hospital for treatment.

The tool has been validated throughout Europe. Now comes the time for it to be evaluated during the PREPARE study, phase III clinical trials by the Institut Bergonié. "*Our goal will be to assess the impact of geriatric interventions in the management of patients 70 years old and older being treated for cancer, detected as 'at risk' by G8*", she explained. The randomized trial will compare the effectiveness of two interventions. Patients in population A are treated based on standard oncological care protocols whereas population B patients also benefit from geriatric care management including patient monitoring by a nurse trained in case management. "*We want to find out whether or not geriatric interventions improve the survival of patients with cancer as already proven in the overall population.*" "*The idea is not to offload onto nursing duties which are extremely important in the treatment but for the nurses to fully participate in the geriatric treatment*", Muriel Rainfray cautioned. This clinical research is all the more relevant since the elderly, like children, are often left out of therapeutic trials. A bad practice that needs to be changed. ■

Lily Bias

DAVID SANTAMARIA

DESTINED FOR THE WIDE-OPEN SPACES OF FREEDOM

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The Madrid native, David Santamaria, joined Bordeaux's IECB (European Institute of Chemistry and Biology) in the summer of 2016 as a cellular biochemist specialised in Kinase cells. Now, he has just created his lab focused on identifying and investigating novel signalling pathways and oncogenic functions that govern the onset of lung adenocarcinoma. His research uses mouse models and tissue organoids.

A trained biochemist, Santamaria received his PhD from the University of Madrid in 1999 under the guidance of Prof. Jorge B. Schwartzman who became his mentor, teaching him cell research methods and experimentation. He owes his revelation for research to Schwartzman – a key figure in his career path, who allowed him to "*open up the doors of knowledge*".

The 4-year post-doc that followed thrust him "*into the incredible universe of Cambridge*" in Prof. Ronald A. Laskey's laboratory, where he rubbed shoulders with no fewer than 15 nationalities of researchers, and decided to focus on the initiation of DNA replication and its connection with cell cycle control. In that setting overflowing with know-how and knowledge, his motivation was at its height, Santamaria recalls in a rush of nostalgia and excitement. And he realizes what a privilege it was to meet certain people: full of emotion, he still remembers Sir John Gurdon (2012 Nobel Prize) "*who it wasn't uncommon to catch a glimpse of through the door of his nearby lab, bent over his microscope at 2 in the morning, at over 70, in formal dress after an official reception!*". The proximity and accessibility of such brilliant, charismatic people are among Santamaria's fondest memories.

Upon his return to Spain in 2003, he joined Prof. Mariano Barbacid's team and spent 14 years with the specialist working together on identifying therapies. On the scale of a researcher's life, that was a rather long period. A period during which one discovery followed another, like the fact that the cell division mechanism has evolved very little between yeasts and humans. More interested in focusing on molecular processes, he decided to pursue his research elsewhere in Europe and picked Bordeaux as his home base. Now, backed by his small, young team, he is currently involved in several projects, including the study proving that the K-RAS oncogene operates in pairs or multimers, demonstrating the importance of those molecule groups in triggering lung cancer.

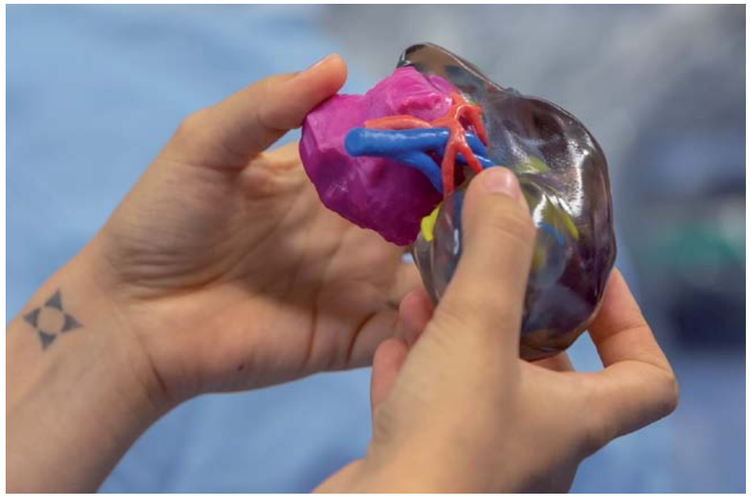
As soon as he settled in Bordeaux, he opted for the quiet life in the Bordeaux suburbs with a yard for his dog and enjoys "*roaming around the market in search of local produce*". What's more, he likes describing himself as someone soon-to-be carrying a basket on his arm, according to him that's the perfect storybook image of the French way of life! He could definitely imagine himself in an old stone house, drawn by the charm of antiques and "*things that have a past*". So he bargain-hunts at flea markets to unearth unusual objects, and loves vintage cars that are nothing like today's standardised vehicles. He drives a black 1973 Austin Mini collector, and especially enjoys rambling around the Médoc vineyards in autumn... But this Latin epicurean's absolute passion is still the mountains, in every shape and size, in every condition, for their biodiversity, their wildlife, their relief, their green forests and their snowy paths where, back when he was 18, he gave ski lessons. And any chance he gets, he goes there to hike, climb... and recharge his batteries with a great sense of freedom.

The same sense of freedom that research gives him, too, "*the only field that lets you ask thousands of questions and spend your time finding the answers...*". ■

Constance Deveaud

3D-PRINTING IN THE FIGHT AGAINST RENAL CANCER

The Bordeaux University Hospital, one of France's biggest kidney surgery centres, is developing the surgery of the 21st century.



Before operating, surgeons can now visualize the location of the tumour (in pink-purple) and its surroundings (vessels, excretory ducts, etc.).

MRIs, CT scans and PET scans… medical imaging has already transformed medicine by making it possible to visualise the inside of a patient's body. But digital simulation is used for going even further by modelling organs and interactions with "surgeon" robots! Practitioners can now plan their operations thanks to these digital organs that allow them to assess the difficulty of the intervention beforehand. Professor Jean-Christophe Bernhard, from the Bordeaux University Hospital (CHU) department of urology, andrology and kidney transplants has taken it to the next level. "*We've developed a 3D-printed model, specific to kidney tumour pathology to improve the quality of operating planning for conservative surgery. The aim is to damage the organ as little as possible at the time of tumour excision.*" In fact, the kidney is a non-palpable, deep organ, and interpreting scanner or MRI cross-sectional images can be complex. In the case of an operation as tricky as partial nephrectomy via laparoscopy with robotic assistance, surgeons need to do a mental reconstruction to picture the tumour on the kidney to be operated on and to foresee the stages of their intervention. The joint project between the Bordeaux University Hospital, the Institute of Urology in Los Angeles (University of Southern California) and the Tokyo (Teikyo University) urology department has led to the development of an innovative 3D-printing technique, producing a life-size kidney based on the patient's medical imaging. Each part of the organ has a different colour: the renal parenchyma is transparent, the arteries are red, the veins blue, the collecting system is yellow and the tumour is pink. "*This model is helpful because, first of all, it makes it possible to picture the tumour's location and surroundings – collecting cavities, vessels – in the overall volume of the organ in order to define the most suitable way to approach it*", Jean-Christophe Bernhard explained. "*We can extract the tumour more carefully to avoid an impaired renal function since in a single glance 3D-modelling makes it possible to assess the complexity of the case, the relations between the tumour and the vessels or the excretory pathways.*" Surgeons now operate over 150 patients a year with this new technique thanks to the quality of the images produced by the CHU's interventional and diagnostic imaging service. The sharpness and accuracy of the 3D model depend on the quality of the images produced!

On top of more accurate planning, robotic assistance provides dissection accuracy. For that matter, integrating 3D modelling directly into the view of the surgical area opens up the possibilities for image-guided surgery. These innovations have been implemented within the framework of the Research and Innovation Fund in Renal Surgery, hosted by the Fondation Bordeaux Université (www.chirurgie-renale-bordeaux.fr).

Lastly, for patients, 3D-printed models have also become a new teaching aid, crucial for better understanding of their pathologies and the intervention they're going to benefit from. These digital sculptures will also be used for teaching future surgeons. "*With realistic printed materials, we'll most likely be able to practice the day before the intervention, a little bit like a pilot who simulates his landing in Chicago or Paris*", Jean-Christophe Bernhard speculated. ■

Didier Dubrana

AUDREY GROS

PROFESSION: LYMPHOMA "PROFILER"

She's tall, young, beaming with joy and personifies the new hospital-university generation. The generation that, thanks to expertise in bio-computing, is participating in the "*industrial revolution*" of genomics research. Her mission is to implement high-speed sequencing, a spearhead technology making it possible "*to study the DNA of tumours and observe a multitude of markers simultaneously: an extraordinary savings in time and gain in data*", Audrey Gros emphasized enthusiastically.

Since the arrival of the Next Generation Sequencer (NGS) in October 2015 in the tumour biology department at the Haut-Lévèque Hospital of the Bordeaux University Hospital (CHU), she has coordinated all the set-up and development procedures. That has led to remodelling the lab, training technicians and biologists, and adding an essential area of expertise: bio-computing. Currently under the supervision of Professor Jean-Philippe Merlio at UMR 1053 (Inserm, University of Bordeaux), her research work essentially deals with cutaneous lymphomas, in close relationship with Professor Marie Beylot-Barry's onco-dermatology department at the hospital.

"*The machine has reached its saturation point*" she said regretfully, requiring a high-speed sequencer co-funded by the Nouvelle-Aquitaine Region and a vision of potential needs. That's why, along with her colleague Eulalie Lasseaux, she created the BNB Club (for Bordeaux NGS Bio-computing) to bring together clinicians and researchers from all backgrounds on the campus to share their knowledge. Inserm's onco-dermatology team is developing preclinical lymphoma models to reconstruct the evolutionary history of the cancer and decipher the cancerous cell anomalies to understand which treatment could fight them.

As a "*lymphoma profiler*", Audrey Gros has analysed aggressive cutaneous lymphomas and is about to publish a new article on identifying markers which predict non-response to treatment of primary cutaneous B-cell lymphomas. The topic has helped draw attention to the whole team's international reputation. Genomics of cancerous cells has become her field of choice, although she wasn't left indifferent by her earlier, one-year stay in Professor Benoit Arveiler's department, specialising in hereditary genetic diseases.

A Paris native, Audrey Gros started out as a pharmacy student. Right in her very first year, it was Professor Moïse Pinto's unusual theatrical teaching methods that caused her to have THE revelation for genetics. He is the one who still inspires her today, as she faces her histology students, to give them as much enjoyment as

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she gets from making her classes energetic and lively. Because she has a taste for teaching and illustrative explanations.

Since her arrival in Bordeaux in 2008, she realises that her "*career was preordained*", guided by her mentor, Professor Nicolas Sevenet, a specialist in constitutional genetics. He supervised her science thesis on hereditary breast cancers in patients with BRCA2 mutations, which she presented in 2013. Since then, her dual career as an associate professor and hospital practitioner (MCU-PH) has led her to divide her time between the laboratory and the Bordeaux University Hospital (CHU), where there's "*a lot of pressure to provide the analyses required for treating patients suffering from lung, colon, melanoma and lymphoma cancers from all over the Aquitaine region*". Along with the diagnoses based on microscopic examinations made by anatomical pathologists, her analyses allow clinicians to prescribe targeted therapies.

Yet despite the young woman's taste for challenges, she also cultivates her sense of family that gives her balance. She enjoys doing creative activities with her two little boys and pharmacist husband, as they await the imminent arrival of a 3rd child... ■

Constance Deveaud

VÉRONIQUE VENDRELY

ALWAYS FORGING AHEAD

What makes Véronique Vendrely tick? An inner force that allows her to make choices – sometimes difficult ones – but "*in the light of experience, I've learnt to trust my intuition and also take more risks*", she said. Even though after secondary school she was drawn to studying medicine for "*the realm of treatment as well as for being in contact with people of all different categories*", at the time she didn't know whether she would become a researcher or a doctor. Her motivation became clearer after specialising in oncology and "*being confronted with a life-threatening disease that requires respect for the patient as a person*", she explained. As a radiotherapist specialised in digestive cancer, she juggles between the clinic, research, teaching and... a family life with "*fortunately, a very helpful*" nephrologist husband and three sons now aged 20, 16 and 9.

Year after year goes by at the pace of the hospital and the UMR 1053 BMGIC lab (Biotherapy of Genetic Diseases, Inflammatory Disorders and Cancers), at the interface between clinical and fundamental research, as well as the technical sciences, omnipresent in that field.

Since it's never too late for new challenges, at age 45, Véronique Vendrely set out on a new career path to become a University Professor-Hospital Practitioner (PUPH) and published her thesis in December 2018 on the "*Sensitization to radiotherapy using pro-oxidant substances in pancreatic cancer*".

Although her decision may seem to have come late, she acknowledges having overcome her doubts and circumvented difficulties "*thanks to experience and the necessary hindsight*" and at the same time, pays tribute to her team's precious support.

All along this "*obstacle course*", on the whole marked by the predominance of men (at the University and at home!), Véronique Vendrely considers herself lucky to have made "*extraordinary encounters*" with some charismatic women, like Sandrine Dabernat, her thesis supervisor who never doubted her ability, Cécile Girault who put her in charge of coordinating clinical tests at the Fédération Francophone de Cancérologie Digestive (FFCD) that she directs, and Te Vuong, head of the radiotherapy department at the Jewish General Hospital in Montreal whose team Véronique Vendrely will join mid-2019 for a year abroad.

Upon her return, she'll be teaching junior doctors, for whom she'll make it a point of honour "*to open doors and not close them*".

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For now, she's working on facilitating the involvement of radiotherapists in fundamental research. The arrival of a pre-clinical irradiator in Talence in the Inserm laboratory, directed by Professor Andreas Bikfalvi, promises new research perspectives. She is consequently setting up irradiation protocols so the instrument can be used by the various research teams.

Currently, she's also participating in the Physical Optics & Radiotherapy Programme in Aquitaine (POPRA), which has brought together very diverse disciplines since 2008.

For work, Véronique Vendrely deals a lot with images. And for pleasure, too. Photography has always counted for her. Recently, she joined *Les Mirettes*, a female collective that created an exhibition based on a theme for a neighbourhood event in Bordeaux. She'll be continuing that adventure simply because she enjoys "*looking at things in a certain way*". ■

Constance Deveaud

Interventional radiology is emerging as an innovative therapeutic solution in the fight against cancer.

Ultrasound coupled with MRI increases treatment accuracy.

ULTRASOUND TARGETING BREAST CANCER

The Institut Bergonié is launching the Breast Resection By High-Intensity Focused Ultrasound (BRIFU) programme to evaluate the effectiveness of MRI-guided focused ultrasound in the treatment of breast tumours. "*Focused ultrasound is used to burn cells in the heart of the tumour*", radiologist Jean Palussière explained. The therapeutic method that destroys cells via hyperthermia has been used for over twenty years in oncology to treat malignant lung, liver, kidney and bone tumours. However, focused ultrasound has the advantage of being the only totally non-invasive technology, requiring no needle introduction. Guiding ultrasound beams by MRI means the exact zone can be located and destroyed. What MRI actually does is provide high-resolution anatomical images with excellent contrast of soft tissues, like breast tissue, identifying the volume of the tumour accurately.

In addition, with MRI, real-time temperature measurements can be performed down to the nearest tenth of a degree (0.1°C), while steering the application of the ultrasound beam. Lastly, this type of imaging offers the possibility of implementing automatic spatial and temporal control of the thermal dose delivered (between 37°C and 100°C). "*Coupling ultrasound with MRI produces extremely high accuracy*", added Jean Palussière, the instigator of the trial involving 20 patients.

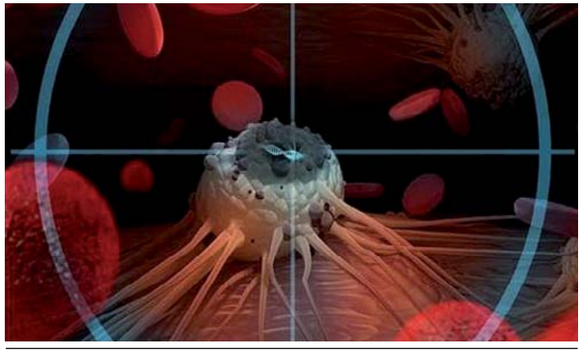
The evaluation is being conducted in partnership with the UCAIR research lab directed by Dennis Parker at the University of Utah. So far, the American laboratory has developed the treatment prototype of breast tumours with the Bordeaux company, IGT (Image Guided Therapy). "The study's findings should indicate to what extent and in what way the technology is effective on limited tumoral volumes," he continued.

The radiologist is also working on another project in synergy with Doctor Isabelle Soubeyran, head of the Molecular Pathology Unit at the Institut Bergonié. The goal is to establish the effects that heating lung tumours has on the patient's immune system. Pulmonary metastases are treated by radiofrequency heating, applied via an electrode placed directly in the metastasis. It's a scanner-guided treatment that has become an alternative to surgery. "One of the issues we're interested in is establishing the impact of heating on the patient's immune response," Jean Palussière explained. To evaluate the effect, blood tests enumerating the lymphocyte populations and circulating tumour cells (CTCs), as well as tumour biopsies before, during and after the treatment are going to be done within the framework of a clinical trial. For now, there are more questions than answers. Does heating cause a peritumoral lymphocyte infiltration to occur? Does the heating cause a release of tumoral cells? Is it possible to quantify the sub-lymphocyte populations activated by the destruction of tumours? Answering these questions is crucial... because immunotherapy is currently one of the major advances in oncology treatments. And if the heating techniques show an influence on the patient's immune reactions, they could then be associated with immunotherapy to increase its effectiveness. ■

Raoul Sancy

TARGETED **THERAPY**

Genetic testing guides clinical practitioners more and more accurately in their therapeutic choices.



Adapted from "Novel Platform Accelerates the Discovery of New, Targeted Cancer Therapies" Sinha S., SRI International

The aim of clinical medicine is to try to treat each cancer based on its molecular profile, and no longer only based on its location and histological analysis. That strategy became possible with the advent of the first targeted therapies, capable of specifically destroying tumour cells displaying a particular molecular defect, i.e. an anomaly in their genes (oncogenes) that gives them higher specificity than normal cells. "*Progress in molecular genetics has shown that a certain number of mutations can accumulate in the life of a tumour and of course in an individual's life*", explained Jean-Philippe Merlio, director of UMR 1053 (Inserm, University of Bordeaux) and Tumour Biology and Biological Resource Centre for cancer at the Bordeaux University Hospital (CHU). "*The tests will be used to spot alterations targetable by the drug as if there were padlocks on the surface of the tumoral cells that the 'key drug' will close and lock to prevent cell proliferation*", he added. In routine clinical practice, to guide the treatment, we already systematically search for a mutation of the Epidermal Growth Factor Receptor (EGFR) gene present in 10% to 15% of lung adenocarcinoma cases, an amplification of the HER2 gene for breast cancer or stomach cancer, a mutation of the BRAF gene for melanoma. In addition, in a given family of cancer (lung, skin, blood), researchers are going to be able to identify specific types of tumours based on the characteristics of the genetic anomaly discovered. That is the case, for example, with lung cancer, which is associated with 40 different mutations of the EGFR gene! That genetic study then guides clinical practitioners in their choice of drugs to avoid chemotherapy, whenever possible, as it indiscriminately destroys all quickly multiplying cells, such as hair cells! Research on mutations is conducted on tumoral samples in one of 28 molecular genetic platforms throughout France. The Haut-Lévêque Hospital and the Institut Bergonié handle that testing for Bordeaux. "*The more progress we make, the more these genetic techniques are perfected in tracking the slightest DNA strand*", Jean-Philippe Merlio continued. With a basic blood test, it is possible to decipher the cancer's development, its response to treatment or its possible relapse. Isabelle Soubeyran, head of the UMR 1218 Molecular Pathology unit at the Institut Bergonié explained: "*As soon as a tumour is present in the body, circulating tumour DNA fragments (ctDNA) or circulating tumour cells (CTC) spread, and end up in the blood. They carry a lot of information that is already used for monitoring patients. But, on the one hand, the real difficulty lies in detecting them and, on the other hand, determining all their meanings.*" In the future, thanks to these blood tests, ultrasensitive techniques should make it possible to establish prognoses, predict treatment effectiveness, search for resistant mutations, and perhaps understand how the primary tumour metastasizes? Needless to say, the prospects guiding their research work are numerous. ■

Raoul Sancy

CAR-T CELLS: THE IMMUNOTHERAPY GAINING GROUND

Forty years after the first allotransplantations, the CAR-T cells technique is opening up new perspectives for patients.

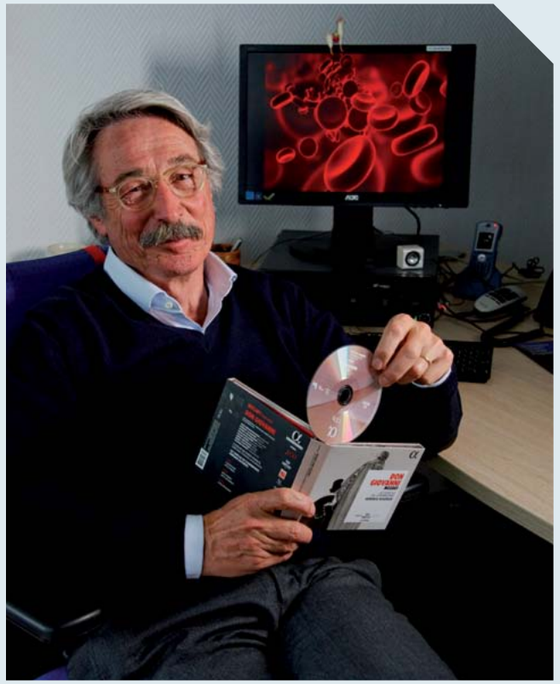
"*It's a disruptive innovation in the health field*", according to the analysis by Professor Noël Milpied, Head of the Hematology and Cellular Therapy department at the Bordeaux University Hospital (CHU). "*Treating patients with CAR-T cell injections is a revolution in the fight against blood cancers such as diffuse large B-cell lymphoma.*" After Paris (St Louis and Robert-Debré Hospitals) and Rennes, the Bordeaux CHU is the third French location to participate in a clinical trial of cell therapy "*in lymphoma refractory to the usual treatments.*" This new treatment consists in genetically modifying the patient's T lymphocytes to educate them to recognize cancer cells. So, CAR-T cells (short for Chimeric Antigen Receptor T-cells) are the patient's T lymphocytes that have been genetically engineered in vitro in such a way as to make them express an artificial receptor, known as "*chimeric*". On their surface, the engineered blood cells express CAR receptors, which are designed so that their extracellular part will recognize the tumoral antigen present on the surface of the patient's cancer cells and kill them! The clinical trials are being conducted with the Kite/Gilead biotechnology lab producing this "*living drug*". Inside the patient's body, CAR-T cells do indeed have the ability to multiply by a factor of 1000 or even 10,000 compared to the number of cells injected. They are also equipped with a "memory" allowing them to subsist for months, providing immune system surveillance to prevent a possible relapse. "*In the case of diffuse large B-cell lymphoma, the probability of relapse is only 10% but still 50% for acute lymphoblastic leukemia*", Noël Milpied explained. "*There's still a long way to go before mastering the treatment and the procedures but I'm pretty optimistic. International studies have proven that the results hold up even though this treatment causes severe, but reversible, side effects.*" An example, the infusion of lymphocytes releases a high number of cytokines possibly causing high fever, a drop in blood pressure and difficulty breathing. There are also neurological side effects that can lead to a comatose state and those very unfortunate episodes require costly care. What's more, we don't actually know the overall cost of this treatment that may be close to €800,000. However, we do know that the potential of "*living drugs*" with lymphocytes is unlimited, thanks to genetic engineering techniques. ■

Living drugs against blood cancer

Didier Dubrana

NOËL MILPIED

BLOOD IN HIS SOUL



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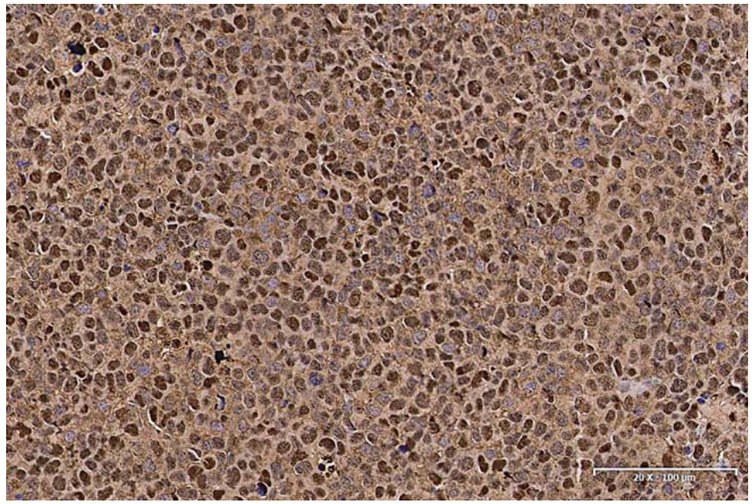
Less than a year away from retirement, like on Day One, Professor Noël Milpied, Head of the Hematology and Cell Therapy department at the Bordeaux University Hospital (CHU) is motivated about the new treatment he is setting up with his team: "*We've started a clinical trial with CAR-T cells based on the use of patients' own immune cells genetically engineered to destroy their tumour cells*", he explained. As a matter of fact, the promising drug has been tested for the past few months on consenting patients in only three French CHUs. "*For someone like me who was around when the first bone marrow allotransplants were made, I think this is an innovation that will go down in history in the treatment of blood cancers.*" Medicine was a true calling for Noël Milpied who "*never dreamed of doing anything else*". He enrolled in medical school in Nantes in 1971. With his internship under his belt, he initially planned on specialising in intensive care, but the compulsory military service was to decide otherwise. "*In 1979, we had no choice!*" He volunteered to do his military service abroad. He was sent to Morocco for a year, to the city of Nador located in the region of the Rif where he practised pulmonology. Once back in Nantes, he heard that a brilliant professor, Jean-Luc Harousseau, had just taken charge of the CHU's hematology department. The latter advised him to go get training in bone-marrow transplantations at the Fred Hutchinson Cancer Research Center in Seattle (USA). So he learned the transplantation technique there. "*It was the Mecca of hematopoietic stem cell transplants. And that's when I got the chance to rub shoulders with E. Donnall Thomas, who was awarded the Nobel prize of Medicine in 1990 (with Joseph E. Murray) for his discoveries concerning cell and organ transplants for the treatment of human diseases*", he reminisced. Back in Nantes again, he was given a position, at barely 37, as University Professor and Hospital Practitioner in the Nantes University Hospital's hematology department. "*A passionate, but especially exhausting, early career*", he said, "*I was regularly confronted with death and when I went home at night, my dermatologist wife and I shared our experiences. She, too, was exposed to the deaths of her HIV/AIDS patients, who were developing Kaposi's sarcoma*". He then added, "*It's most likely not a coincidence that none of our three children wanted to become doctors!!*"

From the start, the gentleman has been deeply committed to his hematology career at the hospital as well as on institutional, national and international levels. In 2005, the famous hematologist and politician from Bordeaux, Josy Reiffers, asked him to take over as head of his department at the Bordeaux University Hospital (Haut-Lévêque). There, he developed the bone-marrow transplantation activity, combining clinical practice, research and teaching. He was elected president of the French Society of Bone Marrow Transplantations and a member of the French National Council of Universities. He has co-authored nearly 400 scientific articles in the field of blood cancers. "*I've probably worked too much*", admitted the head of the Bordeaux University Hospital's Cancer Centre, which also coordinates the Scientific Delegation for Clinical Research and Innovation. However, his upcoming retirement will give him time to enjoy all the Italian, Czech and Russian operas he has always loved. He'll be able to slip away to Bordeaux's Grand Theatre for a performance of La Bohème and its timeless love story between Mimì, the seamstress and Rodolfo, the poet, or to the Paris Opera – where he's been a subscriber for thirty years – to listen to Rachmaninov or Tchaikovsky. But when the weather's nice, he'll definitely grab his board to surf the enjoyable waves of his new life. ■

Didier Dubrana

DECIPHERING **LYMPHOMAGENESIS**

How can the molecular mechanisms of lymphomagenesis be deciphered to improve diagnosis and determine a patient's prognosis?



Diffuse large B-cell lymphoma (DLBCL)

The Lymphomagenesis Molecular Mechanism team at CRIBL (Control of B-cell Immune Response and Lymphoproliferations) UMR CNRS 7276, headed by Professor Jean Feuillard, is interested in transformation mechanisms of B cells in cancer, called lymphoma. Lymphomas are most often characterised by the excessive proliferation of B cells, but also T cells. They affect 11,000 people a year.

"*Our research focuses more specifically on the genes involved in the process leading to the occurrence of two major types of lymphomas. Quick-growing lymphomas, known as aggressive, whose main mechanism is the increased proliferation of cancer cells, and slow-growing lymphomas, known as indolent, whose resistance mechanism is programmed cell death*", Jean Feuillard explained. So what are the genetic determinants involved? We know that these cancerisation processes involve two signalling pathways relying on the activity of c-Myc and NF-κB proteins. The c-Myc protein is involved in the cellular proliferation factor and in numerous cancers, whereas NF-κB (short for Nuclear Factor-kappa B) is especially active in the immune response (inflammatory response, lymphocyte maturation, etc.).

Researchers have already shown that NF-Kappa B is both an activator of B cell proliferation and that it also prompts the immune system to kill, with B cells proliferating! "*The team wants to understand the relationship between aggressive lymphomas and indolent lymphomas and whether MyC and NF-κB can converse for one or the other of the two types of cancers, which are very different*", Jean Feuillard added. The research is pursuing several avenues of investigation. One avenue takes samples of human cells from patients at the Limoges University Hospital that are cultured at the Biology and Health Research Centre (CRBS) where cell lines are developed to study signalling pathways. Transgenic animals have also been developed as the murine model of Waldenström's macroglobulinemia (WM). The first findings published during the most recent conference of the French Society of Hematology report that the mice bearing the MYD88 mutation produce a Waldenström-type indolent lymphoma in 80% of the cases and an aggressive lymphoma in 20%. "*What makes the same mutation produce 2 types of cells*?" Jean Feuillard asked. The UMR CNRS 7276 has also developed nationally- and internationally-recognized technological expertise in the characterisation of hematologic malignancies by flow cytometry and/or molecular biology (diagnostic, prognostic and theranostic markers). Lastly, setting up this research facility within the Limoges University Hospital medical centre has already fostered numerous interactions and complementary endeavours between clinical and fundamental research. ■

Didier Dubrana

CHRISTELLE VINCENT-FABERT

COOKING UP LIFE IN THE LAB

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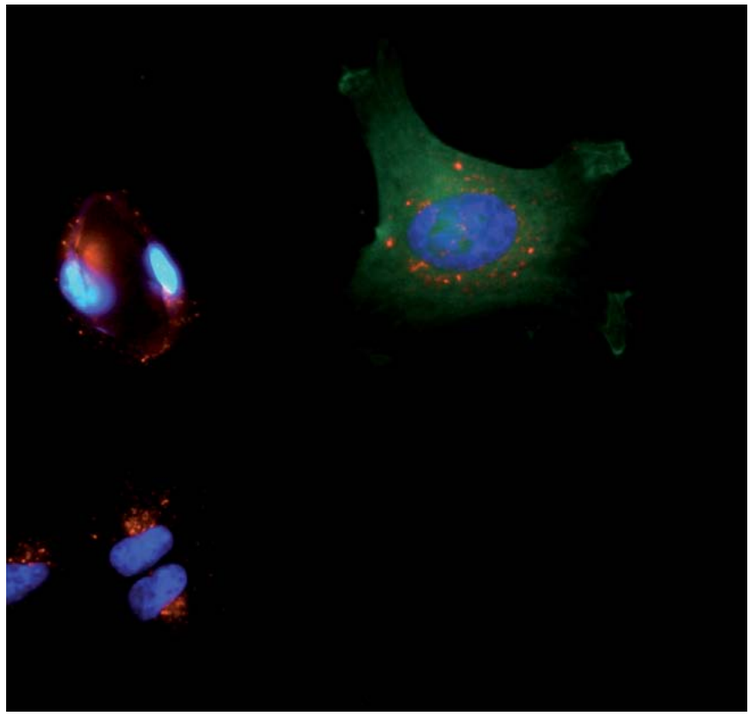
In her delicate, wispy voice, Christelle Vincent-Fabert knows how to explain complex biological processes in layman's terms! As a post-doctoral fellow on the *Molecular mechanisms of B-cell lymphomagenesis* team at the Biology and Healthcare Research Centre (CRIBL UMR CNRS 7276/ Inserm U 1262), she likes taking challenges and meeting them. In 2014, when she arrived in Professor Jean Feuillard's lab, it was to work on Waldenström's macroglobulinemia (WM), a pathology linked to the proliferation of B lymphocytes in the bone marrow and, more rarely, in the lymph nodes and spleen. "*Jean Feuillard asked me to create a transgenic mouse model capable of expressing the protein mutation responsible for the disease*", the young woman said. Mission accomplished even though many other international research groups had been hitting a brick wall for years. "*Now we're going to be able to work on understanding the mechanisms of evolution in this disease that develops very slowly at around age 70 in humans and, who knows, maybe be able to develop specific treatments*", she added.

A few years earlier during her first postdoctoral position in Marseille, she had also worked on another transgenic animal model to study the gene networks involved in the future of hematopoietic stem cells during aging. When asked about her talent for tinkering with mice DNA, unpretentious, she preferred talking about perseverance, about liking challenges that start from scratch. She's got talent! And that's definitely why her lab director did what it took to keep her. As a result, she took the CNRS and Inserm competitive entrance exam. Her passion for science gets her out of the lab on a regular basis to run educational workshops as the Scientibus roams through the Limousin region. It's a vehicle inaugurated in 2004 by Nobel Prize winner in Physics, Claude Cohen-Tannoudji. "*I love going into schools for the day and explaining everyday science in simple words. Biology, chemistry, and even physics – although it's not my favourite field.*" However, when she finally takes off her lab coat, it's to slip on an apron and carry out, in all likelihood skilfully, a few steps worthy of a scientific process: since "*when you follow a protocol in the lab, it's like a recipe*", she quipped. ■

Didier Dubrana

TARGETING **THE MICROENVIRONMENT**

To control tumour growth, researchers decipher intercellular communication.



A tumour is, above all, tissue that exchanges with its microenvironment

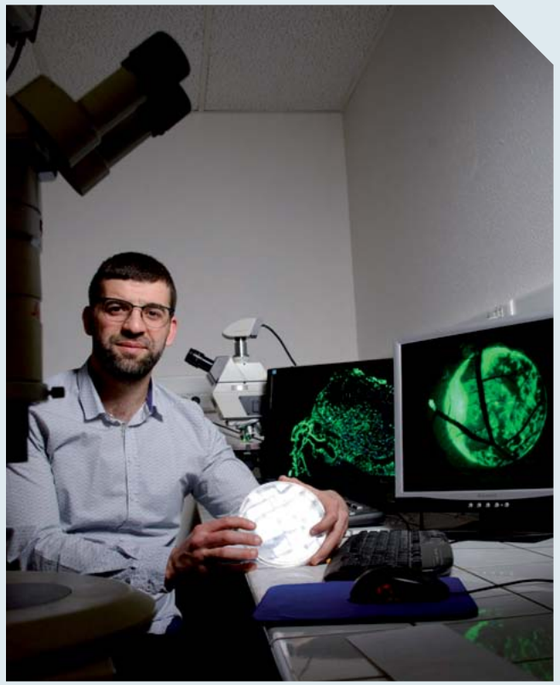
The EA3842-CAPTuR research team (Control of cell Activation in Tumour Progression and Therapeutic Resistance) at the Faculty of Medicine in Limoges targets biological mechanisms involved in tumoral growth and resistance to therapies. Directed by Professors Odile Jauberteau and Fabrice Lalloué, the team has already won an initial victory in the battle by showing the involvement of neurotrophins in oncogenic mechanisms. Until now, those molecules had mainly been identified in neuroscience since they make up a family of proteins indispensable for the survival and differentiation of the neurons of the nervous system (brain, spinal cord, nerves, etc.). "*We discovered that neurotrophins – growth factors in neuronal cells – are also responsible for the growth of tumours, their proliferation and mechanisms of resistance to therapy*" Professor Fabrice Lalloué explained: "*to understand, we had to decipher the means of communication between cells*". A tumour is, above all, a tissue that exchanges with its microenvironment. Its means of communication especially relies on the release of circulating micro(nano)vesicles – exosomes – containing neurotrophin receptors, in particular, that are disseminated around the tumour, which allows their transfer to the surrounding cells. "*It's as if we installed antennae on the cells in the microenvironment capable of picking up the emission of signals – neurotrophins – from the tumour to control or activate that microenvironment*", Fabrice Lalloué explained. That communication affects neighbouring cells as well as remote ones, forming "metastatic niches" as in the case of bronchial cancers. The process can even inhibit the immune system, making tumour development that much easier. The research work conducted by the Limoges team has also described the function of a neurotrophin receptor: sortilin. The sortilin protein could slow down the proliferation of tumours by associating with another receptor that it inhibits: EGFR (Epidermal Growth Factor Receptor), a tumour growth activator.

The CAPTuR team is also involved in the European project SUMCASTEC (Semiconductor-based Ultrawideband Micromanipulation of CAncer STEm Cells), which brings together oncology specialists, physicists and electronics engineers from the XLIM research institute. "*We want to develop biomarkers capable of detecting cancer stem cells by their electromagnetic signatures, in order to create new tools for treatment.*" That is because, even though there are healthy stem cells, there is also a small subpopulation of cancer stem cells that may cause the relapse of certain cancers. And those malignant ones remain hard to identify and treat, due to their resistance to conventional radiotherapy and chemotherapy. ■

Lily Bias

SOFIANE SAADA

THE FREEDOM TO EXPLORE



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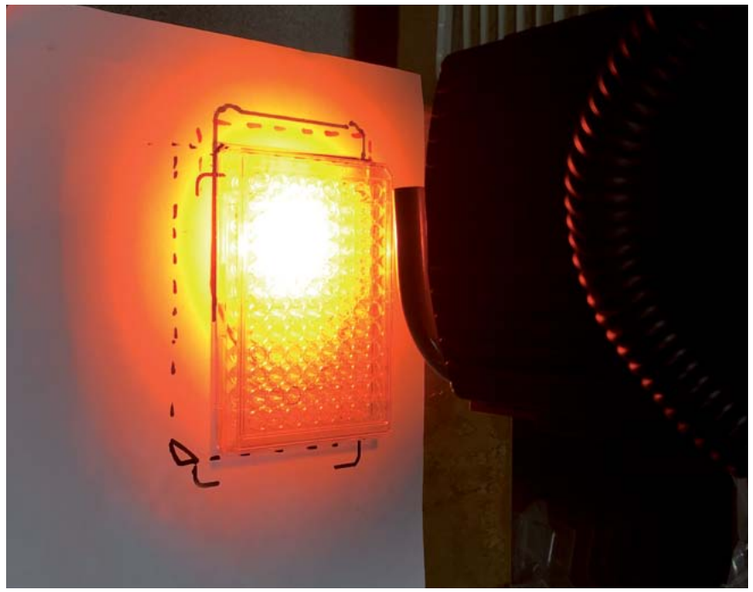
The city of Tizi Ouzou, or Tizi-Wezzu in the Berber language, is where the young Sofiane spent a happy childhood at the foot of the Djurdjura mountains. His mother, a primary school headmaster, and his father, an electronics engineer, gave him the taste for knowledge and science. He, in turn, was to become a purveyor of knowledge "*so as not to let ignorance stagnate*" by creating non-profit organisations running science workshops in his city's libraries while he was still a student in Algeria. After getting his maths and sciences baccalauréat, he enrolled in Mouloud Mammeri University for an undergraduate degree in biology. He left the 'city of flowering broom' (ouzou in Berber) to do a Masters in Biology in Limoges. "*I was interested in everything and I asked one of my professors, Danielle Troutaud, if I could do an internship on her team for an initiation to research in the field of health biology and cancerology.*" Then the young student left for Paris to get a Masters 2 in immunology research at the University of Paris-Est during which he spent seven months at the Henri-Mondor University Hospital to further his knowledge in applied immunology and pathology. He returned to Limoges for his doctorate thesis on the *Neurotrophins and neurotensin function in B-lymphocyte oncogenesis* (in French), working on the EA 3842 team directed by Professor Marie-Odile Jauberteau. He received his doctorate in 2015. "*Like for all my other degrees, I was proud to announce it to my parents who always wanted their children to go to university. And they succeeded! I have one brother who's a computer engineer, another one specialized in materials science and my little sister is doing a degree in mathematics and computer science.*" 2016 is the year he left for a 2-year stint as a post-doc at the University of Pittsburgh Cancer Institute, to work on immunotherapy. "*I always kept in close contact with my mentors in Limoges, my thesis supervisor and Professor Fabrice Lalloué on the CAPTuR team.*" So when the opportunity to go back to Limoges was offered, he jumped at it. Another post-doc is what brought the 33-year old Franco-Algerian back, within the framework of the European project H2020 SUMCASTEC (Semiconductor-based Ultrawideband Micromanipulation of CAancer STEm Cells) on the EA3842 team co-directed by his two mentors and in partnership with Arnaud Pothier from the XLIM lab. The programme was formed by a consortium of several European countries: France, Italy and the UK bringing together physicists, biologists and pathologists for "*transdisciplinary and translational research to identify and evaluate diagnostic and prognostic biomarkers to contribute to the development of new diagnostic tools*".

More specifically, Sofiane Saada works on glioblastoma, the most common brain cancer in adults. "*When a tumour is eliminated, there's a high rate of relapse, caused by dormant cancer stem cells (CSCs) that wake up.*" For the time being, there is no tool to detect and neutralise these cellular "*time bombs*". But recently, thanks to the SUMCASTEC research, it has been determined that their electromagnetic signature is different from other cells. That's the path the biologist has taken to decipher the biophysical and physical characteristics of those cancer stem cells. Although the Limogeot by adoption no longer has much time to referee football matches, one of his hobbies, he likes his new home as much as his childhood homeland for the "*freedom to learn and find out, a day-to-day treat*". ■

Didier Dubrana

LIGHT THAT HEALS

Combining a light source, a photosensitizer and nanoparticles allows better targeting and treatment of cancer cells.



A 96-well microplate – each well containing cancer cells to which photosensitizers were added – is illuminated.

The University of Limoges PEIRENE laboratory directed by Professor Vincent Sol develops photodynamic therapy (PDT) techniques to treat cancer in various fields (dermatology, pulmonology, gastroenterology, etc.). PDT is a complementary therapeutic method based on the benefits of light, which has the property of selectively activating a family of drugs called photosensitizers (PS). In and of themselves, the molecules are not toxic, but if they are simply excited by a light source (laser, fluorescent tube) then they are! Transporting this drug into the heart of a tumour therefore boils down to placing a time bomb that can be set off by a simple beam of light! Vincent Sol explained the photochemical process as: "*while photosensitizers absorb light energy, they transfer it to the surrounding environment, causing the generation of several reactive oxygen species (ROS), including singlet oxygen, responsible for cell destruction. Since the reactivity of these species is limited to their intracellular location, that localized irradiation eradicates tumoral cells while preserving the healthy ones*". Photodynamic therapy induces an oxidant stress that kills cells! To apply the appropriate treatment dose, photosensitizer concentration, its location and the dose of light irradiated can be adjusted. The lab is working on two types of molecule manufacturing: photosensitizers derived from synthetic molecules or extracted from natural substances obtained by modifying the chlorophyll molecule. "*The synthesis of photosensitizers is only one of the stages of our research*", Vincent Sol specified. "*To kill cancer cells, we have to be able to reach them. Yet the bioavailability of photosensitizers is low – since not very water soluble – and those molecules alone can't reach their target. So we're going to help them travel.*" Chemists are grafting specific targeting agents on the photosensitizer: peptides, polyamides or other sugars enhance the solubility of porphyrin as well as its affinity for cancer cells. Attaching photosensitizers to nanoparticles also appears to be very promising, thanks to the Enhanced Permeability and Retention (EPR) effect. Why? Because particles ranging from a few hundred nanometres to a few nanometres tend to accumulate more on tumoral cells than on healthy tissues due to two biological phenomena: the abnormal development of blood vessels and ineffective lymphatic drainage in cancer tissue. The first phenomenon creates larger spaces between the endothelial cells, which allow the passage of nanoparticles. Whereas the second phenomenon keeps rather large particles from escaping from the tumour. The result: completely natural nanoparticles (cellulose) or nanoparticles covered in biopolymers (dextran, xylan, etc.) transporting the photosensitizer stay trapped in the tumoral tissues. Although this research is only in the animal experimentation phase for the time being, the PEIRENE laboratory is one of the only French laboratories that masters the whole chain from molecule manufacturing all the way through to biological modes of action. ■

Raoul Sancy

GUILLAUME CHEMIN

RESEARCHING AND TEACHING

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For Guillaume Chemin, the image of a Swiss knife sums up the researcher's daily routine perfectly: "*A researcher has to know how to do a little of everything with several different tools*". The young lecturer at the University of Limoges School of Pharmacy also does research at the PEIRENE Laboratory where photodynamic therapy (PDT) and photothermal therapy (PTT) techniques are being developed to treat cancer. "*We work with natural molecules – photosensitizers – to test them in oncology*", Guillaume Chemin explained. "*To successfully reach the target, in other words, to reach the tumour cells, we also have to create nanoplatforms using gold nanoparticles to facilitate the passage into the tumour. For the time being, we're working on colorectal cancer cell lines, before moving on to testing, thanks to the development of animal models that' ll be used to validate our molecules.*"

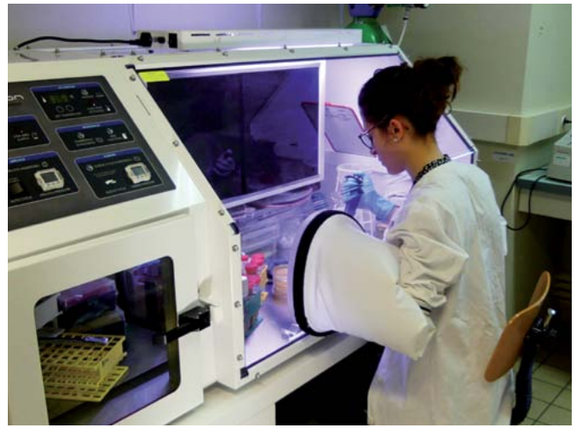
The biologist by training completed his PhD in Immunology with a speciality in Molecular Biology in 2011 while working in UMR CNRS 6101. He has just joined Professor Bertrand Liagre's team at the School of Pharmacy, "*because I've always enjoyed subjects related to human health. Pharmacology is an essential link between medicine and patients, with lots of biology. Besides, when you work on drug development, 50% of what you do is biology and the other 50% is pharmacology*".

All he needed to do, to complete his intellectual balance, was land a teaching position since teaching is another of his passions. Guillaume Chemin has always pursued his scientific career while supervising students, whether in Masters or undergraduate degree programs, or in preschools! "*It's impressive how fast little kids understand and how relevant the ideas they bring up are*", he said enthusiastically. He often thinks about ways to adapt his teaching to "*the new generation that has a different way of learning in front of a screen. I calculated that a pharmacy student has to take in up to 4000 class slides in a semester. And there's something important I've noticed: young people want tangible things and they wish they were already in the professional world. Our teaching has to keep up with those changes to be effective.*" With his Swiss knife always in his pocket – it's a gift from his wife – Guillaume Chemin roams the Limousin countryside on trail runs or ordinary family walks. Above all, he cherishes "*the time we spend together – just the four of us – my two daughters and my wife, who's a researcher like me*". ■

Lily Bias

ENVIRONMENTAL DISRUPTORS HATE YOUR GUTS!

Study of pollutant impact on intestinal flora could explain occurrence of some cancers.

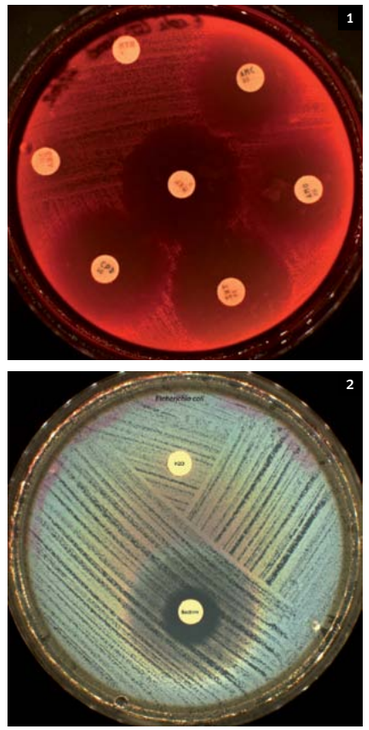


Tests on bacteria from the microbiota cultured in anaerobic conditions.

The Laboratory of Ecology and Biology of Interactions (EBI), a joint CNRS/ University of Poitiers research unit directed by Professor Jean-Marc Berjeaud, is interested in the impact of endocrine disruptors on health. Phthalates, parabens, bisphenol A and other phenols produced by industry (plastics, cosmetics, etc.) are environmental pollutants that end up in our intestines. Can these molecules trigger cancers? "*To answer that question, we study the effects of endocrine disruptors on intestinal microbiota*", said Jean-Marc Berjeaud. Our digestive tube hosts thousands of billions of non-pathogenic fungi, bacteria, viruses and parasites that make up our intestinal flora (or gut microbiota). For the past ten years or so, there has been increasing scientific evidence pointing to the importance of the gut microbiota balance on health. "*Our team is trying to understand the links between the microbiota imbalances and certain pathologies like cancer. We know it plays a role in immune, metabolic and digestive functions. The change in the microbiota – in other words, the functional and qualitative alteration of intestinal flora – is a serious lead to follow for understanding the origin of colon and intestinal cancers*", Jean-Marc Berjeaud summed up. The researchers in Poitiers cultivate about twenty species of bacteria in vitro, selected in the microbiota, which they subject to the "*toxicity*" of endocrine disruptors. They are also seeking to understand how those molecules are "*broken down*" by the intestinal flora to produce new substances whose effects on the organism are not always known. That expertise has given rise to two innovative joint efforts. The first one with the industrialist EUROFINS-CEREP. "*We created a collaborative Public-Private "EBI-CEREP" facility in order to test, on the pharmaceutical industry's request, what happens to medication in the intestine*". The EBI is also working with Hedex (Health Endocrine Disruptors EXposome); one of the research areas emerging from the Centre d'Investigation Clinique at the Poitiers University Hospital (CHU): "*This time we're working on ways to accurately estimate human exposure to endocrine disruptors and how to limit that exposure*", Jean-Marc Berjeaud concluded. ■

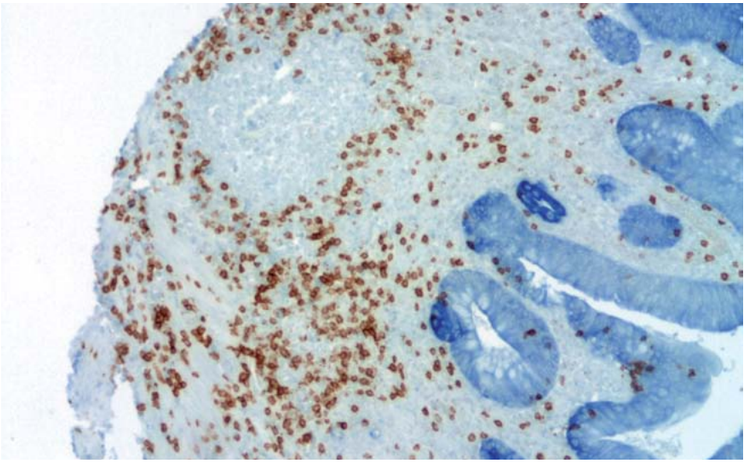
Didier Dubrana

Researchers test in vitro the effect of molecules on colonies of *Escherichia coli* grown in anaerobic (1) and aerobic (2) conditions.



TREATING LEUKAEMIA: THE PROSPECTS OF IMMUNOTHERAPY

The Inserm IRATI research group (ImmunoRegulation, Alarmins and Innate T cells) U1082 in Poitiers is focusing its resources on chronic myeloid leukaemia (CML).



CD8+ lymphocytes (brown) near a tumour (blue)

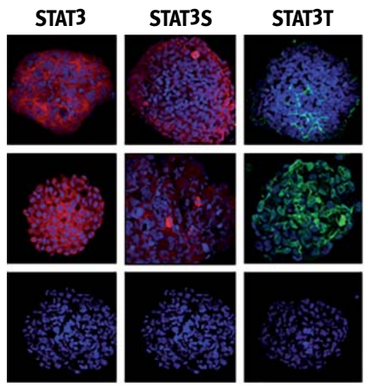
Chronic myeloid leukaemia is a cancer that affects bone marrow cells, where white blood cells in charge of protecting the organism against infectious agents are produced. But genetic alterations can occur when the bone marrow stem cells are maturing into white cells. That causes the formation of "immature" white cells, which cannot ensure their protective functions, and proliferate uncontrollably. In the case of CML, it is the presence of an abnormal chromosome (Philadelphia chromosome) inducing the production of a gene (named "BCR-ABL"), which codes for the synthesis of an enzyme: tyrosine kinase. The consequence is that enzyme's activity in the immature white cells is uncontrolled, making them tumorous. And the cancer settles in! "*Treatments rely on administering drugs that keep the tyrosine kinase enzyme from functioning. Those drugs are tyrosine kinase inhibitors or TKIs*", explained André Herbelin, Research Director at Inserm. The treatment induces remission in nearly 90% of patients but it has side effects and remains costly as well. The ideal solution would be if TKIs could be stopped and replaced by another solution! However, we also know that half the patients who stop TKI treatment have a relapse whereas the other half of patients don't. That phenomenon has yet to be explained! The Poitiers researchers are consequently working on a new prospect: combining conventional chemotherapy with immunotherapy. Immunotherapy is aimed at waking up a patient's immune system so that it destroys or, at the very least, controls the tumour on its own. "*The next therapeutic revolution will be the possibility of stopping the treatment permanently once there's a lasting period of remission. We support that theory since it takes into account the essential role played by the innate immune system and primarily the antitumor power of two innate cell populations: invariant Natural Killer T (iNKT) cells and innate T CD8 lymphocytes*", André Herbelin stressed. Innate T cells are constantly on patrol in our bodies to fight the potential occurrence of cancers. The Poitiers researchers recently demonstrated these two cell types (iNKT and innate TCD8) could, via their antitumor properties, be involved in controlling the disease. The collaboration underway with the Centre d'Investigation Clinique (CIC) at the Poitiers University Hospital (CHU) is aimed at assessing their mode of action. They will analyse the two cell types quantitatively and qualitatively in patients during TKI treatment, and then when patients are discontinuing the treatment. They will also test certain therapeutic antibodies that allow the antitumor properties to be potentiated. Lastly, the findings could be used to guide decisions about the best time for discontinuing treatment or not, and also about using immunotherapy as an option, which could lead to stopping TKI treatment completely. ■

Didier Dubrana

NEW THERAPEUTIC TARGETS

The discovery of new signalling pathways supporting innovative therapies.

For the past fifteen years, the development of targeted therapies has confirmed to what extent precision medicine is relevant. Based on the molecular portrait of a tumour, the right treatment can be given to the right patient. These drugs interact with specific biological molecules called "targets" or "biomarkers", located on the surface of cells or inside them. For example, for lung cancer the EGFR-positive biomarker or the ALK-positive biomarker can be targeted. For breast cancer, the HER2-positive biomarker is the aim... Progress in molecular biology has therefore opened up incredible prospects by increasing the number of targeted therapies for treating cancers as a whole. However, this successful curative strategy does have its limits: there are still relapses, after a certain period of time, unfortunately proving that certain tumour cells resist treatment. "*We've noticed that relapses and metastases originate from a subpopulation of cancer cells – tumour stem cells*", explained Professor Lucie Karayan-Tapon, head of the Cancer Biology department at the Poitiers University Hospital. It has already been established that a tumour is made up of cellular subpopulations but the role of the stem cells seems to be vital since they are apparently also the source of the primary tumour. "*We are currently working on the pathogenesis and characterisation of these stem cells that make up only 1% of the tumour and are, on top of that, extremely heterogeneous*", she added. Using samples from patients operated on for gliomas, the Inserm U1084 Stem Cells and Brain Tumour group that Lucie Karayan-Tapon leads has created some twenty glioblastoma stem cell lines for exploring new targeting pathways: STAT3, RAD51, SHH, Hippo. The search for therapeutic targets is also part of Bruno Constantin's daily routine, as the Research Director in charge of the CNRS team "Channels and Connexins in Cancer and Stem Cells" in the STIM (Signalling and Membrane Ion Transporters) lab at the University of Poitiers. "*The team is studying two types of ion channels present inside cells*", the biologist explained. "*Calcium channels that guide the entry of calcium into the cell and connexin-like channels that normally provide the interconnection between cells. Why? Because our team has already proven that these two types of channels could play an important role in the migration and invasion properties of cancer cells.*" In the case of melanomas, the more invasive the cancer cell becomes, the more it expresses specific calcium channels that increase cell migration. For that matter, the team has started closely collaborating on this topic with the Poitiers University Hospital's dermatology departments. Bruno Constantin concluded: "*Our research confirms that Connexin 43 (Cx43) is involved in the proliferation process of glioblastoma and prostate cancer cells. The research also demonstrates that some calcium channels play a crucial role in the self-renewal of cancer stem cells.*" So whenever targeting is the topic, so are state-of-the-art molecules! That's the field of expertise of IC2MP – the Institute of Chemistry, Materials and Natural Resources lab – in Poitiers. Professor Sébastien Papot, in charge of the "Programmed Molecular Systems" group at IC2MP and co-founder of the company Seekyo, works in synergy with biologists and doctors to design these new molecules. "*We build "smart" molecular systems that contain a chemical programme, within their structure, that's going to steer behaviour in the organism*", the chemical engineer explained. "*These programmed molecules are capable of transporting anticancer agents harmlessly. They can recognize different targets inside tumours and then release the anticancer drug when the tumour is detected.*" These molecular systems are innovative therapeutic vectors that have passed the animal testing phase and have now entered phase I clinical trials on solid tumours. ■

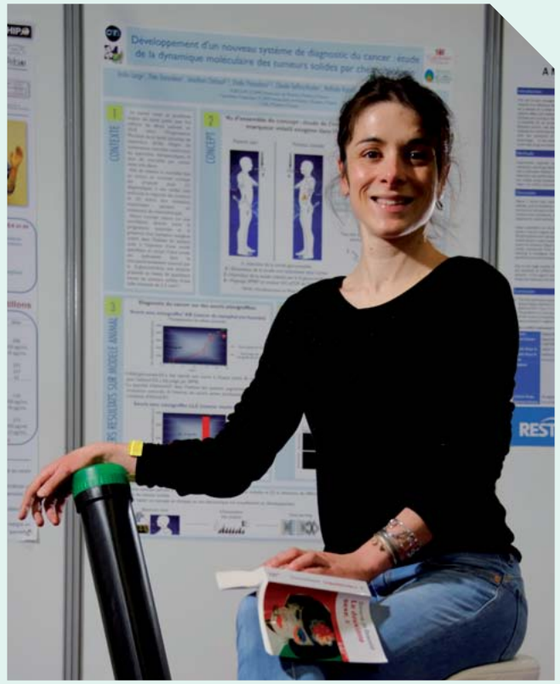


Glioma Stem Cells (GSCs).
First line: GSC-GMB1
Second line: GSC-GMB2
Third line: Control

Raoul Sancy

PAULINE POINOT

WHIFFING THE AROMA OF SCIENCE



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"*I've always loved the sciences.*" Which ones? Mathematics? Biology? And why not chemistry? After being quite a brilliant high school student, upon graduating Pauline Poinot continued to hesitate for a few years more. First she enrolled in prépa, (the intensive 2-year course designed to prepare the best students for the Grandes Écoles) where "*I lasted two weeks, it wasn't for me, too inflexible*", she admitted. Then she enrolled at the university where she studied biology and biochemistry, and finished top of the class at the end of each school year, which led her to an engineering school in Nantes. But "*that still didn't cut it, even though I aced the degree*". Next, she started a doctorate in aroma chemistry in Nantes on *The Study of the influence of processes and formulation on volatile organic compounds responsible for the aroma of bread*... That was it! Pauline Poinot chose not to choose a single field of study. Consequently, she presented her thesis in 2009 on a subject at the interface between several scientific fields of study: chemistry, biochemistry, mathematics and human sciences. After a post-doctorate in proteomics at the French Alternative Energies and Atomic Energy Commission (CEA) in Saclay, she passed the designated competitive exam and became a lecturer at the University of Caen. There, the years that followed were rough, far from family and friends, preparing new classes, fitting in on a new research team, rebuilding a social life and above all, taking care of her son alone while his dad continued to work back in Poitiers. After another competitive exam, she finally landed a new position as a lecturer in 2013 in Poitiers and joined her companion! "*During my thesis, I came across the subject that inspires my current research. I was reading an article that explained dogs were capable of detecting certain types of cancer thanks to their sense of smell.*" Since then, that rather unusual scientific discovery has gained ground. Many institutions, like the Institut Curie, have launched tests with sniffer dogs successfully experimenting this type of screening for breast cancer. The Institute of Chemistry, Materials and Natural Resources (IC2MP UMR 7285) in Poitiers is where Pauline Poinot, a researcher with a multidisciplinary profile, "*draws inspiration for the research aimed at developing a kind of 'breathalyser' to diagnose a large majority of solid cancers*". This type of tool would be designed for general practitioners. "*For the time being, the studies dealing with the diagnosis of cancers via the detection of aromatic compounds are hard to personalise since there is substantial variability between individuals*", the chemist explained. "*So we've developed a strategy that targets a unique volatile molecule whose concentration in the breath increases or decreases depending on whether the tumour grows or shrinks in size.*"

The chemist can also be found at the French National Centre for Space Studies (CNES). "*I also work on detecting markers of life in space, life as we know it on Earth*", she said, filled with enthusiasm. "*We are able to develop research strategies, protocols, and methodologies transposable from one discipline to another even though they seem very remote on paper.*" And when she isn't in her lab, she reads everything, ranging from the great classics of French literature – Camus, Kundera, Céline, Flaubert and Stendhal – to contemporary authors like Beigbeder, Valognes and Foenkinos and "*especially, don't leave out Simone de Beauvoir*", she insisted. She also goes in for sport to evacuate the stress from her demanding job but, above all, she leads a simple life with her family including two young children aged 6 and 3, and a great circle of friends. ■

Raoul Sancy

ÉMILIE CAYSSIALS

NEW BLOOD SETS A FAST TEMPO

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Doctor Émilie Cayssials, a hospital practitioner at the Poitiers University Hospital (CHU), chose hematology "*because it's a specialty that's really dynamic, with close ties to patients and with rapidly changing therapeutics*". Her passion for medicine surfaced "*in the last year of secondary school, after a TV documentary on breast cancer*", she reminisced. "*Initially, I wanted to be a psychiatrist but everything came together gradually and after having wavered between oncology and hematology, I found my calling.*" A career path followed eagerly since she began her internship at barely 25 while doing a Masters 2 in immunotechnology and biotherapy and a university degree in antibiology. She got her PhD in medicine and her graduate degree in hematology in 2015 but the Masters in immunology gave her the taste for research. Consequently, she began a doctorate, which she will present in 2020, under the supervision of Doctor André Herbelin and Professor Jean-Marc Gombert, at the École Doctorale Biosanté (BioHealth Doctoral School) in Poitiers.

At the end of her internship, she decided to focus more specifically on chronic myeloid leukemia (CML), based on advice from her department head, Professor Francois Guilhot. Chronic Myeloid Leukemia (CML) is a cancer that comes into being in bone marrow stem cells. It results from a genetic abnormality specific to those medullary cells. "*That specific genetic abnormality is an abnormal rearrangement of the genetic material during which two chromosomes accidentally switch part of their genes. That's called a translocation. Genes from chromosome 9 are switched with genes from chromosome 22*", Emilie Cayssials explained in an instructive way, as if donning her teaching cap at the Poitiers School of Medicine.

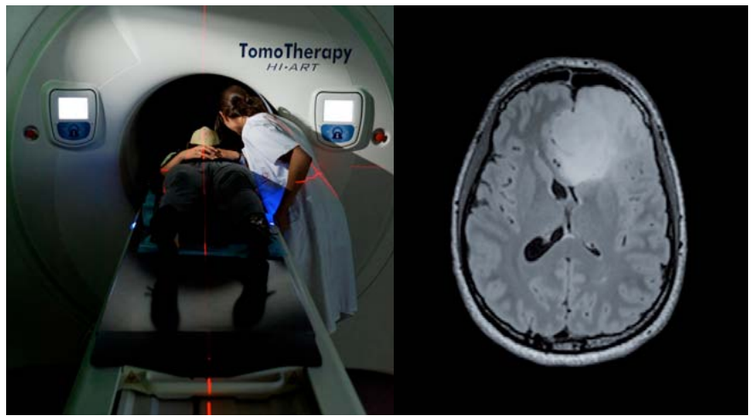
As a result, that particular pathology sets the tempo of her daily routine: patient consultations, monitoring of clinical trials and fundamental research. "*I monitor my patients clinically and some take part in clinical trials or in translational research projects*", she added. The trials are phase II and III, conducted at the regional cancer centre, the Pôle Régional de Cancérologie, or phase I and II trials at the Clinical Investigation Centre Inserm 1402. Her fundamental research conducted in Inserm Unit 1082 deals with non-conventional T lymphocytes (iNKT, CD8+ T cells, Eomes+, KIR+).

The young practitioner's days are definitely busy since, once home, she often has to examine her patients' lab results further in order to adapt their treatment. But she still manages to save time for a few of her passions, like ballet that she's been doing since she was 5, and her role as mother because she wants to "*enjoy my 2-year old son since I don't have time to do much else these days...*" ■

Didier Dubrana

ADVANCES IN **MEDICAL IMAGING**

Medical imaging is much more than a "simple anatomic picture". It can provide information about a patient's cell metabolism and is making progress in leaps and bounds thanks to the abilities of Artificial Intelligence.



Tomotherapy: laser positioning of patient and immobilisation mask

Location of the brain tumour

The I3M (Imagerie Métabolique Multi-noyaux Multi-organes) joint research laboratory in Poitiers brings together the expertise of mathematicians, computer scientists, biologists, doctors and imaging industrialists (SIEMENS). A multidisciplinary collaboration at the service of medical imaging processing, which calls on the latest developments in Artificial Intelligence (AI). That is the explanation given by Professor Christine Fernandez-Maloigne, a university lecturer and researcher at the UMR CNRS 7252, who said: "*We're implementing innovative AI techniques to automatically process and analyse multimodal images, to assist doctors' diagnoses and therapeutic follow-up of various brain, heart or kidney pathologies*". In oncology, research is currently focused on gliomas. With 2500 to 3000 new cases a year in France, gliomas are the most common primary brain tumours. They are also the second cause of cancer in children, behind blood cancers like leukaemia. The I3M Lab conducts research in close association with the neuroimaging department of the Poitiers University Hospital (CHU - Professor Rémy Guillevin). The research relies on the use of a next-generation MRI (Magnetic Resonance Imaging) scanner with high-field strengths. The scanner no longer just obtains two- or three-dimensional views of the brain, it also provides information about organ function, its tissues or its cells, in other words, its metabolism. "*Metabolic imaging, obtained by higher and higher performing acquisition systems, heralds major progress in the non-invasive, in vivo study of many pathologies, both in their clinical treatment as well as in monitoring their progression*", Professor Christine Fernandez-Maloigne specified. "*This new type of MRI reveals the behaviour of several metabolites involved in the development of cancers. Each of the little molecules has a specific spectrum with peak levels typical of the cell behaviour. The relationships between certain metabolites are indicators of the grade of a tumour and its progression*", she added. The Poitiers University Hospital (CHU) is already using the next-generation 3-Tesla MRI scanner, which can be accessed from the operating theatre. The images collected before and during brain surgery are injected into the operating theatre's neuronavigator, which is a kind of GPS for surgical instruments. The neurosurgeon can then visualise, in real-time, the progress of the tumour ablation. "*What's more, to help doctors in their therapeutic choices, we can use the MRI data – anatomical, functional, and metabolic – associated with the patient's other data – biological, genetic, environmental – to detect tumoral zones, define their grade and predict the progression using AI instruments*", she concluded. In the future, thanks to automatic deep learning methods, all the data will be used to establish a sort of ID card of the various types of tumours, enabling better understanding of tumour recurrence phenomena, for example. The research programme has been enhanced by the arrival of a new 7-Tesla MRI scanner with even higher performance. A unique experience in France: the technology will be used in both clinical and fundamental research. ■

Didier Dubrana

THE OCEAN AS A MEDICINE CABINET

Research conducted on seaweed harvested off the coast of La Rochelle may make it possible to discover tomorrow's anti-cancer molecules.

Marine biodiversity is an up-and-coming source of anticancer molecules.

The drugs of tomorrow may be hiding in marine bacteria and seaweed, off the coast of La Rochelle. That's the field of research studied by the BCBS (Biotechnologies and Chemistry applied to Bioresources for Health) team, a CNRS 7266 LIENSs joint research unit directed by Doctor Ingrid Arnaudin. For the past 15 years, the unit has been conducting fundamental research in oncology on the topic of new natural anticancer molecules, by combining the expertise of biochemists, organic chemists, molecular biologists and enzymologists. "*Our goal is to biosource, meaning to identify molecules in the natural environment that could be at the origin of tomorrow's drugs*", Ingrid Arnaudin explained.

"*Undeniably, the genetic diversity of cancers, their resistance to certain treatments, and the overly low molecular selectivity in chemotherapy, all call for the development of new anticancer substances.*" The marine flora has adapted to environmental changes by developing a whole range of molecules/metabolites. An outstanding source to explore for new anticancer substances! To date, over a hundred molecules have already been obtained by the laboratory. However, it will be years before their structure can be mastered well enough to achieve effective anticancer activity.

Carrageenans, a family of sulphated polysaccharides extracted from red seaweed, may be one of the therapeutic solutions. Used as a thickening and stabilizing agent in the food industry, these polysaccharides also have anticancer properties! For chemists, it's a perfect model of study since the molecule is well known. It can also be vectorised as multifunctional nanoparticles to improve and detect its accumulation in tumours. That's what Hugo Groult does on the team. The BCBS researchers have already identified the potential target of these polysaccharides: heparanase, an enzyme active in tumours and their microenvironment, that usually remains silent. "*Our objective is to show that these sugars have the ability to inhibit heparanase activity associated with remodelling the extracellular matrix and identify the impact of that inhibition in tumour progression*", Ingrid Arnaudin added. "*So it's a promising therapeutic target when you know its key role in degrading the cellular matrix, and promoting tumour angiogenesis and metastatic phenomena.*"

Many other avenues are also being explored in the lab for the use of marine microalgae as a source of new pigments with anticancer activity. Consequently, "*we have identified carotenoid pigments capable of directly killing melanoma cells, limiting their metastatic ability or sensitizing them to the effect of anticancer drugs used in clinical practice*", which makes it possible to consider combined treatments or nutritional interventions to improve the effectiveness of chemotherapy and limit its side effects.

Certain marine bacteria are also being studied in the lab. From *Micrococcus* to *Shewanella*, and including *Tenacibaculum*, *Bacillus*, *Pseudoalteromonas*, or *Vibrio*... they develop on the coastal rocks, in tidal flats, seaweed or on boat hulls, in particular thanks to their adhesive strength. The competition between microorganisms is tough, and bacteria secrete anti-adhesive compounds possibly to eliminate competitors.... As such, the team's past research has already shown, for example, that a *Pseudoalteromonas*, belonging to the lab's collection, was capable, via the production of a protein compound, of inhibiting the adhesion of other bacteria. It is precisely those anti-adhesion compounds that the laboratory is interested in because "*we know that the adhesion of cancer cells to blood vessels remains a determining factor in the disease*", Isabelle Lanneluc added. The range of compounds synthesized by marine bacteria, still little known, is vast and opens new research perspectives. And last but not least, the laboratory also synthesises and functionalises original, small heterocyclic chemical compounds, mimicking natural marine substances. "*Ten years of research have highlighted new leaders displaying inhibitor activities with sub-nanomolar values on kinases, and sub-micromolar values on cell lines*", Valérie Thiéry said.

The effectiveness of all these new compounds derived from the marine environment is being studied in vitro on cell lines... Further results are eagerly awaited. ■

Didier Dubrana

› ONCOSPHÈRE Partnering up against cancer

A NEW MULTIDISCIPLINARY ECOSYSTEM, DEVOTED TO THE FIGHT AGAINST CANCER, COMES INTO BEING

The Oncosphère illustrates a joint ambition shared by the political will, scientific excellence and economic momentum in Nouvelle-Aquitaine – France's largest territory – that has made shrewd use of the recent merging of regions.

Every year, an average of 37,000 new cases of cancer are diagnosed in Nouvelle-Aquitaine, accounting for 10.4% of the total in metropolitan France. In men, prostate, lung and colorectal cancers make up more than half of the cases whereas women are concerned by breast, colorectal and lung cancer. "An intolerable plague," Nouvelle-Aquitaine President Alain Rousset said. "In the future, the transdisciplinarity of research is what's going to make it possible to find innovative, effective solutions to fight this scourge that has an impact on so many families". Cancerology is definitely experiencing a new era of research and scientific discovery that holds hope for significant advances targeting patients in the upcoming years. Technological progress in imaging, digital, modelling or physics is opening a field of possibilities that is more than promising. However, cancer is still the leading cause of death from disease in France: it is one of the 21st century's biggest public health challenges.

To meet that challenge, the region's anti-cancer strike force has come together under the name Oncosphère. The project came into being as a result of the symbiosis between the political will and scientific excellence at the universities and research institutes located in Aquitaine (Inserm, CNRS, Inria, INRA, CEA, etc.). Nouvelle-Aquitaine's five university campuses have now agreed to define this new 'environment' of multi-site cooperation to join forces and increase the impact of their research. The hospitals and University Hospital Centres in Bordeaux, Limoges and Poitiers and the Bordeaux Centre for the Fight against Cancer, are also an integral part of this project paving the way for patient-oriented developments. In 2017, the federation of the region's health clusters and centres (Alliance Innovation Santé Nouvelle-Aquitaine) launched the first phase of a 'cancer road show' , which brought this public health issue to the fore in Limoges, Poitiers, Pau and Bordeaux.

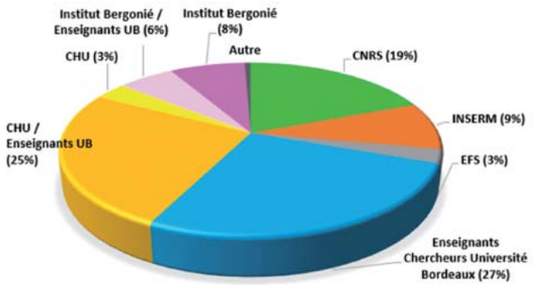
"*Our aim was to bring together industrialists, academics, researchers and clinicians to extend their opportunities for liaising, once the territories had been merged*" Alain Rousset explained. "*We also wanted to showcase the skills and get-up-and-go of the actors in a field that I consider highly strategic for the region. It was also the chance to develop opportunities for partnerships and business between the Nouvelle-Aquitaine stakeholders through B2B meetings*". As far as research goes, the Oncosphère project was promoted by Pierre Soubeyran, UMR 1218 (Inserm, University of Bordeaux) director, who explained: "*In recent years, cancerology has generated an effective interdisciplinary culture for the development of integrated research, which has been recognized twice by the SIRIC label (See box). In addition, we're also reaping the benefits of extensive groundwork in scientific facilitation carried out by the Cancéropôle GSO – the interregional network for cancer research – and the substantial complementarity of topics between the regional research sites. Our project will ensure the long-term development of interdisciplinary approaches. What's more, it's in line with the Region's strategy and in particular with the five aims of the Regional Plan for Higher Education, Research and Innovation*". All the main players are now very determined to get up and running, offering treatments that are ever-more effective and better

adapted to each patient's profile and tumour, and that generate as few side effects as possible. Françoise Jeanson, Nouvelle-Aquitaine regional council member and representative for health and the Silver economy explained: "*For this fight, the Oncosphère is going to unite excellence in medicine and biology as well as in technology, digital, human and social sciences. Support for the network of researchers will be accompanied by support for projects to structure university-hospital sites, adapted to scientific projects*". The region is striving to become an attractive European and International network in this field: following neuroscience (Neurocampus) and cardiology (IHU Lyric), cancerology is now the field that will testify to Nouvelle-Aquitaine's scientific momentum. "*These innovations also need to come into being in companies,*" Francoise Jeanson insisted. "*At times it's a pity to see the brain drain (from France) going to enrich China or the United States.*" For that very reason, the Region is investing nearly a million euros in ImmuSmol, a biotech company collaborating with Institut Bergonié, to encourage innovation, and especially the development of immunotherapy research. After surgery, radiotherapy and chemotherapy, immunotherapy is definitely opening up a fourth avenue of treatment for cancer. Although some immunotherapies already have marketing authorisations (See article p30), those promising treatments are still in the clinical trial phase or additional studies are required to understand the biological mechanisms involved. The research unit ImmunoConcEpT (CNRS, University of Bordeaux), recently boosted by researchers committed to cancer research, thanks to support from the University of Bordeaux and the Regional Council, is in optimal conditions for contributing to this momentum. In the same way, technology and clinical research round each other out in Rein 3D Print, a project conducted by the Bordeaux University Hospital in kidney cancer with the Regional Council's support. For the University of Bordeaux, "*Setting up the Oncosphère testifies to the wisdom of the various players in cancerology,*" University president Manuel Tunon de Lara explained. "*Health is obviously making its way into labs more and more. Bordeaux's strength is that it's a multidisciplinary university that can meet the Oncosphère project's demands, on all counts.*"

This project is therefore a unique opportunity to develop interdisciplinarity in a competitive ecosystem. It will make it possible to increase scientific production and regional attractiveness while supporting the creation of innovative companies in the health sector. Oncosphère's stakeholders will strive to develop partnerships with patients and society to facilitate the development of new advances for the benefit of the aging population, as well as to increase awareness of those advances in Nouvelle-Aquitaine and beyond, on the international scale. ■

New architectural lines and modernised facilities at the Institut Bergonié.

Chercheurs OncoBio permanents de rang A et B de l'Oncosphère bordelaise



Three questions for...

Manuel TUNON de LARA

University of Bordeaux, President

université de BORDEAUX

What's your point of view on the creation of the Oncosphère in Nouvelle-Aquitaine?

I am naturally pleased with the creation of the Oncosphère, which will allow us to expand our collaborations, to intensify cancer research in Nouvelle-Aquitaine and therefore to become more efficient. The emergence of the Oncosphère falls in line with what has been our strategy for several years in Bordeaux, as we had started to join our oncology research units before the creation of the University of Bordeaux in 2014. Today, four joint research units between the university and Inserm are merging. Together with the CNRS group of the Institute of Cellular Biochemistry and Genetics, they will make up a core of 350 researchers, lecturers/researchers and PhD students in the field of oncology, to whom we can add nearly 700 more, working for example in the areas of health technology or social science. Here in Bordeaux, with the CHU and the Cancer Centre (CLCC) - Bergonié Institute, this will represent a community up to the challenges in the field, and which can still be strengthened through the regional approach offered by the Oncosphère.

What role does medical research play at your university?

Medical research cannot be seen in isolation from the rest of scientific research! Clinical research carried out on patients relies upon a more fundamental research conducted in labs. It needs heavy infrastructures and lies within the framework of European and international networks. Thus, I'd rather refer to health research in a broad meaning as it is an essential component of the research carried out at the university. The CHU, as a result of a specific organization between hospital and the university, and the CLCC play a major part in this approach as they represent a privileged field of training and research for academics. In the health field, as in other areas of scientific excellence, the university is a driver of progress for science and society.

How do you think this additional production of fundamental and applied knowledge can be transferred for added value?

Beyond the already very rich production of knowledge, the structuration of our cancer research implies that a whole ecosystem is being built on the site of Carreire, with the hospital, the University of Bordeaux and patients' associations. Moreover, several start-ups have been created these past years as a result of the University of Bordeaux research activities, in particular in the field of technology. Training tomorrow's health care providers is another of our priorities. This is the reason why we have just created this past fall 2019 a specialization in Cancerology for our Master in Biology-Physiopathology. The Oncosphère community in Bordeaux also has the project of creating a Graduate School (Ecole universitaire de recherche) in Oncology in order to offer a program of excellence in this area, from Master's degree to PhD. ■

Three questions for...

Serge HUBERSON

Vice-President of Research, University of Poitiers

© Ricardo Esteves

What's your point of view on the creation of the Oncosphère in Nouvelle-Aquitaine?

The Oncosphère is a networking approach boosted by the Region to promote collaboration between university centres that include a health department. The University of Poitiers hadn't organised its cancer research in the form of dedicated research units, but instead divided the research up into different labs. The initiative has therefore been incorporated within the broader framework of technological innovation in health, which is one of the key areas that structures health research in Poitiers, with imaging and transplantation. At the same time, better networking between the existing teams makes it possible to transfer the research conducted on cancer more specifically and build a project creating a new team devoted to cancer. So for us, it's a project whose consequences are already very positive.

What role does medical research play at your university?

Undoubtedly like any university partnered up with a CHU, medical research plays a key role structuring our university landscape. In Poitiers, there are three key areas:

1- Research in Health/Biology involving joint research units with Inserm (neurobiology, transplantation, anti-infective pharmacology) or CNRS (ion channels)

2- The Clinical Investigation Centre (CIC) ensuring continuity between the CHU and the university

3- Multidisciplinary research combining technology and health, driven by partnerships between biology-health labs and engineering institutes (PPRIME and IC2MP), as well as the MSHS.

How do you think this additional production of fundamental and applied knowledge can be transferred for added value?

The transfer of this research can mainly be done in two ways:

- *On one hand, the continuity between the labs and the patient, ensured by the CIC, allows the patient to benefit from new technological advances more quickly leading to better disease management, ranging from screening to treatment.*
- *And on the other, technological innovations can lead to strengthening businesses in the health field or to the emergence of start-ups thanks to substantial support provided by the University of Poitiers for the creation of Joint Research Laboratories (SIEMENS, Eurofins-CEREP, CONICs-Med, Seekyo...).* ■

Three questions for...

Alain CÉLÉRIER

University of Limoges, President

What's your point of view on the creation of the Oncosphère in Nouvelle-Aquitaine?

It's a tool that brings people together! Even though there are teams and major synergies on this topic at each location, creating a multidisciplinary network focused on cancer in the Nouvelle-Aquitaine region will make it possible to increase existing interactions between the teams, as well as establish new interactions and synergies to make access to national and international programmes easier. As such, we'll be increasing our visibility in international scientific competition.

What role does medical research play at your university?

Biomedical research constitutes one of the centres of excellence at the Limoges University Hospital and University, one of its signatures. Setting up the Limoges Oncosphère site within the University will basically expand the influence and visibility of the centre, already internationally recognised for the quality of its teams.

How do you think this additional production of fundamental and applied knowledge can be transferred for added value?

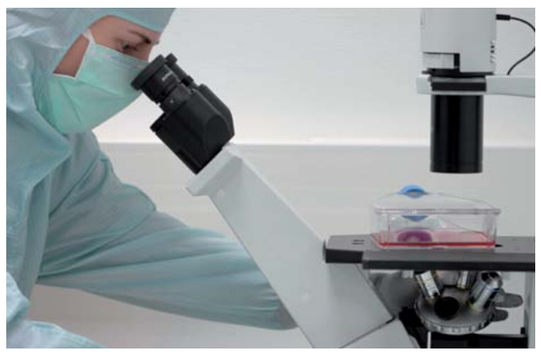
The project makes it possible to associate businesses with fundamental research, to boost the regional potential. It's going to foster scientific emulation and strengthen the development of businesses, facilitate the establishment of start-ups in the field of biotechnology applied to cancer in our region. The project will also make our region more attractive to researchers and facilitate the teams' access to EPST (Public Scientific and Technical Research Establishment) labels in the field of cancer research. It will also provide the possibility of creating new partnerships with national pharmaceutical companies. ■

NEW MASTER'S DEGREE IN **CANCER BIOLOGY**

In close cooperation with the "Oncosphère" project, a "Cancer Biology" degree track was recently created within the "Biology and Health" Master's degree at the University of Bordeaux. The training programme consolidates, enriches and broadens the oncology-related curriculum at the Bordeaux campus in conjunction with the other educational partners in the Nouvelle-Aquitaine region (Poitiers, Limoges, La Rochelle). The Master's in Cancer Biology is a two-year multi- and inter-disciplinary course, open to the international community, which takes into account the wide range of approaches in modern oncology. Students are given an opportunity to study abroad within the framework of internships in laboratories or companies in several countries (Brazil, Canada, USA, UK, Netherlands, Portugal, Spain).

The curriculum leads to the acquisition, application and development of knowledge and skills in cancerology by addressing emerging areas such as fundamental biology, clinical oncology and translational research. The training programme is based on a partnership with major research institutes like the French National Institute of Health and Medical Research (Inserm) and the French National Centre for Scientific Research (CNRS).

Upon completion of the two-year programme, students may pursue their academic path at the doctorate level as well as work directly in private (clinics, biotechnology companies) or public (hospitals, Inserm, CNRS, Univesity of Bordeaux) laboratories.



ONCONAEN: THE ANSWER TO THE EUROREGIONAL CHALLENGE OF GERIATRIC CANCER

Cancer is the leading cause of death in the Euroregion, Nouvelle-Aquitaine Euskadi Navarre, accounting for 30% of elderly deaths. Businesses and many other Euroregion referent stakeholders have joined forces against this health issue since early 2018 within the framework of the ONCONAEN project.

Supported by the Euroregion, ONCONAEN, whose leader is the Basque Health Cluster, is aimed at creating an observatory in geriatric oncology and a plan of action for the sector and public authorities. Since its launch, the structure has organised several "intercluster" meetings to encourage public-private cooperation. ONCONAEN is the continuation of a historical joint effort sponsored by the regional authorities, partners of the Euskampus-Bordeaux campus, the cross-border Chamber of Commerce and Industry (CCI) Bihartean as well as companies in the bio-health sector (Basque Health Cluster, SODENA, GIPSO, cluster TIC Santé).

WHAT'S A **SIRIC**?

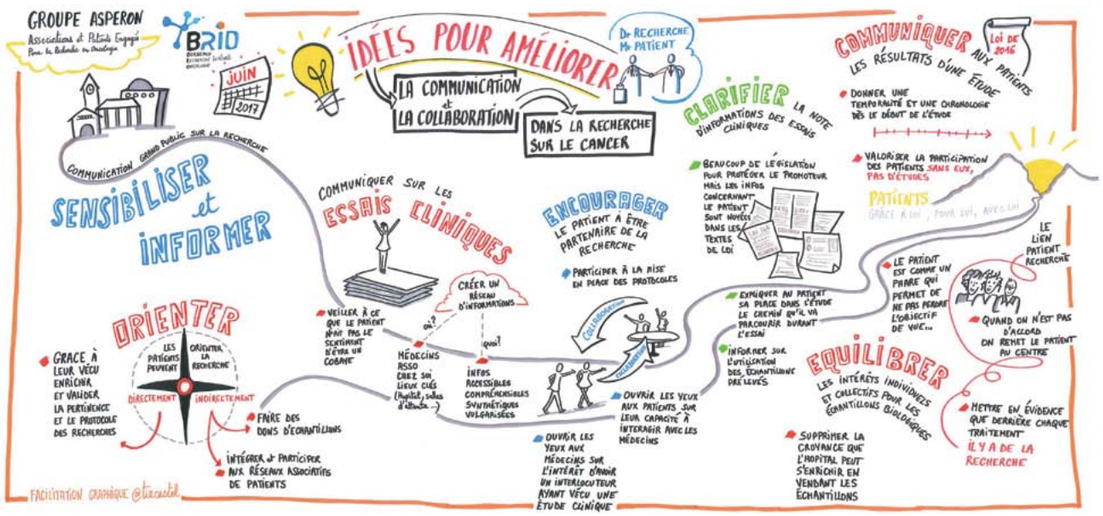
SIRICs – Integrated Cancer Research Sites – were initiated by the second Cancer Plan in 2009. Their objective is to improve the quality of research organisation, knowledge production and the transfer of innovations to all potential beneficiaries (patients, doctors, hospital staff, etc.) In the 2018-2022 period, SIRIC BRIO (for Bordeaux Integrated Research in Oncology) has been awarded the label for the second time in a row. That recognition reinforces the organisation of Bordeaux cancer research by singling out three main themes: sarcomas, oncogeriatrics and the microenvironment of tumours. It is also worth mentioning BRIO's initiative aimed at bringing patients closer to research by setting up **ASPERON & Co**, a collective of patients, ex-patients, caregivers, volunteers from associations and professionals from the health and research community.

PATIENTS AND PROFESSIONALS: PARTNERS IN RESEARCH

Taking into account patient experience – a praiseworthy approach – gives meaning to unique, collaborative research work, bringing together all the stakeholders and professionals involved in the care management process.

At BRIO (the Bordeaux Integrated Cancer Research Site – SIRIC), we're convinced that the relationship between patients and cancer research needs to be expanded and enhanced. A patient's experience of living with disease, his or her perspective and specific needs should make it possible to shed light on research, making it more relevant, effective and transparent. Driven by that conviction, BRIO is striving to get patients involved in various aspects of research and get them to contribute, on their level, to the development of a still relatively-new, but rapidly-expanding, field in France.

Regardless of the sector of society, it makes sense to get all the people affected by a project involved. Of course, in the age of social media, everyone wants to give their opinion, but involvement implies there is a genuine exchange that makes it possible to set up services and products in line with everyone's needs and win the public over



better. In situations like these, citizens, service users and consumers take part in deciding community budgets, designing products, and improving the organisation of services, for example.

Patient knowledge known as "experiential" (sometimes called "lay knowledge") is different from, and complementary to, a professional's "expert knowledge". Shared medical decision-making takes into account not only these two types of knowledge but also the patient's priorities. The latter becomes a "partner" in the healthcare relationship. One patient's experience can also be very useful to another patient – without ever infringing on the medical field. That is what some support groups and associations provide between old and new patients.

It is still rare for (ex-)patients to play a role in medical or paramedical training courses, but initiatives are starting to be implemented in Bordeaux and elsewhere. As such, patients become "partners" in the training courses. As for administrative bodies in the healthcare sector (French Agency for the Safety of Health Products - ANSM, French High Authority for Health - HAS, French National Cancer Institute - INCa, etc.), they have all more or less set up committees including service users / patients, in hopes of making the health system more compatible with the needs in the field. Several University Hospitals (CHU), including the ones in Bordeaux and Poitiers, also have patient-partnership projects.

What about research that is inevitably further from the patients' immediate concerns related to treatment? "Translational" research is obviously conducted FOR patients, if possible with the findings being disseminated TO patients and the public, in addition to professionals. However, BRIO has considered the prospect of working WITH patients, so that public research could be made more accessible, and truly in tune with the population. With the help of the French League against Cancer, patients already review clinical study information sheets and suggest possible modifications to improve their legibility or make the protocol more "acceptable" to patients.

In 2016, BRIO and a few founding patients created ASPERON & Co., a collective of associations and patients committed to research in oncology and the professional community, by bringing together people interested in the patient-researcher link. That open community (which is not an association itself) includes cancer patients, ex-patients, caregivers and association volunteers as well as health and research professionals who recognize themselves in its values. The collective's aim is to think up and run collaborative projects, to improve communication and collaboration between patients and cancer research.

Consequently, ASPERON & Co prepares events and resources, validated by professionals and patients, to help others understand cancer, research and its findings. A joint effort with Bordeaux anatomical pathologists led to a laboratory tour to understand the diagnosis of cancers, then the creation of a photo exhibition, flyer and public event. The project was entitled "That fragment of us that stays at the hospital…". Other events – co-created by patients, experts and actors – have dealt with the link between immunology and cancer, as well as access to innovation for patients.

For example, the collective is also interested in communicating about clinical studies or issues related to the consent given by patients for the use of their cells or data. Workshops allow professionals and patients (or caregivers) to exchange ideas on topics of common interest, with all the participants' voices carrying the same weight.

For certain specific needs (i.e. to participate in certain committees or projects, for example), distinctive patient profiles are sought (with company management skills, scientific skills or specific medical experience). However, within the ASPERON & Co collective, all patients, ex-patients and caregivers are welcome. No special knowledge is required, which is different

from "patient-experts" who have often been trained.

Not all patients necessarily want to get involved. That desire varies from person to person, and evolves over time. However, whether it is to accompany other patients or to help improve the care or research system, patients who want to get involved, must inevitably have the ability to take a step back from their personal experience. Nevertheless, each case and each perspective is unique and the patients aren't being asked to represent THE voice of all patients, but to speak on their own behalf. Some patients that get involved alongside BRIO belong to support groups or associations, others don't.

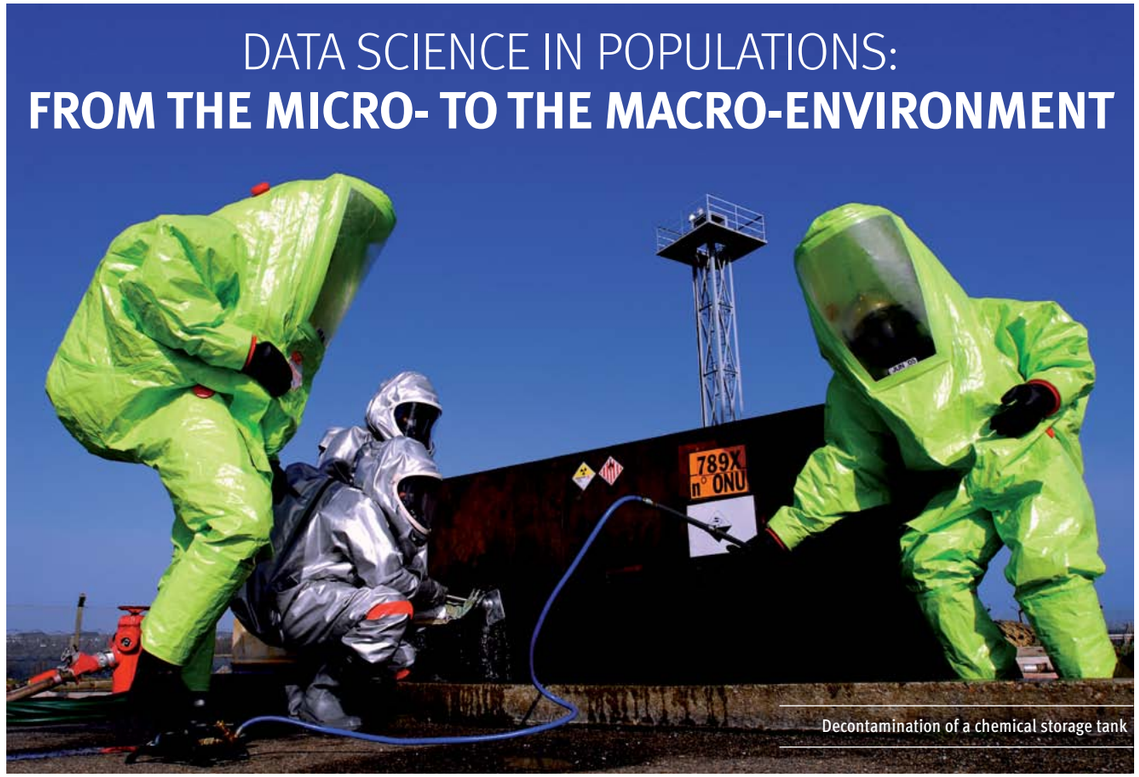
The advantage of the collective is that it offers different degrees of involvement, for patients and professionals alike. Some support the approach from afar and keep themselves up-to-date, others come to certain events to give their opinions, and still others get more involved in choosing or managing projects.

They are all participating in a major innovation as far as the research community goes. Recognizing how worthwhile the partnership is between patients and professionals should make it possible to take the approach further, as is the case in other countries, where patients are involved in certain research projects, give their opinions about the relevancy of certain projects, or suggest research topics. Cultural evolution takes time but the momentum has begun in Bordeaux. The experiments conducted with BRIO and the successful initiatives undertaken received the National Cancer Institute's approval at the time of the new SIRIC accreditations, as well as international encouragement. The BRIO experience is now serving the Oncosphère project, which aspires to be open to society and patients. ■

Nathalie Caplet

For more information on BRIO's actions with patients, as well as events and ongoing projects, visit:
http://patients-siric-brio.com

DATA SCIENCE IN POPULATIONS: FROM THE MICRO- TO THE MACRO-ENVIRONMENT



Decontamination of a chemical storage tank

Epidemiology attempts to trace the "causality chain" likely to trigger a disease or impact patient prognosis.

Biological research on cancer explains the development and progression of cancer cells, but the role and mode of action of many factors are currently still poorly known. What role does genetic heritage play in the onset of cancer? How can we elucidate the association between the occurrence of a cancer and the professional or environmental exposure to many high-risk substances and situations? How can we take into account all the other factors related to a person and his surroundings, and do so throughout his lifetime? Some of those answers are provided by research conducted in populations (epidemiological studies) by the UMR 1219 EPICENE (Epidemiology of cancers and environmental exposures) team co-directed by Professors Simone Mathoulin-Pélissier and Isabelle Baldi. Epidemiology is a relatively new discipline and its expertise relies on an extremely wide range of sciences: medicine, biostatistics, pharmaceutics, ergonomics, toxicology, etc. It's the "*armed division*" of the country's public health policy: "*Our team studies the onset of cancers as well as the future of populations (with and without cancer)*", explained Simone Mathoulin-Pélissier, "*Thanks to multidisciplinary approaches, our team has developed specific methods for measuring exposures to different agents like pesticides, nanoparticles, electromagnetic fields, asbestos… To understand the future of populations, we also use major national and international databases such as cancer registers, national clinico-biological databases or cohorts*". Bordeaux epidemiology has distinguished itself by, among other things, maintaining extremely efficient cancer registers (which participate in surveillance nationwide) and ensuring the follow-up of numerous cohorts. "*Fifty percent of the cases in the Nouvelle-Aquitaine population are listed in a cancer register*", Isabelle Baldi said "*as opposed to barely 23% for France as a whole. We also have cohorts that have allowed us to study – some for several decades – the impact of cancer in the elderly, the predominance of certain rare cancers or the health of specific populations such as farmers*". This field is precisely the one in which EPICENE research has often made headlines in scientific reviews by sounding the alarm on the effects of pesticides on the rural population's health, notably regarding their role in the occurrence of cancers like brain tumours and sarcomas. It is worth pointing out that France – Europe's leading farming country – is also ranked 5th in pesticide use worldwide! Nonetheless, the job remains huge with regards to the thousands of pesticide substances that have been used in France. The toxicological properties and health effects of these products remain, for the most part, to be determined. That is why EPICENE epidemiologists undertake genuine in-the-field investigations. "*We need to have good knowledge of the exposures before being able to develop the tools essential to epidemiological studies*", Isabelle Baldi explained. "*We call on ergonomists to clearly identify a person's exposure at a particular work station. Knowledge of their job history is also required, because that makes it possible to define the intensity and nature of the exposure.*" And Simone Mathoulin-Pélissier concluded: "*We strive to better comprehend the chain of causality between all the factors possibly linked to the onset of cancers and to their prognosis.*" It's a gargantuan task since, for example, for one identified factor, the impact can be different depending on whether it's a man or a woman, depending on age, co-occurrence of high-risk behaviour (alcohol, tobacco, etc.) and even depending on the socioeconomic level…! With that in mind, the link with an individual's biological data has developed over the past few years and has consequently led to complex analyses. In addition, this research needs to be maintained over time because it often takes up to fifteen years before significant findings start to emerge. That is when solutions are put forward to prevent or reduce the risks in the general population or in certain professions, and the team's researchers called on to back up the scientific facts. ■

Raoul Sancy

Antenna at cellular base station emitting electromagnetic waves

AUDE LACOURT

ALL ROADS LEAD TO THE PATIENT

© F. Guénet/Divergence Images

It only took one class in public health at the Hygiene, Health, Environment Institute of Technology (University of Bordeaux) for Aude Lacourt to choose her career path in health. That "*revelation*" led her to ISPED (Institute of Public Health in Epidemiology and Development), which allowed her to make THE encounter of her professional life during her final apprenticeship for her first-year Master's degree. Patrick Brochard, head of the Health, Work & Environment team (UMR 897 Epidemiology and Biostatistics), noticed the organised, meticulous young woman and "*took her under his wing*", she said. It was her first contact with the asbestos public health issue, which confirmed her interest in pursuing with a second-year Master's in research and specialising in environmental causes of cancer. That occupational medicine professor, a reference in his field, never ceased to stimulate and motivate her. He is the one who supervised her thesis on the theme of asbestos and pleural mesothelioma. He is also the one who motivated her to do a two-year postdoc in Montreal. She still talks about it, her eyes shining, full of optimism that the incredible experience inspired in her, even though far from her husband and her regional Lot-et-Garonne origins.

The interest Aude Lacourt has in the environmental aetiology of cancers is due to its impact on disease prevention. But that had yet to fulfil her need for contact with patients, so the researcher with the atypical career path, is rounding out her education, with an equivalence in medical school where she has just been accepted in the second year. "*I needed to feel useful*", she said, totally "*projecting myself between research and clinical practice*". Since the young woman doesn't undertake anything without being totally involved, in no time she became head of the public health pole within the "Carabins de Bordeaux", the local medical student association.

Now, on the EPICENE team, under the supervision of Simone Mathoulin-Pélissier and Isabelle Baldi, she is focusing her research on environmental issues and sarcomas. She is busy setting up a study that will make it possible to gather data about exposure to a large number of harmful substances, with the idea being to use an integrated approach to harmful substance exposure.

Currently, she's participating in the Etiosarc project, recently affiliated with Integrated Medecine of Sarcoma (IMS) aimed at documenting the still too-incomplete aetiology of sarcomas. The idea is to check if exposure to certain environmental pollutants can explain the sarcoma occurrence rate. In collaboration with professor Antoine Italiano, she is also involved in the biological part of the approach, understandably integrating interactions with the environment. The aim is to deploy the study in 15 French departments and recruit close to 2000 cases. Drafting the ambitious programme's protocol took three years and the team can now begin including cases in the study: "*integrity and precision*" will be required to establish and analyse the databases.

Nevertheless, perseverance doesn't frighten Aude Lacourt. An athlete through and through, she's used to half-marathons and triathlons on a competitive level, where she can measure both her "*mental strength and physical power*", the perfect complementary pair that leads to success. However, for lack of time in her busy schedule, running is limited to weekends only. But she keeps in shape on a day-to-day basis at the handlebars of her bike – easy to spot among all the others with its set of child seats one behind the other – taking her four-year-old twins all around town. ■

Constance Deveaud

ALAIN MONNEREAU

THE EPIDEMIOLOGY OF THE HUMANITIES

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Alain Monnereau is a happy man and fulfilled researcher because optimism, perseverance and awe are the favourable winds that blow around him. "*In every class, I went into raptures about everything*", he said. And nothing has changed since his student days. The grandson of Libourne winegrowers went all out to become the doctor he had set his hopes on being, most likely since he was 7 or 8 and shaken by a close family member's battle with Hodgkin's disease.

From the start of his clinical training, he studied medicine via a detour through the humanities, studying ethnology as well as social and cultural anthropology: "*A very good customer at the Bordeaux Faculty of Liberal Arts*", enrolling and acquiring degrees! His life principle: forge ahead, be ever-curious and insatiable, learning from books and from others. The phrase "*The world is my representation*" by Blaise Cendrars – an author who has stuck with him since he was 20 – became his leitmotif. His first tangible contact with hematology came at the blood transfusion centre working a summer job. According to him, his multiple courses of study have allowed him to live one experience after another like "*rebirths*".

For his study of medicine and the social sciences, he shipped him off to Africa: Burkina Faso as an extern, sent by his professor of tropical medicine, Michel Le Bras; later to the Casamance in Senegal for his military service as a volunteer in a pilot vaccination programme. A revelation for epidemiology when, from all of his 26 years, he conducted his first surveys and was the local head of an NGO!

From then on, he looked for internships "*as far away as possible from Bordeaux, between Reunion Island and… Oloron Sainte-Marie!*". At 30, he focused on epidemiology and Public Health once and for all at the Institut Bergonié alongside Professors Pierre Soubeyran and Bernard Hoerni. When the question of the thoroughness of therapeutic tests was raised in 1998 while defending his thesis on lymphomas, the idea of a Cancer Register germinated. His DEA on lymphoma incidence in the Gironde, supervised by his mentor Roger Salamon, laid another stone for the future tool that finally came into being in 2002.

In the wake of research by the epidemiologist Jacqueline Clavel, Alain Monnereau set up the register of hematologic malignancies in the Gironde, and analysed part of the case-control study on risk factors for lymphoma in France (ENGELA). Another thesis (in science, this time) and new data on hematologic malignancies. Going so far as to join an international consortium in order to get "a higher number of cases providing additional clarifications to zoom in closer on rarer lymphomas or exposures", he added.

In 2011, an American adventure began for a year at Stanford with his spouse and sons. There, he worked "*in ideal conditions with highly qualified people*" to further the links between Hodgkin's lymphoma, UVs and alcohol; and participate in large-scale initiatives, in particular on the role of constitutional genetics in the development of those pathologies.

He is now setting up a group of 6000 lymphoma patients, throughout France to assess both the environmental and biological factors on the future of the disease.

Because he has been on the receiving end so often, Alain Monnereau likes to give. He is involved in chairing the French Network of Cancer Registers (Francim), is chairman of the InterLymph Consortium and has been supervising his first doctoral students since 2015… when he's not teaching Hatha Yoga for a non-profit "*to pass on that enthusiasm about taking care of yourself!*" However, originally, he started yoga to work on his breathing for the saxophone! Since music, in its most eclectic expression "*from Sergei Rachmaninoff to Lou Reed*" holds a prominent place in his life! ■

Constance Deveaud

PATIENT & FAMILY TIME

After 15 years of research, the human and social sciences have established the urgency of creating a new profession at the doctor/patient interface in hospitals.

It wasn't until 1998 that the French League against Cancer (Ligue contre le Cancer) organised the "*first cancer patient convention*". Patients and their relatives were able to talk about their suffering, doubts and loneliness for the first time – the day-to-day life of patients who hadn't had the right to speak in public until then. In fact, that quite unintentional code of silence placed doctors at the core of all the conversations and questions. By speaking openly about it, the discussions shook up the relationships between medical professionals and patients. There was a strong demand for creating a place run by "*non-medical, ancillary staff*" who would listen to patients and could provide them with support during their ordeal. The Institut Gustave Roussy in Villejuif provided a solution right away by creating the first Meeting and Information Facility (ERI = Espace de rencontres et d'information), which came into being in 2001. That neutral territory made it possible to cover all the issues that were not strictly medical. How to live with cancer? What are the repercussions on the family? The "live with" was at the heart of that facility. The French Law passed on March 4, 2002 related to the rights of patients and the quality of the health system officialised those protective measures and led to in-depth societal reflection on illness. In 2006, Karyn Dugas, took charge of another pilot ERI devoted to managing the information provided to parents whose children were being treated in the Gustave Roussy's Child Cancer Department. In that facility, she saw a new issue arise right away: how to maintain a school routine for teenagers with cancer. She set up a pilot project "*back-to-class support for patients treated in the child and teen cancerology department*", in partnership with Zoé Rollin, a researcher at the Institute of Interdisciplinary Research on Social Challenges at the University of Paris 13 (now an associate professor at the Paris Descartes University).

Four years later, the project concluded with an unprecedented analysis published by the *Bulletin du Cancer* entitled "*Evaluation of a programme for teenagers going back to high school*". The article raises the importance of the project, which "*legitimises what families have to say and enables teams to have better awareness of invisible disabilities*", explained Karyn Dugas, now health support coordinator at the Bordeaux University Hospital (CHU). But the evaluation interviews also bring to light the weak points of a compartmentalised administrative system. Like in the case of Karim, a 17-year high school student: "*in fact, the information didn't get through because the school physician knew about everything; she really did what she needed to do except she didn't notify the form teacher he had that year*". Or another example, Karyn Dugas added: "*Quite often the knowledge that the form teacher, the main school counsellor or the nurse has about the cancer isn't passed on to the other educational staff*". In fact, the communication problems are often related to the lack of teamwork between the secondary school teachers on these issues. For that matter, having a teenage cancer patient enrolled in school is unusual. It causes concern due to the lack of information about the situation and due to the questions raised by the other students in the class: "*When you say cancer, "death" is implicit even though the majority of teenagers (15-19 yrs. old) recover*", Karyn Dugas specified. The initial exploratory project, which won the Unicancer Federation 'Innovation' Award – was followed by the creation of a Nouvelle-Aquitaine-based observatory monitoring young cancer patients' return to school. It has now been replaced by the non-profit CARRY-ON and its partner web platform, aimed at facilitating the school/university experience for young patients with cancer or a rare disease.

Head of the Research Department in Social and Human Sciences, Professor Eric Dugas (2nd from left) with his team at the University of Bordeaux.

The Bordeaux University Hospital (CHU) integrated those recommendations quickly and, what's more, decided to create a position for a health support coordinator at the Maison MARADJA (Aquitaine Resources for Teens and Young Adults). The hospital facility, that had already been accommodating the families of teenagers with cancer has now been given a wider scope. "*Support and services for teenagers and young adults with cancer, in relation to their social inclusion – scholastic, university and professional – are now interviewed and studied by a multidisciplinary research team* from the University of Bordeaux*", explained Éric Dugas, Professor of Educational Sciences and leader of the EMELCARA project for students suffering from cancer or a rare disease, funded by the European Social Fund (ESF, ex-Aquitaine, 2016-2019).

"*The research showed that the statements made by parents and their children suffering from a rare disease were comparable to those of cancer patients.*" Different pathologies but similar issues regarding day-to-day life and its uncertainty. "*For example, a teenager with Crohn's disease initially treated in paediatrics is then going to be sent to a department for adults and consequently lose the support services for his schooling!*" The issues related to rare diseases were therefore included in the research with the support of Professor Didier Lacombe (UMR 1211, Inserm, University of Bordeaux, Rare Diseases: Genetics and metabolism). "*Thanks to the findings from the EMELCARA project we can plan and organise a new type of support*", said Éric Dugas. But all the stakeholders in the field – doctors, nurses, sociologists, psychologists – already acknowledge that it is urgent to create a profession for coordinators who provide support to patients in the target group. Because patient and family time is not hospital time, this emerging, non-medical, ancillary profession is of utmost urgency. It could be called "*health and life journey coordinator*" at the crossroads of a territory's health facilities and services. ■

Didier Dubrana

* Educational sciences, sociology, psychology, psycho-sociology, management science/marketing with the CHU doctors, and oncologists. The main pilot members of the project are: for the University of Bordeaux and LACES (EA 7437), Bénédicte Courty (associate professor), Dugas Éric (University Professor), Lucas Sivilotti (PhD student); and Zoé Rollin (associate professor, Paris Descartes University) and Karyn Dugas (Project leader and health support coordinator, Bordeaux CHU Pellegrin/MARADJA).

PSYCHOLOGICAL ASPECTS IN ONCOLOGY: BETWEEN CLINICAL PRACTICE AND RESEARCH

Bruno Quintard, a University of Bordeaux professor in Health Psychology, works on different areas of research in psychology, such as how patients and their loved ones adjust to various types of medico-hospital stress: personal experience of treatment of a chronic disease, particularly cancer.

In Quintard's opinion, it is especially important to conduct "*observations and take into account the issues health professionals encounter on the job in order to provide research and scientific expertise to enhance their practice in oncology*". The will to do just that can be illustrated by the close collaboration with psychologist Nena Stadelmaier from the Institut Bergonié (DISSPO-CARE Department). Along with other university professors and professionals, the two of them have been conducting various studies based on two topics for over ten years.

The first study followed up on the 2003-2007 Cancer Plan. The latest one led to setting up a tool for Diagnosis announcements and Caregiver Support Time (TAS), used by nurses or radiographers, allowing them to evaluate patients' needs for 'Supportive Care'. To help healthcare professionals identify patients' needs for psychological care better, they adapted a semi-directive interview tool, initially developed by a German team and known as PO-Bado (Basic Documentation for Psycho-Oncology). The tool proposes an approach that combines screening, listening and a supportive relationship, which was demonstrated in an initial study published in the journal *Psycho-Oncology* (2014). "*We've seen a move towards a relational attitude that is more centred on the patient's subjective experience and allows an exchange that's open, but guided by the healthcare professional*", they explain. The standard version of the tool adapted into French (published in *Behavior Therapy*, 2016) and its short version were used with 372 patients. The studies received funding from the Fondation de France and the Regional League against Cancer. The PO-Bado interview guide has since been released for use in other oncology departments.

The second research topic studied by Bruno Quintard and Nena Stadelmaier, with a pilot group, is currently underway and has received financial support from the APICIL Foundation, PalliaAquitaine, and the Regional League against Cancer. It deals with exploring the situation of family caregivers, whether health professionals or not, who are confronted with the serious illness of a loved one. The aim is to get a better grasp of the specific aspects and interactions between family caregivers, patients and medical teams (article published in *Médecine Palliative*, 2018); other articles are currently being prepared. ■

WHEN SOCIOLOGISTS EXAMINE DOCTORS

Sociologists study knowledge dissemination in biomedicine and the delayed recognition of innovations.

In Bordeaux, cooperation between health sociologists and doctors began motivating research over 20 years ago. In the 2000s, the theme of innovation became the focus of studies following a request by Doctor Jean Palussière, an interventional radiologist at the Institut Bergonié. Thanks to the development and improvement of techniques that were only slightly invasive, or even non-invasive, radiology was no longer confined to diagnosis alone and was gradually becoming therapeutic! At the time, the still-unrecognized innovation was poorly covered, or not covered at all, by the French social security system. In administrative-speak, it boiled down to the "procedure not being listed" on the social security index. Patients could therefore not always benefit from the procedure and surgeons looked on the new non-invasive treatment unfavourably. According to Béatrice Jacques and Pascal Ragouet, both sociology researchers at the Centre Emile Durkheim (UMR 5116, CNRS, Sciences Po Bordeaux, University of Bordeaux), innovation altered the organisational balance between the different departments and people involved, and raised lots of questions. "*The radiologist asked us about the organisational recognition of radiology as an activity and its innovations. How were collaborative relationships established between the various stakeholders when a new technology was being implemented?*" Pascal Ragouet explained. After three years of research, interviews and observations in operating theatres in the University Hospitals of Marseille, Strasbourg, Toulouse and Bordeaux, Béatrice Jacques concluded: "*With the move from diagnosis to procedures with a therapeutic purpose, interventional radiology brought a new definition of the speciality by the practitioners and led to a reconfiguration of the relationships between medical specialties. The friction between disciplines and the negotiating didn't make the institutional recognition easier and also partially explained the issues related to indexing the procedures.*" Interventional radiology now constitutes an effective alternative to conventional surgery, but it remains a significant example of resistance to discovery. At present, the convergence between scientific and industrial spheres is omnipresent in the biomedical field. "*The issue of transferring knowledge and, more generally, innovation is at the heart of our research*", Pascal Ragouet added. "*Currently, we are looking into resistance to in-house discovery in scientific fields in general, and resistance that occurs when the issue of translating those discoveries to the medical field arises.*" That research path – very recently opened – proposes to tackle the phenomena of delayed recognition in the field of oncology via the notion of "sleeping beauties" (SB). A Sleeping Beauty refers to a scientific paper that, once published, receives very few citations in an initial period lasting over 10 years (sleeping period) and which, suddenly, is heavily mentioned after being used in a researcher's publication (the Prince's kiss). "*The study of sleeping beauties has proven to be very interesting in the exploration of knowledge dissemination mechanisms, of which the translational processes in biomedicine are an example*", the sociology researcher concluded. ■

Lily Bias

MATH WIZARDS IN WHITE COATS

Doctors call on mathematicians to produce new cancer monitoring tools.

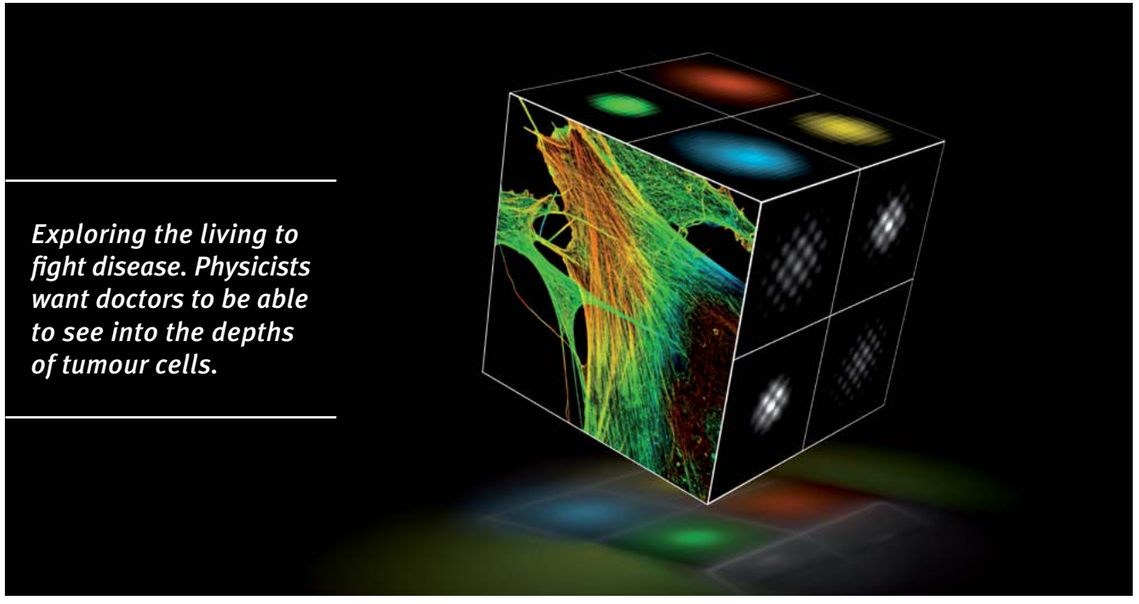
INRIA mathematicians creating digital double of a patient's tumour

Upon entering the Bordeaux Institute of Mathematics (IMB), you expect to come across champions in geometry, probabilities and other random models. With over 150 university lecturers-researchers and 120 doctoral or post-doctoral students, the facility unites the cream of the crop of Bordeaux mathematicians in a joint research unit (CNRS-Bordeaux INP-University of Bordeaux). Doctor Olivier Saut, who works there, has a special mission: he spends his day focused on the fight against cancer with the aim of "*deriving an equation for the disease in order to create a digital double of a patient's tumour*". He's in charge of Inria's Oncology Modelling team (MONC) bringing together imaging (MRI, PET or scanners) doctors, biologists, and IT engineers, etc. Together, those scientists run a project "*that revolves around three clearly-defined areas of research*", he explained. "*We're trying to understand cancer mechanisms better. We're helping develop new therapeutic approaches and above all, we're developing disease monitoring and decision-making tools*". The goal: help doctors or biologists understand and predict tumour growth, or even control it and more accurately assess the response of the cancer to a particular treatment, in a clinical context or in preclinical studies. The originality of the research work is that it is based on the daily experience of oncologists from several hospital facilities (such as the Institut Bergonié in Bordeaux, the Bordeaux and Bondy University Hospitals (CHU), and Humanitas Research Hospital in Milan).

For over six years now, doctors have been collaborating with the MONC team to evaluate the aggressiveness of different types of cancer. In the case of lung cancer, the equations have helped understand the progression of metastatic growth with the goal of targeting the most dangerous metastases for destruction first. For intracranial meningioma, the joint efforts with Bordeaux CHU neurosurgeons have made it possible to monitor tumours to evaluate their growth and know when to operate. "*The diagnosis aid makes use of several fields of mathematics*", Olivier Saut specified. "*Cancer cell modelling falls in the field of partial differential equations. But those equations have to be solved by computers. Consequently, we call on the field of scientific computing. Lastly, to integrate the various parameters specific to each of the patients, like the division rate of cancer cells, we draw on the field of data assimilation*". The quality of the software developed by the MONC project team recently caught the attention of SOPHIA GENETICS, a global leader in data-driven medicine. The company not only purchased the license to the software that enables the evaluation of tumour growth but also recruited one of the MONC team's mathematicians, Thierry Colin who initiated the research. The goal being to market this AI so that clinicians have an exhaustive tool integrating genetic data as well as data from medical imaging. ■

Didier Dubrana

Exploring the living to fight disease. Physicists want doctors to be able to see into the depths of tumour cells.



3D SELFI AND CARBON NANOTUBES: MICROSCOPY OF THE FUTURE

"*See the invisible*": that could be the motto of Bordeaux's Digital Photonics and Nanosciences Laboratory (LP2N-CNRS, IOGS University of Bordeaux), which has been developing high-resolution optical microscopy methods for applications in biology over the past several years. To understand the living, we have to decipher the three-dimensional organisation of biomolecules – proteins – making up biological matter. A giant step was made in 2010 with the arrival of so-called "*super-resolution*" microscopy making it possible to observe the 3D organisation of biomolecules inside thin biological cells isolated one from another. Now, Laurent Cognet's team at LP2N is going even further. "*We've developed a new optical concept capable of detecting, then locating a unique molecule in 3D with nanoscopic accuracy, marked by fluorescence within a thick, complex biological specimen*", the CNRS researcher explained. The technique named SELFI (for self-interference) allows a molecule to be localized under several layers of cells, inside tissue (up to 50 µm). The technique adapts to any optical fluorescence microscope and has proven to be extremely consistent and reproducible.

The performance, published in *Nature Methods*, should allow the exploration of molecules on tumour biopsy specimens. A first! "*This new ambition falls within the "Sciences and Technologies for Oncology" objective of the new Regional Oncosphère network that strives to promote joint efforts and interfaces between researchers with technological expertise, biologists and clinicians*", Laurent Cognet said. Every day, the progress in optics reveals a little more about cell organisation.

At the same time, in 2017, a joint effort between the LP2N and Bordeaux neuroscientists made it possible to explore the extracellular space of neuronal tissues thanks to the combination of new infrared probes based on carbon nanotubes and super-resolution microscopy. The technique, published in *Nature Nanotechnology*, will also be used in cancerology to explore the tumour microenvironment, which seems to play a major role in the development of the disease. "*The goal is to work at very high resolution on tissues that are as intact as possible*", Laurent Cognet concluded, adding "*maybe even in vivo*". ■

Didier Dubrana

MIREILLE BLANCHARD-DESCE

RADIANT DETERMINATION

For Mireille Blanchard-Desce a good day involves a glance at a photo of her two daughters – free-thinking, close-knit young women she is proud of and talks about with the emotion of a mother as attached to family as she is to defending the status of women, which she embodies with force. Her whole career she has proven her ability to advance alongside Nobel prize winners and distinguish herself with the humility of those who advocate working together as opposed to competing.

From her hometown of Antony south of Paris to Bordeaux's ISM (Institute of Molecular Sciences) where she now directs the Molecular Photonics research group, Blanchard-Desce has won renown in the field of science, yet that fame still somewhat surprises her. With a grandfather who was a senior civil servant and a mother who was a scientific engineer, rare for the times, she was always torn between science and literature. In high school, her scientific baccalaureate (with high honours) didn't keep her from taking a few electives – ancient Greek and French – for fun... Despite receiving the highest possible mark on her math final "*for having solved a problem not on the curriculum!*" she says she didn't realise back then that she was motivated by "*the equation and the diagram because I reason the old-fashioned way*".

Admitted to the exclusive post-secondary school Louis-Le-Grand in Paris, she had to "*make her way in a boys' world*". Russian literature helped her cope, inspiring her eldest daughter's first name. Then she entered the École Normale Supérieure (ENS) where she graduated top of her class. She never really chose between physics and chemistry either: specialising in both with a graduate degree in chemistry at the Pierre & Marie Curie University (UPMC), a French teaching degree in chemistry, and then another graduate degree and a doctorate in organic chemistry, encouraged by Professor Jean Marie Lehn.

In 1985, at the prestigious research establishment Collège de France "*in the temple of protected knowledge*", she relished in the opportunity of learning alongside the elite but in an environment as difficult as women were few. She worked under the supervision of Lehn, a specialist in supramolecular chemistry and 1987 Nobel prize winner, who proofed her first publication in the scientific journal *Chemical Communications*. Under the watchful eye of that visionary who taught her independence, she presented her thesis in 1989, "*working the American way, and developing my own subject on conduction in molecular wires for nonlinear optical applications*". She continued her one-year post-doc at the Institute of Physico-chemical Biology (IBPC) in Paris, "*in a totally unknown world*" driven by her favourite topic – light (electrons and photons) – and for the energetic properties of photosynthesis: "*bioenergetics is a terrific model in chemical energy*", she said enthusiastically. Following her mentor Lehn's advice, she went back to the ENS to set up a chemistry lab, and co-head a team specialised in the engineering of photonic molecules. In 2000, she began anew in Rennes, putting together a team devoted to molecular photonic activity, in the lab directed by Professor Michel Vauthier. Her taste for projects and her resolve never waned for twelve busy years, including six managing a unit for the development of molecular multiphoton processes. And on top of that, several publications and scientific recognition in bibliometrics. Bordeaux's ISM recruited her in 2011 as head of a research group to create the PHOENIX team, opening up new joint efforts between chemistry, neuroscience, optics and OncoSTIM – the work group in which Blanchard-Desce has played an active role in the emergence of onco-photonics. One publication has followed another, with her research on phototherapy leading her to focus on vectors delivering cytotoxic molecules to tumours, while her three patents, filed in 2016, 2017 and 2019, have opened numerous possible applications for anticancer therapy.

Passionate about equations, reading and defying all forms of stereotypes, she admits to enjoying line dancing or watching the quirky medical series *House*... The connection? Maybe the sense of community? ■

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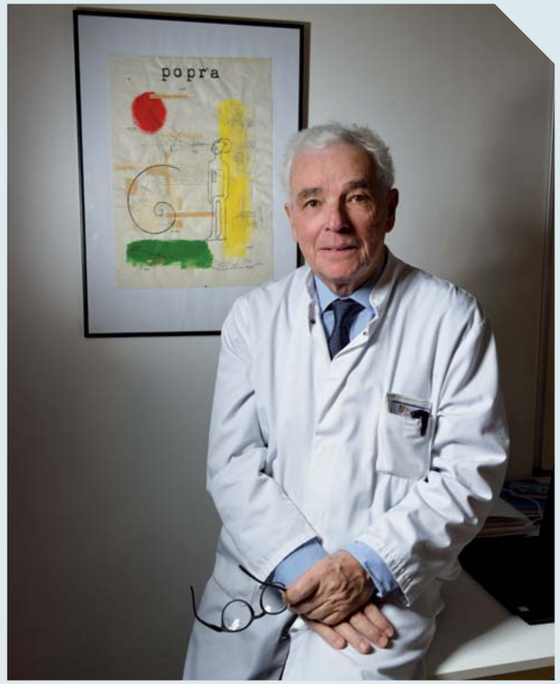
Constance Deveaud

GUY KANTOR

IN SEARCH OF COMMON BONDS



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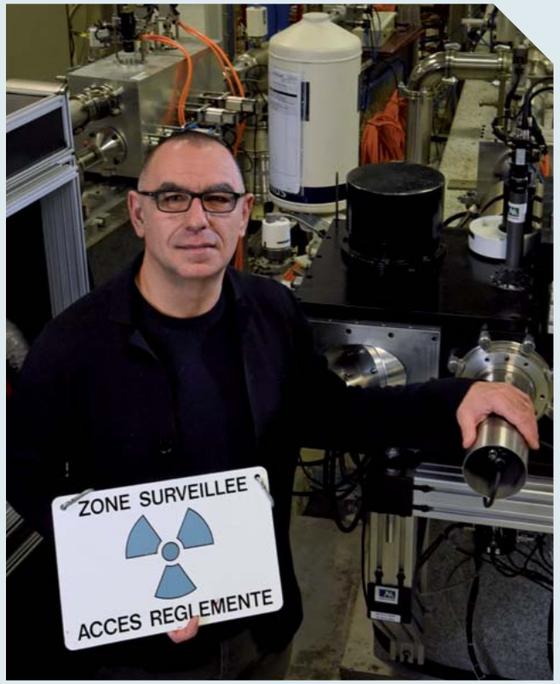
As if it were yesterday, Guy Kantor remembers the first cancer patient he saw as a young, barely 23-year-old medical student. He has worked on the "*roughest of the rough*" cases, he says, treating children with sarcomas, or young adults developing brain tumours! A very careful, reasoned choice: "*you have to be empathetic to ensure a sense of humanity when treating someone; but how do you also avoid sympathy and more fusional contact?*" he asks. "*You have to be detached to remain clearheaded in the face of serious situations but how do you also avoid denial and evasion when facing overly at-risk, wearing situations that are sources of exhaustion?*" The professor and radiation oncologist at the Institut Bergonié places the patient at the centre of everything he says and even more so at the centre of his life as an oncologist. An ever-evolving speciality that requires developing ever more precise and effective therapeutic tools. That works out nicely because Kantor – a guy who briefly hesitated between engineering and medical school – "*has always liked medical instruments, big machines, complicated things where there's technology involved*". And in this field, Guy Kantor has built himself quite a reputation. In less than twenty years, he has actively contributed to upgrading medical techniques used in French and international radiation therapy by participating in 5 national programmes for innovative therapeutics and by equipping the Institut Bergonié with ultra-high performance machines. In 2005, when the Institute's director, Josy Reiffers, suggested that Guy Kantor contact the researchers at the Bordeaux Faculty of Sciences, the foundations of an unprecedented partnership were laid between mathematicians, physicists, biologists and doctors. Right away, the dialogue was established incredibly easily, despite the diverse scientific horizons.

Mathematics made it possible to set up a provisional chart for the growth of a tumour. Biology studied the tissue repair systems related to radiation therapy while physics fine-tuned and accelerated the dose calculation models. That "Dream Team" created lasting bonds with our guy, always at the centre of an anti-cancer war machine, calling on the production of X-rays via lasers or on proton accelerators to manufacture isotopes used as markers or treatments. Out of all the people he met, Jean-Luc Feugeas, a physicist at CELIA (Centre Lasers Intenses et Applications) is the one with whom Guy Kantor was to begin an intellectual sparring match, and just mentioning it lights up his face. The scientists, now friends, were to venture out on the path of Art and Science. The doctor ordered a painting from the physicist "*illustrating the world of treatment*". That gave rise to the identity and style guide for POPRA, a scientific research programme, but also to cARE, a painting staging the complexity of the patient-caregiver relationship, via the composition of a unique, minimalist line, representing, among other things, the fruit of the dialogue between patient and doctor. That painting, hanging in Guy Kantor's office is the illustration of the otherness in treatment. It always gets back to that with Guy Kantor: "*you have to understand the other person*". After over 45 years of medical practice and moving mountains, he whispers in the course of the conversation: "*I can rest easy. I'm satisfied. My wife and I were able to take care of our children with love and, in all likelihood, opened up the scope of possibilities for them*". The eldest is an ophthalmologist and the youngest, a philosopher. ■

Didier Dubrana

HERVÉ SEZNEC

HIGH-PRECISION TARGETING



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When he first started out, his job was in molecular genetics. The young Hervé Seznec had just finished his PhD at the Necker-Enfants Malades Hospital in Paris and his post-doc in Strasbourg when he applied for a position as a researcher by taking the CNRS exam. Unsuccessfully… almost. He was admitted on the reserve list! There were too many applicants in view of the limited number of positions available. For that matter, in the Spring of 2004, that was one of the demands that motivated the uprising of all the public sector researchers in favour of the "Save Research" movement. After several weeks of orderly demonstrations, the civil servants partially won their case: French prime minister Jean-Pierre Raffarin opened the taps to pump funding into a few positions. A godsend for our young biologist called on by the physicist Philippe Moretto, Director of a CNRS and Bordeaux University research platform, who offered him the following deal: "*you're being assigned a research position, but you'll be joining a team of physicists!*"

Once the initial surprise was over, Hervé Seznec immediately grasped the challenge: "*I had to leave my comfort zone behind to do biology in a totally different way. That had never been done and I found the scientific challenge twice as interesting, much more than the actual position I was being offered*". So he agreed to become an innovative actor on the AIFIRA Platform (Multidisciplinary Ion Beam Applications in the Aquitaine Region) of the Bordeaux Nuclear Research Centre. At the time, he had to develop experiments on a cell irradiation beamline to study the biological effects of radiation. Accelerated ion beams with a voltage of up to 3.5MV were targeted at living cells in culture. "*So I ended up surrounded by physicists. A dialogue was established to re-think the experiments together. But before understanding each other, first you have to agree on the meaning of words. For example, a physicist's statistics aren't the same as a biologist's!! I had to explain biological concepts to physicists and vice versa. I went back and reviewed all my old physics class notes to bring myself up to speed*". Now, the geneticist relishes in the scope of the task achieved thanks to that team work. The biologist and the physicists built an outstanding research tool, considering there are only four facilities in the world with this type of beam entirely dedicated to biology.

Hervé Seznec also designed and managed the construction of an L2-type laboratory to conduct experiments on cell cultures safely. Those cultures make it possible to assess the effect of "low-dose" exposure on the occurrence of cancers. The team is improving the effectiveness of radiation therapy without destroying healthy tissue in the process. "*We can deliver the dose we want where we want it. In the cell nucleus or in the mitochondrion. We can observe the DNA molecules we want to damage, in real time*", he says, fascinated. Unfortunately, the French administration has not always known how to classify the cross-disciplinary researcher and his research. Still, at forty-something, he has stayed on course, through thick and thin, at the expense of a career advancement path fairly unrepresentative of his level of responsibility! No matter! The man devotes himself to the Japanese art of bonsai that makes him zen, he loves world cuisine and treats himself to ocean getaways in Lacanau to surf the long, straight waves… ■

Didier Dubrana

BIOLOGY **IN 3D**

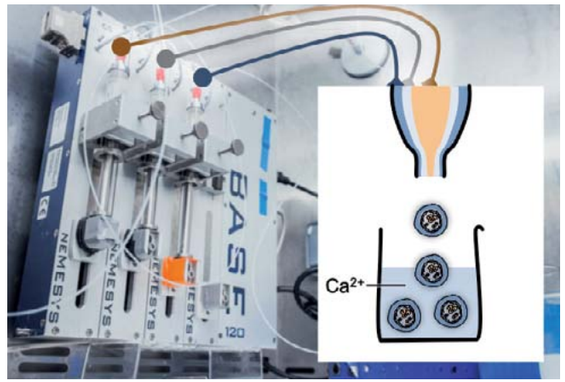
By inventing a kind of 3D Petri dish to grow and observe cells, biophysicists are widening the potential of the optical microscope in biology.

For the past several years, the physicists at the IOA (Aquitaine Institute of Optics) in Talence have been exchanging with the oncologists at the Institut Bergonié. "*Our goal is to raise scientific questions together*", explained Gaëlle Recher, research associate at the CNRS. To answer them, they call upon two major fields of science: biophysics and biology. These days, it is specifically the question of mechanotransduction in cancer that is at the centre of their experiments. In response to the question "*What do you mean by mechanotransduction?*" Gaëlle Recher specified: "*It's the different phenomena ranging from mechanoreception to its physiological response and including the transmission of the signal to the cell, enabling biological systems to integrate information about the environment and about themselves, and to modify their properties as a result of changes in the physicochemical system*". It's what happens when a tumour grows. The tumour gradually needs more room and is subjected to mechanical pressure by the surrounding tissues which induces a change in the behaviour of the tumoral cells. Consequently, the cells that have become mobile and potentially metastatic escape from the tumour and invade other tissues. The study of that phenomenon requires live *in vivo* observation of the cellular self-organisation and tissular morphogenesis.

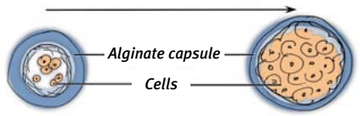
And to do so, the Institut Bergonié came to the right place: The Institute of Optics is at the forefront of optical imaging in biology! From single plane illumination microscopy to 3D-printing of microscope parts, the researchers are solving the mysteries of living things like never before. However, while live 3D high-resolution microscopy techniques are developing rapidly, their use in oncology had been hampered until now due to the lack of a *"3D-tumour model"*. In plain language, the solution had to be found for growing cells in volume under the eye of the different types of microscopes. "*We invented a kind of 3D Petri dish*", Gaëlle Recher said. "*We encapsulate the cells in sub-millimetre (alginate) hydrogel shells. Consequently, the 3D cancer cell cultures can be observed. The model makes it possible to test drug effectiveness or resistance. It's used for understanding how cells self-organise.*"

Its field of application is huge. For that matter, a patent application has been filed for the invention by SATT Aquitaine (Aquitaine Science Transfert). ■

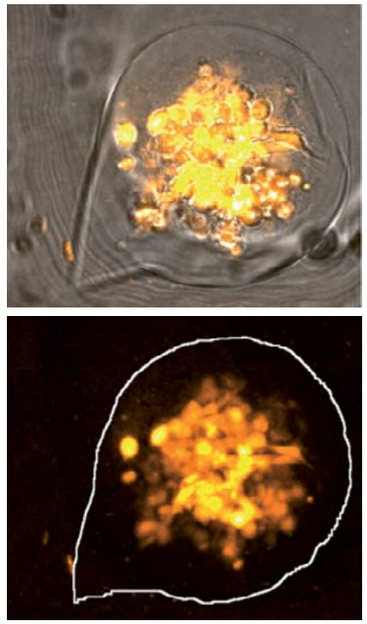
Raoul Sancy



Encapsulation device



As the cells multiply inside the alginate capsule, they apply a mechanical force which deforms the walls, making it possible to calculate the aforementioned force.



Two views of capsules imaged in wide-field microscopy.

VANJA SISIRAK

THE CITIZEN OF THE WORLD WHO ENJOYS DISSECTING MECHANISMS

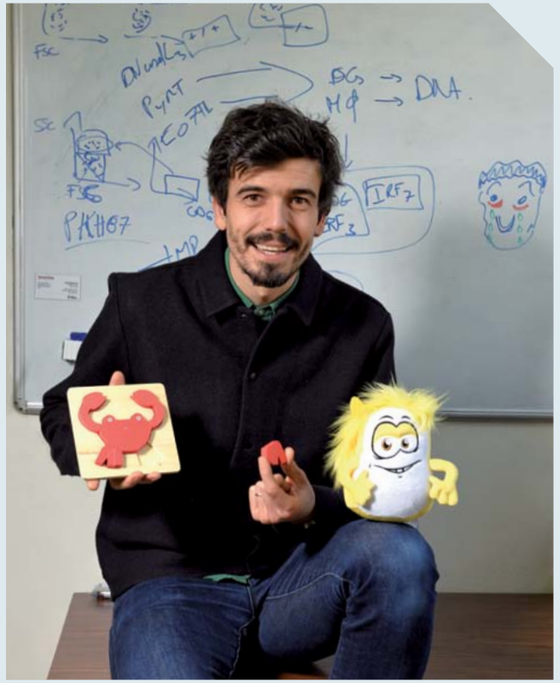
Don't bring up the dreariness of the Haute-Savoie valleys where he spent his first French years upon arriving from Bosnia in 1993. Right from the start of his studies in Lyon, Vanja Sisirak sought the contact with major cities, cultural profusion and movement. At home, he speaks English with his American wife, Bosnian with his two young children and French, of course, because the family moved to Bordeaux "*for the best life balance*".

Vanja Sisirak began his career in biology, then attended the Ecole Normale Supérieure (ENS) where he appreciated the workload in the lab and the resources allocated to learning "*through and for research*". Surrounded by international researchers from all fields, his time at the International Agency for Research on Cancer (IARC) in Lyon opened his eyes to the world. The cross-disciplinary approach stimulated him, motivated by the molecular aspect of oncology and his interest in dissecting mechanisms.

In 2005, he met two key people: Doctor Christophe Caux, his thesis supervisor and Doctor Nathalie Bendriss Vermare, his "*mentor*" who introduced him to "*the incredible universe of how the immune system functions*". Both doctors offered him the opportunity to work on a project in partnership with a laboratory in Dallas, where the first humanized mouse models were being tested in oncology. He came back from Dallas, six months later, more mature, and focused on the study of dendritic cells, which are antigen-presenting cells that act as messengers with the immune system: "*like in a game of Pac-Man*", he explained, making use of a sketch...

In 2010, he presented his thesis on the role of plasmacytoid cells (the dendritic family) in breast cancer and demonstrated the existence of tumour molecules inhibiting the capacity of those cells to produce interferons, which play an important role in the induction of anti-tumoral immunity. Progress that now has led to research on the factors of that blockage "*in order to establish new therapeutic targets to boost the control of tumours through the immune system*", he specified.

The post-doc that followed took him to Columbia University in the city of New York where Dr Boris Reizis had just opened his lab based on a new mouse model, totally deficient in plasmacytoid dendritic cells, allowing their exploration in multiple contexts. Consequently, Vanja Sisirak widened his field of research to systemic lupus. Another discovery about the function of plasmacytoid cells and their contribution to lupus. Another publication leading to therapeutic perspectives for patients suffering from lupus.



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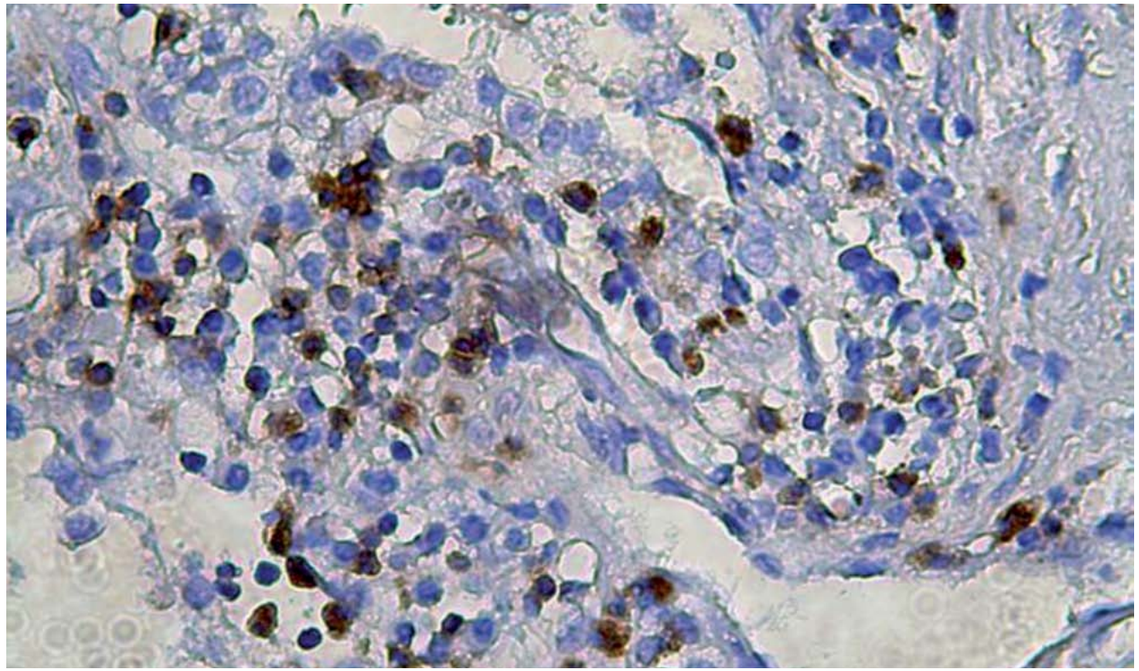
In New York, Vanja Sisirak also took a closer look at the issue of the DNA buildup released by dying cells. He completed his postdoctoral research in 2017 with the publication of his conclusions on the role of a particular DNase deficiency, manufactured by dendritic cells.

Back in France in 2017 he was recruited by Professor Patrick Blanco in Bordeaux. Thanks to the IdEX Junior Chair programme and lots of backing, he decided to combine the expertise from his thesis and his post-doc topic. Within the ImmunoConcEpT unit, *the Tumor DNA Sensing* team's mission, headed by Vanja Sisirak now 36, is taking that direction. "*Before you can be committed to anything whatsoever, first you have to be a part of it*", he said. So when he practises a sport "*it's to have a good time as a team*" whether it's badminton or basketball. And when he's not publishing scientific articles... he spends time on blogs "*to further my knowledge of subjects I'm interested in, get more information and in the end, master them*", he admitted: like African music (a souvenir of his past in New York as a DJ in an African bar), or exhibitions visited one place or another... ■

Constance Deveaud

HOPE IN **IMMUNOTHERAPY**



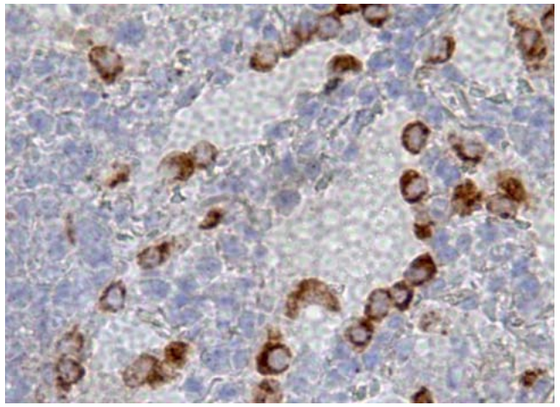
Immunohistochemical labelling: analysis of CD4 expression by T cells infiltrating the tumour of a patient with non-small-cell lung cancer (NSCLC).

Bordeaux-based onco-immunology and cancer immunotherapy have organised themselves in a centre of excellence united under the banner of ImmunoConcEpT (IMMUNOlogy from CONCepts to ExPeriments and Translation, CNRS UMR 5164 - University of Bordeaux).

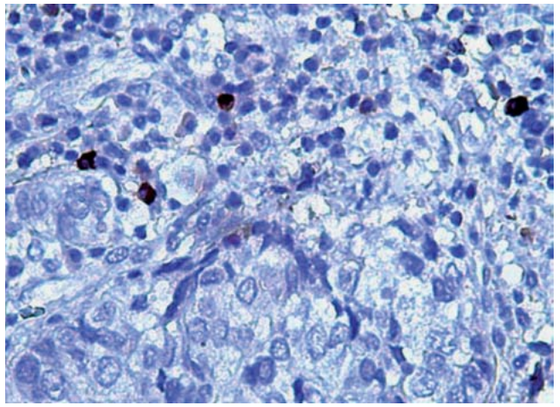
We know that our immune system can recognise and specifically eliminate tumour cells. That discovery has paved the way for many immunotherapeutic approaches based on the stimulation of cytotoxic immune cells – including T cells – causing the selective destruction of cancer cells. Some of those therapies have produced very promising results leading to substantial remissions and clinical responses for various types of cancer. They have brought about significant improvement in the overall survival rate.

However, many patients respond only slightly, or not at all, to 'immunomodulatory' therapies. Why? "*The absence of response is especially due to a blocked immune system, resulting from the multiple strategies deployed by the tumours, which leads to the establishment of a highly immunosuppressive environment*", explained Doctor Nicolas Larmonier, university lecturer and researcher at ImmunoConcEpT UMR 5164. "*Reducing or eliminating those immunosuppressive phenomena can improve the effectiveness of the therapeutic interventions, whether they are immunotherapies or even conventional therapies*", he continued. For example, many cancers generate myeloid-derived suppressor cells (MDSC) as one of many tumour-immune escape strategies. Those cells further cancer development and dissemination. They are capable of inhibiting anti-tumour immunity and promoting the metastatic and invasive properties of tumour cells. Nicolas Larmonier's team is therefore focusing its research on characterizing those MDSCs. "*We want to define the impact of the environment and the stage of tumour development on the functional and phenotypic profile of MDSCs*", Nicolas Larmonier added. That's why they're asking questions such as: "*What is the role of MDSCs in preparing pre-metastatic niches and the spread of cancer cells? How can their presence be correlated with the degree of cancer severity and the response to conventional treatments or to immunotherapy?*" All these questions are guiding the research of the ImmunoConcEpT teams directed by Julie Déchanet-Merville. Within the framework of her team, certified by the French League against Cancer, she is also exploring that path of immunotherapy. "*We're studying the role of gamma-delta T cells that are capable of recognizing and specifically killing certain tumour cells, such as glioblastoma cells or colon cells. We want to understand the functional and molecular mechanisms of the interactions between gamma-delta T cells and tumour cells. For example, we've demonstrated that they recognize antigens specifically expressed on the surface of tumour cells. The tumour antigens could be used as vaccines to stimulate anticancer immunity.*" By recruiting Maya Saleh, currently a professor at McGill, ImmunoConcEpT has also been able to develop new research on efficacy markers for immunotherapy and its adverse effects, especially focusing on the role of the microbiota and myeloid cells. The project enabled Maya Saleh and ImmunoConcEpT to secure the prestigious ARC Foundation funding, 'Recruiting Emerging Leaders in Oncology' 2019.

Immunohistochemical labelling. Analysis of CD208 expression by T cells infiltrating the tumour of a patient with non-small-cell lung cancer (NSCLC).



Immunohistochemical labelling. Analysis of CD103 expression by T cells infiltrating the tumour of a patient with non-small-cell lung cancer (NSCLC).



The ImmunoConcEpT laboratory is also developing its research on chronic lymphocytic leukemia (CLL), a blood cancer that accounts for 30% of all forms of leukemia. The disease primarily occurs in people over the age of 60 and affects B cells, which help the immune system function and defend the body against pathogens (bacteria, viruses, fungi, etc.). B cells are normally produced in the bone marrow. When affected by CLL, some of those cells become immortal, multiply abnormally and gradually invade the bone marrow, blood, spleen and lymph nodes. The phenomena leading to the immortality of B cells, and therefore to CLL, are still poorly determined. "*Better understanding of the cell mechanisms that cause the cancerous transformation of B cells is therefore essential. Our team is focusing its research on another population of white blood cells: T cells. They play a major role in regulating the immune system and consequently B cells*", explained Dorothée Duluc, University of Bordeaux associate professor. "*Our study deals with immune cells called T follicular cells that play an essential role in the antibody-producing mechanism and thus a major role in the response to infection.*"

Hence ImmunoConcEpT, via its translational and fundamental research, has asserted itself as one of the spearheads of cancer immunotherapy within the Oncosphère. ■

Lily Bias

MAËL LEMOINE

PHILOSOPHY THAT CARES

What is the pathological phenomenon? That's the question central to the research conducted by Maël Lemoine who observes that "*even if all living beings are sick, we don't have a theoretical definition of disease*". Without a "*unified framework*", there's no specified theory except for literature mostly dealing with disease and its phenomena. As such, the philosopher decided to approach the study as closely as possible to biomedical sciences since "*they stick to disease*" he explained.

Before choosing that topic as a field of research, Maël Lemoine said his academic path in philosophy was a classic one, at the Ecole Nationale Supérieure (ENS). He then went on to get a French teaching degree (Agrégation) before doing his doctorate on the history of philosophy in 2002. His revelation for the "*philosophy of medical science*" occurred the same year he taught his first medical students, "*who were not easily taken in, asking specific, meaningful questions*". He also remembers his audience's teasing banter during a course dealing with the influence of Descartes on medicine as the first "immortalist". A sort of scepticism that students seem to have forgotten in recent years.

Maël Lemoine enjoys lecturing in front of 800 people, fairly unruly atmospheres, and adapting to his audience. Although he continues to teach at the Medical School and the Faculty of Philosophy, research and the biomedical world are what motivate him and keep him busy with "*a totally pragmatic vision of biology and research*". Everything that can be useful becomes an absolute priority. By choosing to study disease, he wants to serve both patients and treatments.

Between 2011 and 2017, while based in Tours on an Inserm Imaging/Brain team, he studied the biological mechanism of depression. That was his first experience of research work, acknowledged by the publication of his first scientific article co-authored with neurobiologist, Catherine Belzung.

Shortly afterwards, he moved to Bordeaux to join the group of philosophers led by Thomas Pradeu, and working on the ImmunoConcEpT team. He was warmly welcomed by the Bordeaux scientific community, "*totally contrary to the strong prejudices against philosophy*". And in Bordeaux, the setting was conducive to furthering his research project on "*the links between aging and cancer*".

In Bordeaux, the group of philosophers is rather unique in the world. Collaborative and entirely devoted to clarifying terms, theory consolidation, reflecting on methods and the strategic prospective in research, the group practices what Thomas Pradeu has named philosophy in the sciences. Alongside Thomas Pradeu, Professors Jean-François Moreau and Maël Lemoine, doctoral students, postdoctoral researchers and international guests keep coming. The "extramural institute" (philinbiomed.org) is structured to promote its highly-active synergy. Seminars and conferences are frequently organised to build on the interactions, raise questions and be proactive. "*Researchers concentrate on the facts and we (focus) on building concepts that support them*", Maël Lemoine explained. The goal is to give rise to new joint efforts and shed specific light on the most specialised topics of research, with a view to excellence. Similar to the tea ceremony in Japan whose complexity and precision the philosopher is fond of, when the ritual reveals its underlying logic.

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Reading medical and scientific articles takes a prominent place in the day-to-day life of this hard worker, enthusiastic about life in Bordeaux. Although the Breton likes having the ocean nearby, he chose to settle down in the lush green countryside so he can slip on his running shoes at a moment's notice and train for his annual marathon out in the open. ■

Constance Deveaud

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