2016
Institut Pasteur Annual Report

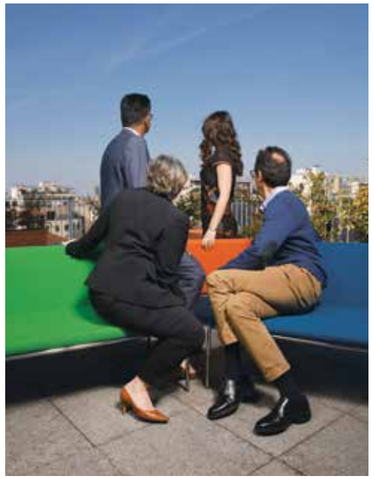
PASTEURIANS

Institut Pasteur







PASTEURIANS

What sets the Institut Pasteur apart is the men and women working every day towards its universal mission – fighting threats to human health across the world. These men and women are Pasteurians.

Being a Pasteurian means demonstrating inventiveness and determination to prevent, diagnose and combat diseases, and also to develop knowledge for the medicine of tomorrow.

Being a Pasteurian means remaining receptive to all life science fields through a global and universal approach to health care issues.

Being a Pasteurian also means sharing the humanist values that have guided the foundation since it was set up by Louis Pasteur 129 years ago.

Being a Pasteurian means acting on behalf of, and with, others.

CONTENTS

Profile

The Institut Pasteur is a foundation officially recognized for charitable status. Its mission is to help prevent and treat diseases, mainly those of infectious origin, through research, education, and public health initiatives.

€319.5M
budget

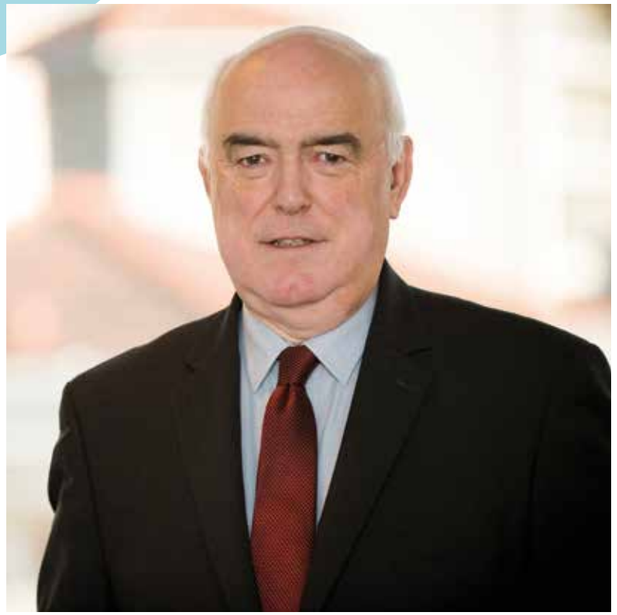
10
Nobel Laureates

33
Institut Pasteur International Network member institutes

13
technological platforms

Approximately 130
research units

Interview with Christian Vigouroux,
Chairman of the Board of Directors



"Institut Pasteur staff are bold nomads who strive for meticulousness, the very essence of the scientific mind."

THE INSTITUT PASTEUR IN THREE WORDS:

Bold
Meticulous
Nomadic

You were elected Chairman of the Board of Directors on November 28, 2016. How do you feel after just under a year in office?

As I said during the New Year ceremony in January, I am proud to be part of the daily life of scientists at this foundation. The Institut Pasteur has an extraordinary history and must uphold the same level of excellence in the future. It is an international institution whose active and pertinent research serves as a benchmark. And it needs to raise its profile even higher in the coming years! "As Chairman of the Board of Directors, and working alongside senior management and all the stakeholders, this is my commitment to the foundation's missions."

What, in your opinion, are the Institut Pasteur's main strengths?

It has three. First, the quality of its research, which is recognized across the globe. The Board of Directors and senior management keep a close eye on the key indicators that enable it to maintain its position in this field. Secondly, of course, its expertise in health – curiosity in the laboratories always goes hand in hand with possibilities for public health. There is constant exchange between research and its applications for the health of populations. As an example, I would like to mention a paper presented by a young researcher during the last Board of Directors meeting (each meeting now begins with a short scientific presentation). He explained how his work on the evolution of certain viruses is not only contributing to fundamental scientific knowledge but also helping to adapt public health guidelines so that these viruses do not pose a threat to humankind. Finally, the Institute's third strength is education. The Institut Pasteur's reach in terms of research and health attracts students from all over the world. And essentially, these three strengths – research, health and education – reinforce each other.

What is your vision regarding the Institut Pasteur International Network?

When people outside of the foundation refer to the Institut Pasteur International Network, which is made up of 33 institutes worldwide, there is always a touch of envy! The network enables knowledge and expertise to be shared throughout the world. It also ensures a unique presence in many areas affected by emerging diseases, inspiring both an ambition for research and research projects. The network is very diverse in terms of organization and function but it brings together a wide-ranging community of men, women, and institutions that are committed to the same missions, values and principles of scientific cooperation and sharing. Most of the institutes are national organizations that have very close links with the local populations, healthcare and scientific institutions, and the local authorities. This proximity is both unique and essential for taking effective action, particularly during a health crisis. We must continue to support, run and develop this network, as we are currently doing, by guaranteeing mobility for our personnel and researchers and education for all.

How would you define the role of the Board of Directors?

The Board of Directors protects the institution and its continuity and organization, monitoring its results. It is not another senior management team! Having dealt with urgent governance issues in an effective and impartial way in the first few months, we are now focusing on the main strategic goals (initially, the scientific targets but also goals related to human resources, finance and equipment). Following its election, the board reapproved the current 2014-2018 strategic plan and is closely following its implementation. It is now up to us to work on a new plan for a subsequent cycle. We are doing this with all the governing bodies and department heads at the Institut Pasteur. I also believe that the role of the Board of Directors is to safeguard the independence of the institution whilst, at the same time, being aware of its interdependence at many levels. We must therefore enter into dialog and, if necessary, cooperation agreements with stakeholders from the worlds of research and higher education. We also need to anticipate risks. General inspectorate reports, which rightly pointed out various areas of concern, have helped with this. Risk mapping, carried out by the former Board of Directors, has also been useful. In the future, we particularly need to find ways to be even more active when it comes to raising funds and developing income generated by our activities. Finally, we must manage our financial reserve effectively to ensure that the foundation is always able to step into action. And may I remind you that the Board of Directors is open to all points of contact – it meets with the various Institut Pasteur staff members involved in the running of our foundation (Scientific Council, laboratory heads, General Meeting board, Works Committee and CHSCT members, etc.). The Board is responsive, fully focused on its task and continues to work tirelessly.

What will the Institut Pasteur be like in a few years' time?

An outward-looking institution! This is already the case. For the Institute to maintain this key quality, we need to recruit the very best researchers from France and abroad. We must also focus on ambitious, cooperative and innovative research. And we must never forget that, behind all this research, there are populations in difficulty. This is the case with the recent outbreaks of Zika and Ebola, two viruses we continue to fight. So, we must remain pioneers, like Louis Pasteur was in his time.

"The Institut Pasteur must increase its international visibility by 2020."

Interview with Christian Bréchot,
President

"Fundamental research for the benefit of medicine and health across the world – this is the Pasteurian tradition."

What are your thoughts on the past year?

In spite of the governance crisis we experienced, 2016 was an outstanding year. We recruited many top-level researchers and worked to constantly improve scientific profiles internally – since my arrival in 2013, we have created 23 new units and 16 five-year groups within the Institut Pasteur. Our research centers, such as the Center of Bioinformatics, Biostatistics and Integrative Biology (C3BI), continued to develop. In particular, the French National Research Agency supported the C3BI's ambitious INCEPTION program, an interdisciplinary program aimed at understanding the emergence of diseases and their impact on society, thanks to contributions from life sciences, mathematics and bioinformatics. We also boosted our facilities, particularly with the acquisition of Titan, the world's most powerful microscope. In addition, we launched several transversal programs (a major vaccine program, a study into interactions between microbes and the brain, a study between infection, metabolism and cancer, etc.), in order to strengthen synergies between the various scientific disciplines. Our scientific papers increased considerably in number and they had a more far-reaching impact on scientific literature. There were also a great many invention disclosures and patents (71 and 32 respectively in 2016). All these achievements, following on from an initiative launched in 2014 with the strategic plan, make us justifiably proud of what we have accomplished.

How would you describe the current global health situation?

It is highly paradoxical. We live in a world where major advances have been made since the early 20th century in terms of vaccines, antibiotics and antimicrobial drugs. But, we are still in danger of major outbreaks, and antimicrobial resistance is a key issue. We currently need to tackle emerging and re-emerging infectious diseases (such as those caused by the Zika and Ebola viruses), and also the rise in noncommunicable diseases, such as cancer, neurodegenerative and metabolic diseases. In this context, the Institut Pasteur has a unique global position – it produces knowledge through fundamental research. It is also a major stakeholder in public health, monitoring and infectious disease response. Thanks to its international network, the Institute is able to operate in France and across the globe.

What can you tell us about this network and its work?

The international network is the focus of our strategy. We significantly strengthened the network in 2016 by setting up major scientific consortiums, which notably analyze resistance to malaria treatments. I'm particularly thinking of the KARMA study, which resulted in the first global mapping of resistance to artemisinin. In addition, within the network and the Center for Global Health, we set up an emergency unit called the Outbreak Investigation Task Force, which is capable of rapidly responding to health crises. Finally, we focused on researcher careers within the network and will continue to promote this initiative.

The network was very active on the Zika front line in 2016

Together with the network, the Center for Global Health organized the Zika Summit* in Paris in April. The aim of this international conference was to share current Zika research findings. Supported by original scientific papers, researchers from the network described the links between Zika, microcephaly and Guillain-Barré syndrome. They also conducted several modeling studies that enabled health authorities in Martinique, in particular, to anticipate hospital care for patients. In fact, a recent assessment of papers on this subject shows that the Institut Pasteur is the world leader on the topic, notably ahead of the US Center for Disease Control.

"At the Institut Pasteur, research thrives on tremendous curiosity and a desire for cross-disciplinarity."

The network even gained a new institute!

The decision to set up the Institut Pasteur in Guinea was made in 2014 to ensure continuity in the fight against Ebola. This new institute perfectly illustrates how we work – first in emergency situations to tackle the outbreak, then over the long term through research, public health and education.

Where does the Institut Pasteur stand in relation to its various partners?

Our work obviously falls within a national strategy for research as well as European policy, represented mainly by the European Research Council (ERC). In 2016, we signed numerous agreements with various French research institutions – universities and *grandes écoles* (École Normale Supérieure), the first COMUE (Association of Universities and Higher Education Institutions) (Paris Sciences et Lettres), research organizations (CNRS, INRA, CNES), the Institut Curie and CNAM. We also continued our business development and technology transfer efforts targeting companies. Finally, fundraising campaigns for donations and legacies proved successful both in France and abroad. If 2016 is anything to go by, I am sure that 2017 will be a great year!

THE INSTITUT PASTEUR IN THREE WORDS:

Excellence
Pasteurian spirit
International

** With the support of the Institut Pasteur, the Bill and Melinda Gates Foundation and the Wellcome Trust, and in partnership with the World Health Organization.*

2016 highlights

February

AN AMBITIOUS SCIENTIFIC PARTNERSHIP BETWEEN CURIE AND PASTEUR

The Institut Curie and the Institut Pasteur signed a five-year partnership agreement on February 18. The aim of this agreement is to strengthen scientific cooperation between the two institutes, to pool their resources and to step up their training initiatives.

March

ZIKA AND MICROCEPHALY: THE FIRST TRIMESTER OF PREGNANCY IS THE MOST CRITICAL

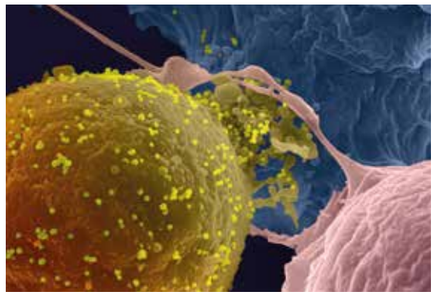
Analysis of data from the 2013-2014 Zika epidemic in French Polynesia by scientists from the Institut Pasteur, Paris, and their French Polynesian colleagues, confirmed the incidence of grouped cases of microcephaly and quantified the risk of microcephaly associated with the virus. This research drew on innovative mathematical modeling techniques.

Discovery Award/Appointment Event Scientific event

March

A CAUSAL LINK BETWEEN ZIKA AND GUILLAIN-BARRÉ

Thanks to data collected in French Polynesia, researchers from the Institut Pasteur, the CNAM (French National Conservatory of Arts and Trades), the Institut Louis Malardé, the French Polynesia Hospital Center, and the Paris Public Hospital Network (AP-HP) showed that infection by the Zika virus is responsible for an increase in the number of cases of Guillain-Barré syndrome, a severe form of limb paralysis accompanied by respiratory impairment.



March

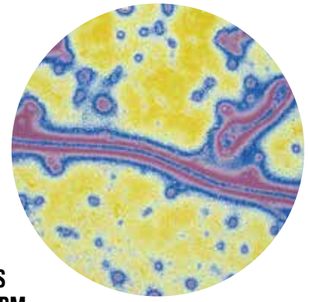
AIDS: ANTIBODIES CAPABLE OF ELIMINATING HIV-INFECTED CELLS

Some effective antibodies recognize cells infected with the human immunodeficiency virus (HIV), and trigger their destruction by the immune system. This discovery sheds new light on the mechanism of action of these specific antibodies, which are currently undergoing clinical trials.

April

INTERNATIONAL ZIKA SUMMIT 2016

The Institut Pasteur, World Health Organization, Inserm, the Research Institute for Development (IRD), the Wellcome Trust, and the European Commission invited researchers and experts working on Zika – a global public health emergency – to a summit on April 25-26. The 500 participants shared initial findings from current research and discussed future steps.



May

THE EBOLA VIRUS PERSISTS IN THE SPERM OF SURVIVORS OF THE EPIDEMIC

An international study conducted by scientists from the IRD, Inserm, and the Institut Pasteur, together with their Guinean partners at Donka University Teaching Hospital, Macenta Hospital, the National Institute of Public Health, and the University of Conakry, confirmed the persistence of the Ebola virus in the sperm of survivors of the Guinea epidemic for at least nine months after recovery.

June

GLOBAL MAPPING OF RESISTANCE TO ARTEMISININ

The first global mapping of resistance to artemisinin (the KARMA study) confirmed that resistance to the main drug currently used in the treatment of *Plasmodium falciparum* malaria is, for the moment, confined to Southeast Asia and has not spread to Sub-Saharan Africa. The KARMA study, conducted by researchers from both the Institut Pasteur in Paris and the Institut Pasteur in Cambodia, involves a large consortium of institutions, including 13 members of the Institut Pasteur International Network.

July

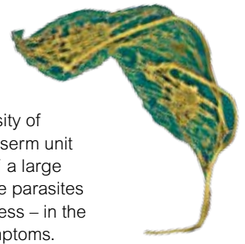
THE INCEPTION PROJECT SELECTED AS PART OF THE INVESTING IN THE FUTURE PROGRAM

The INCEPTION* project was one of five projects selected by the French government on July 7 as part of the "Convergence Institute" call for proposals (Investing in the Future program). INCEPTION is a big data project, in the field of biology, to describe and understand the notion of the emergence of infectious and non-infectious diseases for individuals or populations.

** Convergence Institute for the emergence of pathologies through individuals and populations.*

September

SLEEPING SICKNESS, PARASITE IN THE SKIN



In partnership with the University of Glasgow, an Institut Pasteur/Inserm unit demonstrated the presence of a large quantity of trypanosomes – the parasites responsible for sleeping sickness – in the skin of individuals with no symptoms. A new lead for screening for this disease.

October

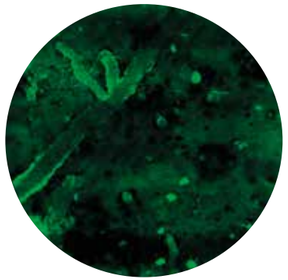
AFRICANS AND EUROPEANS HAVE GENETICALLY DIFFERENT IMMUNE SYSTEMS

… and Neanderthals had something to do with it. In a study published in the prestigious journal *Cell*, scientists deciphered the immune responses of 200 African and European individuals. These populations do not respond to infections in the same way due to genetic control and remodeling through natural selection. This groundbreaking work sheds new light on susceptibility to disease and paves the way for the personalized medicine of tomorrow.

November

EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE

Diagnosing Alzheimer's disease early is a major challenge today. In the lab, scientists discovered a way of detecting the markers of this disease as early as possible. Llama antibody fragments (Nanobodies™) were able to cross the blood-brain barrier and reach the brain. Combined with a green fluorochrome, they bind to lesions that characterize Alzheimer's disease and can be detected by fluorescence microscopy.



December

CONGRATULATIONS ARE IN ORDER FOR THE PASTEUR IGEM 2016 TEAM!

The Institut Pasteur recognized the work of 19 students from the Pasteur iGEM team on December 9.
At the end of October, their Mos(kit)o project was awarded three trophies and a gold medal at the International Genetically Engineered Machine (iGEM) competition, run by the Massachusetts Institute of Technology. This kit is designed to detect and map mosquito vectors carrying pathogens.

December

OPIORPHIN: CLINICAL TRIALS TO START LATE 2017

Opiorphin, a molecule naturally secreted in humans, was discovered at the Institut Pasteur in 2006. It has proved just as effective as morphine without the side effects, such as cardiorespiratory problems. Researchers from the Institut Gustave-Roussy, Inserm, Paris-Sud University, the Paris Public Hospital Network (Bicêtre Hospital), and the Institut Pasteur made this discovery in animals. The first trials in humans should begin at the end of 2017.

Discovery Award/Appointment Event Scientific event

Awards and appointments in 2016

PEOPLE APPOINTED TO THE RANK OF PROFESSOR

ROBERTO BRUZZONE
Co-Director of the HKU-Pasteur Research Pole

DAVID PRANGISHVILI
Group Leader in the Molecular Biology of the Gene in Extremophiles Unit

LLUIS QUINTANA
Scientific Director of the Institut Pasteur, Head of the Human Evolutionary Genetics Unit

SYLVIE VAN DER WERF
Head of the Molecular Genetics of RNA Viruses Unit

APPOINTMENTS

FRANÇOISE BARRÉ-SINOUSSI
Professor at the Institut Pasteur. Awarded the Grand Croix of the Legion of Honor

FRANÇOIS SPITZ
Elected member of the European Molecular Biology Organization (EMBO)

CHRISTINE PETIT
Elected member of the US National Academy of Sciences

MICHAEL NILGES
Elected member of Academia Europaea

LAURE BALLY-CUIF
Elected member of the European Molecular Biology Organization (EMBO)

SHAHRAGIM TAJBAKHSH
Elected member of Academia Europaea

FRANÇOIS SCHWEISGUTH
Elected member of Academia Europaea

CARMEN BUCHRIESER
Elected member of the European Academy of Microbiology. Elected member of Academia Europaea

THOMAS BOURGERON
Elected member of Academia Europaea

PATRICE COURVALIN
Elected member of the European Academy of Microbiology

JEAN-MARC GHIGO
Elected member of the American Academy of Microbiology

ARNAUD ECHARD
Elected President of the French Society for Cell Biology

PATRICK FORTERRE
Elected member of the European Academy of Microbiology

DAVID PRANGISHVILI
Elected member of the European Academy of Microbiology

SPENCER SHORTE
Founding President of the European CTLS association (Core Technologies for Life Sciences)

JEAN-CHRISTOPHE OLIVO-MARIN
Fellow of the Society of Photo-Optical Instrumentation Engineers (SPIE)

HONORS AND PRIZES

JEAN-PIERRE CHANGEUX
Guest researcher at the Department of Neuroscience
Olav Thon Foundation's International Research Prize

ARTUR SCHERF
Head of the Biology of Host-Parasite Interactions Unit
Allianz Foundation Research Prize
Jacques Piraud Prize, French Foundation for Medical Research (FRM)

PHILIPPE SANSONETTI
Head of the Molecular Microbial Pathogenesis Unit
Microbiology Society Prize Medal

CHRISTINE PETIT
Head of the Genetics and Physiology of Hearing Unit
Hugh Knowles Prize

SPENCER SHORTE
Head of the Imagopole
Thérèse Lebrasseur Prize

CHRISTOPHE ZIMMER
Head of the Imaging and Modeling Unit
Thérèse Lebrasseur Prize

PETYA VIOLINOVA KRASTEVA
Postdoctoral fellow in the Structural Biology of Bacterial Secretion Unit
Jacques Monod Prize

DARIA BONAZZI
Researcher in the Pathogenesis of Vascular Infections Unit
Kaluza Prize for Excellence in Graduate Student Research from the American Society for Cell Biology, L'Oréal-UNESCO For Women in Science French Fellowship

MARC LECUIT
Head of the Biology of Infection Unit
"Grand Prix Robert Debré"

PATRICE COURVALIN
Guest researcher at the Department of Microbiology
Sanofi-Pasteur Senior Award

SYLVAIN BRISSE
Head of a research group in the Microbial Evolutionary Genomics Unit
Louis-Daniel Beauperthuy Prize

ANAVAJ SAKUNTABHAI
Head of the Functional Genetics of Infectious Diseases Unit
René & Andrée Duquesne Prize

LALEH MAJLESSI
Researcher in the Integrated Mycobacterial Pathogenomics Unit
Georges, Jacques and Elias Canetti Prize

NICOLAS MICHALSKI
Researcher in the Genetics and Physiology of Hearing Unit
"Agir pour l'audition" Early Career Scientific Prize

DAVID DIGREGORIO
Head of the Dynamic Neuronal Imaging Unit
Pasteur Vallery-Radot Prize

SIMONETTA GRIBALDO
Researcher in the Molecular Biology of the Gene in Extremophiles Unit
Pasteur Vallery-Radot Prize

LAURE BALLY-CUIF
Head of the Zebrafish Neurogenetics Unit
Janssen Award from the French National Academy of Medicine

RICHARD DELORME
Researcher in the Human Genetics and Cognitive Functions Unit
Jean Valade Prize

PIERRE-MARIE LLEDO
Head of the Perception and Memory Unit
Roger de Spoelberch Foundation Prize

MICHAELA MULLER-TRUTWIN
Head of the HIV, Inflammation and Persistence Unit
Puyoo Award

ROBERTO TORO
Group Leader in the Human Genetics and Cognitive Functions Unit
Open Science Prize

XAVIER MONTAGUTELLI
Mouse Functional Genetics Unit
Georges Zermati Prize

JÉRÔME GROS
Head of the Morphogenesis Regulation in Higher Vertebrates five-year group
EMBO Young Investigator Program Award

NADER YATIM
Postdoctoral fellow in the Immunobiology of Dendritic Cells Unit
Albert Sezary Award from the French National Academy of Medicine, and University Award from the Val-de-Marne Departmental Council

In the Institut Pasteur International Network

DIDIER MÉNARD
Researcher at the Institut Pasteur in Cambodia, Phnom-Penh
Jean-Pierre Lecoq Prize

RIDHA BARBOUCHE
Head of the Laboratory of Transmission, Control and Immunobiology of Infections (Institut Pasteur in Tunis)
Sadok Besrour Foundation Prize for Research

NEW FIVE-YEAR GROUPS

HUGUES ASCHARD
Statistical Genetics

LUCIE GLOVER
Trypanosomes Molecular Biology

MÉLANIE HAMON
Chromatin and Infection

MARCEL HOLLENSTEIN
Bioorganic Chemistry of Nucleic Acids

CHRISTOPH SCHMIDT-HIEBER
Neural Circuits for Spatial Navigation and Memory

NEW UNITS

Units set up in 2016

LAURE BALLY-CUIF
Zebrafish Neurogenetics Unit

PHILIPPE GLASER
Ecology and Evolution of Antibiotic Resistance Unit

IVO MUELLER
Malaria: Parasites and Hosts Unit

LUCIE PEDUTO
Stroma, Inflammation and Tissue Repair Unit

PIBnet (Pasteur International Bioresources Network), jointly directed by:

FRANÇOISE DROMER
Molecular Mycology Unit

ODILE GELPI
Medical Affairs and Public Health Department

International joint units (UMI) set up in 2016

UMI in parasitology

GÉRALD SPAETH
Head of the Molecular Parasitology and Signaling Laboratory, Institut Pasteur in Paris

GUANGXUN MENG
Director of Research in the Innate Immunity Unit, Institut Pasteur of Shanghai

UMI in vaccinology

FUMIHIKO MATSUDA
Kyoto University (Japan), Integrative omics study of immune response to influenza vaccine

ANAVAJ SAKUNTABHAI
Head of the Functional Genetics of Infectious Diseases Unit, Institut Pasteur in Paris

UMI in malaria

JEAN-CHRISTOPHE BARALE
Head of the Biology of Malaria targets and Antimalarials Group, Institut Pasteur in Paris

DIDIER MÉNARD
Head of the Malaria Molecular Epidemiology Unit, Institut Pasteur in Cambodia

UMI in leptospirosis

ALEJANDRO BUSCHIAZZO
Head of the Protein Crystallography Unit, Institut Pasteur in Montevideo

MATHIEU PICARDEAU
Head of the Microbiology Laboratory, Institut Pasteur in Paris

ERC GRANTS

JAMES DI SANTO
Head of the Innate Immunity Unit
ERC Advanced Grant for his project ILC_REACTIVITY (Biological determinants of ILC reactivity for immune responses in health and disease)

ELISA GOMEZ-PERDIGUERO
Head of the Macrophages and Endothelial Cells Unit
ERC Starting Grant for her project ResidentMacroPhage (Development, maintenance and functions of resident macrophages)

Research

The Institut Pasteur is committed to conducting outstanding research to improve health across the world. This means adopting an open, collaborative and innovative approach to the research we do.

PASTEURIANS

"The Institut Pasteur's legacy drives its commitment to medical research."

"I am 100% Pasteurian", stresses Philippe Sansonetti, a trained physician and microbiology researcher. He has held posts in hospitals and also directed several research units at the Institut Pasteur (in bacteriology, cell biology, etc.): *"During my career, I have seen so many technological advances that have contributed to breakthroughs in human health. We observed cells, then molecules, and now we'll be observing life at atomic level thanks to the most powerful microscopes ever, like the Titan microscope soon to be installed on campus! Remembering how our predecessors overcame hurdles to understand living organisms should give us hope and encourage us to increase our efforts to improve health for all."*

PHILIPPE SANSONETTI
Head of the Molecular Microbial Pathogenesis Unit at the Institut Pasteur, and professor at the Collège de France

PASTEURIAN EMBLEMS

"A microscope that says a lot about progress in biology."

Like many other laboratory artifacts belonging to illustrious Institut Pasteur scientists, Félix d'Hérelle's microscope is preserved at the Pasteur Museum. *"I'm delighted to set eyes on this object again, 100 years after bacteriophages were discovered by this microbiologist. We are too quick to forget the past and its lessons"*, warns Philippe Sansonetti, who recently took a step back through time when he described the world before vaccines in his book* of the same name. We are too quick to forget the human toll taken by diphtheria, polio, tuberculosis, measles and Spanish flu. But, thanks to progress in science, the number of deaths from these infectious diseases has been considerably reduced.

* Vaccins, *Philippe Sansonetti, published by Odile Jacob, 2017*

Center for Bioinformatics, Biostatistics and Integrative Biology (C3BI)

The C3BI is driven by the ambition to become a leading national and international center for all matters related to bioinformatics, associated disciplines, and their applications in biology and human health. Launched in 2015, the C3BI has already achieved significant success, with the INCEPTION project, and very positive feedback from scientists on campus concerning the Bioinformatics and Biostatistics HUB.

The field of biology is currently undergoing deep-rooted, irreversible changes, with the emergence of "omics" data (genomes, transcriptomes, structures, etc.) that have wide-ranging applications, especially in the field of health.
To analyze and exploit this "big data" efficiently, biology is becoming a computational science which increasingly uses mathematical modeling, statistics and IT.
Launched in 2015 to address these challenges, and boosted by several recruitments, in 2016 the C3BI became a joint service and research unit with the CNRS (USR 3756), that is affiliated with the Institute of Biological Sciences (INSB), the Institute for Information Sciences and Technologies (INS2I) and the Institute of Ecology and Environment (INEE).
The C3BI's activities are multidisciplinary and cross-sectoral, ranging from basic research to the provision of services for experimental units and cores, and including training designed to improve the skills of the Institut Pasteur as a whole – and especially its young scientists – in these fields.

Two closely linked components

• **The research area** is an umbrella structure for affiliated research units. Units that existed before the C3BI was set up are still primarily affiliated to their scientific department, but generally those in the process of being set up are mainly affiliated to the C3BI. The methodological skills of scientists in these units range from mathematical modeling to algorithmics and statistics (including bioanalysis methods and deep learning).
The C3BI has eight units and three G5s*:
- Structural Bioinformatics;
- Mathematical Modeling of Infectious Diseases;
- Imaging and Modeling;
- Human Evolutionary Genetics;
- Human Genetics and Cognitive Functions;
- Microbial Evolutionary Genomics;
- Evolutionary Bioinformatics (set up in January 2016);
- InBio: Experimental and Computational Methods for Modeling Cellular Processes (set up in January 2017);
- G5 Spatial Regulation of Genomes;
- G5 Statistical Genetics (set up in mid-2016);
- G5 Decision and Bayesian Computation (set up in January 2017).

• **The bioinformatics platform** offers a range of bioinformatics and biostatistics services. It performs analyses for scientific units, creates data processing pipelines within platforms and provides training. These services are aimed at all the units on the Paris campus as well as the Institut Pasteur International Network. The platform coordinates the activities of three entities: the Bioinformatics and Biostatistics HUB, the International Group for Data Analysis, and the Systems Biology expert group.

First visible results

Since the C3BI was set up, it has recruited 28 new advanced research engineers, including nine in 2016 (from 220 applicants), and created four new research units or G5s. The latest unit (InBio: Experimental and Computational Methods for Modeling Cellular Processes) is the result of a joint project with the French National Institute for Computer Science and Applied Mathematics (INRIA).

The C3BI's research units are recognized for their expertise, with several publications in 2016 in leading scientific journals including *Cell, Science, The Lancet, PNAS, Nature Communications, Nature Genetics, The American Journal of Human Genetics, Nucleic Acids Research, Genome Biology, AIDS, Nature Methods* and *Algorithmica*. Their research covers topics including the epidemiology of infectious diseases (Ebola, Zika and HIV), human genetics, modeling of genomes and the cell nucleus, and molecular modeling using ultra-high-resolution NMR approaches.

In two years, almost 190 projects have been submitted to the HUB; more than 60 of these have now been completed and around 40 have already resulted, or will soon result, in publications. Ten strategic projects for the Institut Pasteur, approved by the C3BI steering committee, involve the HUB on a long-term basis. These include the PIBnet project *(see p. 50)*, which offers the tools needed for the analysis of microbial genomes for monitoring diseases and the emergence of diseases; research into SUMOylation and its impact on chromatin, cellular plasticity and cancer; the classification of giant viruses in the tree of life; and research into the unique regulation mechanisms of *Leishmania*.

The C3BI is also actively involved in scientific training and activities, both on campus and at an international level. A bimonthly seminar regularly attracts around 40 participants. Courses have been run within the International Network, in Dakar, São Paolo, Casablanca, Hanoi and Paris. The HUB played a major role in ten courses run on campus in 2016, representing a total of 280 hours of training and 800 hours of supervision. The courses launched this year include genome assembly, searching for variants, transcriptome and metabolic pathway analysis, experimental design, descriptive analysis and statistical testing.

** G5: a 5-year research group geared towards promising young scientists.*

1

80%

of people said they were satisfied or highly satisfied with the services offered by the Bioinformatics and Biostatistics HUB, scoring it 15.5/20 in a satisfaction survey among Institut Pasteur scientists who have worked with the C3BI.

THE INCEPTION PROJECT

The C3BI teams also played a key role in the development of the INCEPTION project on integrative and multidisciplinary approaches for research into the emergence of pathologies through individuals and populations (the "Convergence Institute" call for proposals launched under the 2016 Investing in the Future program). INCEPTION has a budget of €12 million over ten years and will involve all the Institut Pasteur units, via calls for proposals, training and scientific activities, working in synergy with our partners (CNRS, Inserm, INRA, CEA, AP-HP, Paris Sciences et Lettres, Paris-Diderot University and the *"Frontières du Vivant"* – FdV – doctoral school).

1 - The Bioinformatics and Biostatistics HUB team in March 2016.

Center for Global Health

The Center for Global Health (CGH), directed by Professor Arnaud Fontanet, was set up in September 2014 to consolidate the global health activities carried out by Institut Pasteur teams worldwide. Its work is focused on three strategic priorities: research to improve human health, outbreak investigation, and training for tomorrow's scientists.

Research to improve human health

In cooperation with the Department of International Affairs, the CGH organized the launch event for the **Global Health Scientific Advisory Board** (GH-SAB), held in Paris on June 8 and 9, 2016. Seventeen international experts and around 50 Institut Pasteur scientists were in attendance to discuss major current and future challenges. Two priority areas for global health research were proposed: antimicrobial resistance and malaria. In late 2016, the CGH and the Department of International Affairs held three working days with representatives of the Institut Pasteur International Network on these themes to encourage the development of research projects that address these priorities.

Outbreak investigation

• **Deployment of members of the Outbreak Investigation Task Force (OITF).** More than 50 scientists from ten International Network institutes, specializing in a variety of disciplines including epidemiology, virology, entomology, social science and veterinary medicine, joined the Task Force. OITF members were deployed on technical and support missions to strengthen efforts to combat emerging viruses:
- the MERS (Middle East Respiratory Syndrome) coronavirus: Saudi Arabia, Qatar, Jordan, South Korea;
- Ebola: Sierra Leone, Guinea;
- Zika: Brazil, Mexico, Cape Verde, French Polynesia, French Guiana;
- H5N1 avian influenza: Cameroon;
- yellow fever: Democratic Republic of Congo, Angola.

• **Training for scientists in outbreak investigation.** The CGH ran two courses on "Investigating outbreaks linked to emerging infectious agents" in 2016. The first, which took place in April in Paris, attracted 21 participants, including 17 International Network scientists who are now in the OITF. At the request of the Qatari Ministry of Public Health, a second course was run in Doha in October 2016 for 35 participants from the Qatari Ministry of Public Health and Ministry of the Environment, the Hamad Medical Corporation, Hamad General Hospital and the Primary Health Care Corporation.

• **Zika Task Force.** In January 2016, in response to the emergency situation posed by the Zika virus, the Institut Pasteur, with the support of the CGH, set up a Zika Task Force to coordinate the efforts of its scientists. Five broad areas were targeted: developing molecular and serological tests to diagnose the Zika virus; developing vaccines; carrying out epidemiological research; analyzing vector competence and mosquito control measures; and using animal models to improve understanding of the pathogenesis and transmission of the virus. By the end of 2016, more than 80 scientific papers on the Zika virus from 12 institutes in the Institut Pasteur International Network had been published.

INTERNATIONAL ZIKA SUMMIT, APRIL 25-26, 2016

With the support of the Institut Pasteur, the Bill & Melinda Gates Foundation and the Wellcome Trust, and in cooperation with the World Health Organization, the CGH co-organized the first International Zika Summit, attended by more than 500 public health scientists and professionals from all over the world working on the Zika virus. The summit also provided an opportunity to produce a MOOC entitled "In the footsteps of Zika… approaching the unknown", in partnership with the University of Geneva, Paris-Descartes University and the MOOC Factory team from the Virchow-Villermé Center. Since August 2016, this MOOC has been available on request via Coursera and almost 5,000 students have enrolled.

Digital training for future scientists and leaders in global health

• **Pan-African Coalition for Training in Research and Public Health (PACT).** Working in close collaboration with the Institut Pasteur International Network, the Department of International Affairs, the Education Department and MAASC, the CGH provided its support to strengthen the academic and scientific partnerships underpinning the five regional training projects that make up the PACT *(see inset)*. From July to December 2016, the CGH led think tanks with the Wellcome Trust, the African Academy of Sciences, the Fogarty International Center, TDR (the World Health Organization's Special Program for Research and Training in Tropical Diseases) and the Medical Education Partnership Initiative. The aim is to develop an alliance that will promote long-term synergies between scientists and students in French-, English- and Portuguese-speaking Africa. This will involve joint training programs, networking between host laboratories, partnerships with the private sector and improving women's access to management positions in research and public health.

• **Global Health e-Academy.** As part of its efforts to provide as many people as possible with access to training, the CGH has opened up its network to the PACT program and offered its expertise in designing and organizing MOOCs, with the aim of boosting the range of high-level courses in public and global health run by the International Network in partnership with African, European and American universities.

In late 2016, the CGH embarked on an international consortium project – the Global Health e-Academy – with the Virchow-Villermé Center, to develop a digital portal listing nearly 300 available global health MOOCs. These online courses, developed by internationally renowned universities, can provide useful educational resources for teaching staff alongside instructor-led training.

THE FIVE REGIONAL TRAINING PROJECTS IN THE "PACT" PAN-AFRICAN COALITION

• First- and second-year Master's program in Bioinformatics and Biomathematics at Gaston Berger University, in partnership with the Institut Pasteur in Dakar;
• University diploma in Medical Genetics and Genomics at the University of Tunis El Manar, in partnership with the Institut Pasteur in Tunis;
• Second-year Master's program in Medical Microbiology at the University of Yaoundé 1, in partnership with the Pasteur Center in Cameroon;
• Second-year Master's program in Malariology at the University of Félix Houphouët-Boigny in Abidjan, in partnership with the Institut Pasteur in Côte d'Ivoire;
• Second-year Master's program in Preparation and Response to Epidemics at Gamal Abdel Nasser University of Conakry, in partnership with the Institut Pasteur in Guinea.

Center for Innovation and Technological Research (Citech)

The Citech is a technological hub with two main objectives: to advance innovation and technological research, and to meet the immediate and future needs of the biological projects developed on campus and within the Institut Pasteur International Network. The Citech is now organized into technology and service units (UTechS).

New organizational structure for the technological platforms

In 2016, the Citech held discussions to devise a new organizational structure for the Institut Pasteur platforms and the Central Animal Facility, with the aim of optimizing the services available on campus, developing technological activities, providing career development opportunities for the staff involved, and establishing an effective structure for technological research and development. These discussions resulted in a proposal for a new organizational set-up and the creation of a series of technology and service units (UTechS). All the UTechS share the same governance and operational procedures; they are affiliated with both the scientific departments and the Citech. The first stage in the rollout of this new organizational structure took place in 2016. A specific evaluation process was introduced, involving the Institut Pasteur Scientific Council and a committee of international experts specializing in the management of technological platforms. Following the first evaluation phase, which took place in the last quarter of 2016, it was decided to set up five UTechS:

- Photonic Bio Imaging (Spencer Shorte);
- Ultra Structural Bio Imaging (Jacomina Krijnse Locker);
- Biomics (Sean Kennedy);
- Mass Spectrometry for Biology (Julia Chamot-Rooke);
- Translational Science (Milena Hasan).

The last of these five is jointly managed with the CRT *(see p. 48)*. The reorganization process will continue in 2017. The next areas to be addressed are protein science and animal resources.

Significant highlights and new technologies

The year 2016 was marked by a number of scientific achievements and the development and implementation of new methods, technologies and equipment:

- resolution of the structure of human neutralizing antibodies complexed with the Zika virus envelope protein, by the Crystallography Platform in collaboration with the Structural Virology Unit;
- first publication by the Mouse Genetics Engineering Center of the use of new CRISPR/Cas9 technology to generate a double KO mouse model (Tmem176a/Tmem176b), in collaboration with Cédric Louvet (ITUN, University of Nantes);
- demonstration that VHHs, or nanobodies, can cross the blood-brain barrier and bind to intraneuronal targets and that, conjugated to fluorophores, they offer a non-invasive approach for diagnosing Alzheimer's disease;
- installation of the first Orbitrap Fusion Tribrid mass spectrometer (Thermo Fisher Scientific) in France, for the development of new proteomics methods;
- development in the Ultrapole of a correlative optical-electron microscopy protocol for the high-throughput acquisition of images in native cryogenic conditions using a Leica Cryo CLEM, followed by 3D analysis via cryo-electron microscopy;
- installation in Biomics of a Pacific Biosystems Sequel sequencer to sequence long DNA/RNA fragments for a variety of applications.

The Citech is also involved in the upcoming introduction of a Single Cell Center for single-cell analysis (with funding from the SESAME regional program) and founded the Fab Lab, directed by Albane Imbert, to facilitate the production of experimental prototypes.

Networking: CTLS, ARBRE-MOBIEU, IPIN-TI

Involvement in European and global technological networks is vitally important for the Citech, facilitating scientific exchange and staff mobility, and stimulating technological innovation. The Citech members took several effective steps in this direction in 2016. The Core Technologies for the Life Sciences (CTLS) initiative became an official association under the direction of Spencer Shorte (President) and Patrick England (Vice-President). Its biennial conference in Heidelberg in June attracted some 250 delegates. The ARBRE-MOBIEU biophysics network, founded by Patrick England and Thomas Jowitt (Manchester), received EU funding via a COST Action. The Citech also applied to join the Core for Life (C4L) association. Within the International Network, the "Institut Pasteur International Network – Technology Initiative" (IPIN-TI), coordinated by Spencer Shorte, was also launched.

Associated units and external academic and industry partners

One of the Citech's aims is to promote interactions with stakeholders in technology for life sciences, in both the academic and industrial spheres, to support the joint development of new methods and tools and to provide them with privileged access to the Pasteurian community. To this end, the Citech developed an internal network of associated research units and G5s. This initiative began in 2016 with the secondment of Citech engineers for R&D projects, and is set to continue on a more formal basis in 2017-18. The Citech is also committed to establishing strategic partnerships with external stakeholders. In 2016, a major agreement was signed between Konica Minolta and the Imagopole to develop innovative imaging probes that will be used in drug discovery. Another important initiative was the creation of a new regional scientific network, selected as a Field of Major Interest (DIM) by the Greater Paris Authority at the end of 2016. This DIM, Empowering Life Sciences with Innovative Technologies (ELICIT), is coordinated by the Citech and the Pierre-Gilles-de-Gennes Institute for Microfluidics. This initiative will be stepped up in 2017 with a regional call for proposals.

Emerging technologies call

The Citech launched an internal call for proposals with the aim of providing funding for the initial stages of technological R&D projects. The first projects selected under the call will begin in 2017.

Cell Biology and Infection

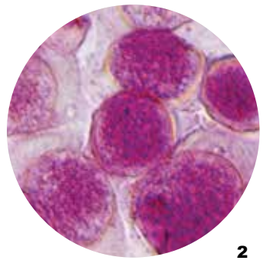
What mechanisms govern normal cell function? How do different types of infectious agents interact with their targets? Using cutting-edge technologies including genomics, proteomics and imaging, as well as new cell, tissue and animal models, this research department sheds light on the intricate workings of microbes and cells. The research teams analyze comprehensively how cells function under normal and pathological conditions.

Understanding infectious mechanisms requires detailed research on cellular function during pathogen challenge. It is also crucial to characterize the conditions required for the delicate balance between the commensal flora and the host. A number of teams of the department are focusing their efforts on a particular infectious agent, while others focus on gaining a thorough knowledge of the cell itself, independently of the presence of infectious agents. A detailed understanding of cell functions is essential for providing an explanation of infection and other pathological mechanisms. In this context, one of the department's strengths lies in the implementation of new models for host-pathogen interactions and in the implementation of quantitative computerized tools to analyze cells. All departmental activities are closely linked with the development of new technologies – including imaging, image analysis, genomics and postgenomics – via a multidisciplinary, integrative approach. The department is directed by Chiara Zurzolo.

HOW *CHLAMYDIA TRACHOMATIS* HIJACKS ENERGY STORES FROM ITS HOST

Chlamydia trachomatis is the most common bacterial cause of sexually transmitted infection and is a major cause of infertility. These bacteria multiply inside host cells, within an internal compartment called a vacuole. The vacuole protects the parasites from many host defense mechanisms. However, it also blocks direct access to nutrients, and the parasites must develop complex mechanisms to acquire these. In the case of *Chlamydia trachomatis*, it is known that the vacuole is rich in glycogen, an energy storage molecule. The team led by Agathe Subtil has explained how this occurs. Firstly, the bacterium hijacks the glycogen synthesized by the host and sequesters it inside the vacuole. Secondly, it synthesizes glycogen directly in the vacuole, using sugar units obtained from the host. This dual strategy fulfills the nutritional needs of the bacteria while the host loses access to its own energy stores.

Source: eLife, *March 2016*



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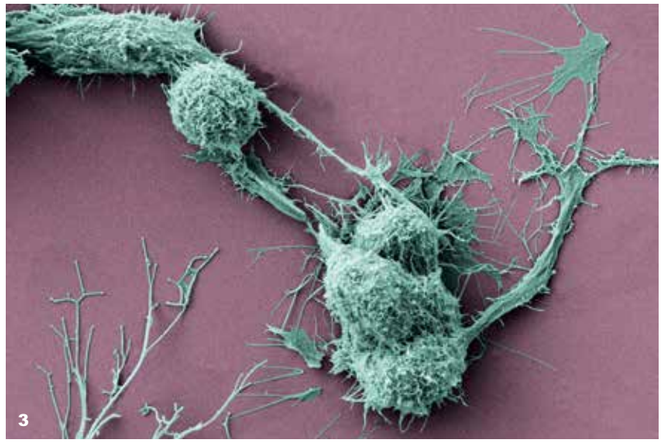
1 - Neurons linked by nanotubes spreading α-synuclein fibrils (in red). 2 - Cells infected with Chlamydia trachomatis. *3 - Two neuronal cells connected by a nanotube (TNT).*



3

PARKINSON'S DISEASE SPREAD VIA "NANOTUBES" BETWEEN NEURONS

Synucleinopathies, neurodegenerative diseases such as Parkinson's, are characterized by the accumulation of pathological aggregates of the protein α-synuclein in the brain. Scientists from the Membrane Traffic and Pathogenesis Unit, directed by Chiara Zurzolo, demonstrated that pathological α-synuclein fibrils travel between neurons inside lysosomal vesicles through tunneling nanotubes (TNTs), a new mechanism for intercellular communication. The scientists propose that cells overloaded with α-synuclein aggregates in their lysosomes dispose of this material by hijacking TNT-mediated intercellular trafficking. After being transferred through TNTs, the fibrils are able to recruit the soluble α-synuclein protein and induce its aggregation in naive cells, thus explaining how the disease spreads. These compelling findings, together with previous research from the same team, allow us to envision the general role of TNTs in the propagation of prion-like proteins in neurodegenerative diseases, and identify TNTs as a new therapeutic target.

Source: EMBO J., *Oct. 2016*

UNCOVERING *LISTERIA MONOCYTOGENES* HYPERVIRULENCE BY HARNESSING ITS BIODIVERSITY

The Biology of Infection Unit headed by Marc Lecuit, in collaboration with Sylvain Brisse, published a large-scale study in *Nature Genetics* based on almost 7,000 strains of *Listeria monocytogenes* – the bacterium responsible for human listeriosis, a severe foodborne infection. Through the integrative analysis of epidemiological, clinical and microbiological data, they have discovered that virulence is highly heterogeneous within the *Listeria monocytogenes* species, and identified hypervirulent clones. Comparative genomics led them to discover gene clusters specific to these clones, one of which was demonstrated experimentally as involved in cerebral and fetal-placental listeriosis. In addition, this research indicates the importance of using new reference strains, which are representative of the hypervirulent strains identified here, for experimental research on *Listeria monocytogenes* pathogenesis.

Source: Nat Genet., *March 2016*

AWARDS FOR SCIENTISTS

- **Arnaud Echard:** elected President of the French Society for Cell Biology.
- **Marc Lecuit:** winner of the Grand Prix Robert Debré.
- **Jean-Christophe Olivo-Marin:** elected as a Fellow of the Society of Photo-Optical Instrumentation Engineers (SPIE).
- **Philippe Sansonetti:** Microbiology Society Prize Medal (United Kingdom).
- **Spencer Shorte and Christophe Zimmer:** Thérèse Lebrasseur Prize awarded by the Fondation de France.
- **Spencer Shorte:** founding President of the European association CTLS (Core Technologies for Life Sciences).

Developmental and Stem Cell Biology

1

How does a cell acquire its identity? How does an organ begin to form? We still know relatively little about the mechanisms involved in the "building" of animals, including humans. This research department is committed to improving our understanding of these mechanisms, which are largely responsible for the way tissues and organs are maintained in adult individuals.

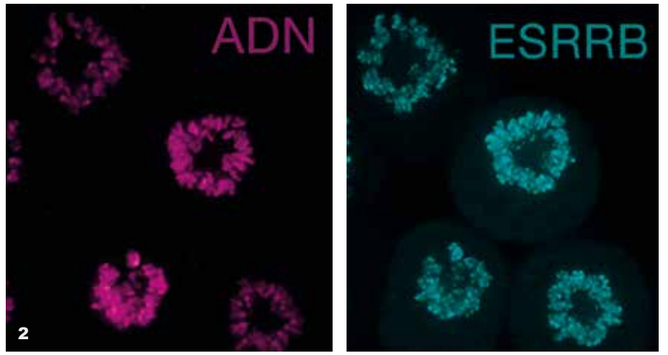
As embryos develop, the fertilized egg gives rise to multiple cells that form the basis of the specialized cells that make up our organs. Research into embryonic cell fate, tissue and organ formation, and the regeneration of these tissues and organs in adults, is the focus of the department's work. Its scientists use a variety of experimental approaches to examine all aspects of the biology of cells and organisms, from epigenetic control of gene expression to cell movements that help shape embryos. Their research sheds light on the rules, often common to all living beings, that underpin development in embryos and adults. Understanding how tissues are formed also means understanding how they regenerate and repair themselves, which can pave the way for innovative therapeutic approaches. Recent research in the department focused on the formation of esophagus muscle tissue, its regeneration and how it changes during aging; on identifying the genes responsible for "disorders of sex development" in humans; and on heart formation in mice and congenital heart defects in humans. The department is directed by François Schweisguth.

SENESCENT CELLS FACILITATE CELLULAR REPROGRAMMING FOR TISSUE REPAIR

A major challenge in the field of regenerative medicine is how to reprogram differentiated adult cells into other cell types for tissue repair. While major progress in nuclear reprogramming has been achieved over the past ten years, further studies are needed to regulate this process for tissue repair.
Scientists from the Cellular Plasticity and Disease Modeling Group and the Stem Cells & Development Unit (Institut Pasteur/CNRS), set out to further understand the reprogramming of skeletal muscle stem cells *in vivo* and identify factors that could promote this process during muscle regeneration. Surprisingly, they found that cellular senescence, usually associated with aging, cancer and inflammation, facilitated the reprogramming of muscle cells and they identified a cytokine involved in the acute phase of inflammation as an important factor for this reprogramming. This study discovered an unprecedented role of senescent cells in cellular reprogramming. A key challenge now will be to harness the beneficial effect of senescence for regenerative medicine and healthy aging.

Source: Cell Stem Cell, *Dec. 2016*

1 - Mouse embryo development. 2 - Mitotic chromosomes, showing their DNA (purple) and ESRRB (turquoise).



2

A KEY FACTOR IN MAINTAINING STEM CELL PLURIPOTENCY

How do daughter cells reproduce the properties of their mother after cell division? And how, in some cases, do they change these properties? These two closely related questions are vital to the study of developmental biology. These cellular decisions are guided – or controlled – by transcription factors that activate or repress the expression of specific batteries of genes. As a general rule, with every cell division, the links between these transcription factors and their target genes are abolished. But can we be sure that this applies to all such links? No – some transcription factors remain linked with their targets during division. Scientists in the Epigenetics of Stem Cells Group demonstrated this for ESRRB, a transcription factor which controls the ability of pluripotent stem cells to self-renew. When these cells begin to divide, ESRRB remains bound to its target genes, enabling the daughter cells to quickly activate the genes needed to maintain pluripotency. This discovery sheds new light on the mechanisms involved in maintaining pluripotency and opens up new avenues for developing the cell reprogramming strategies that form the basis of regenerative medicine.

Source: Nat Cell Biol., *Oct. 2016*

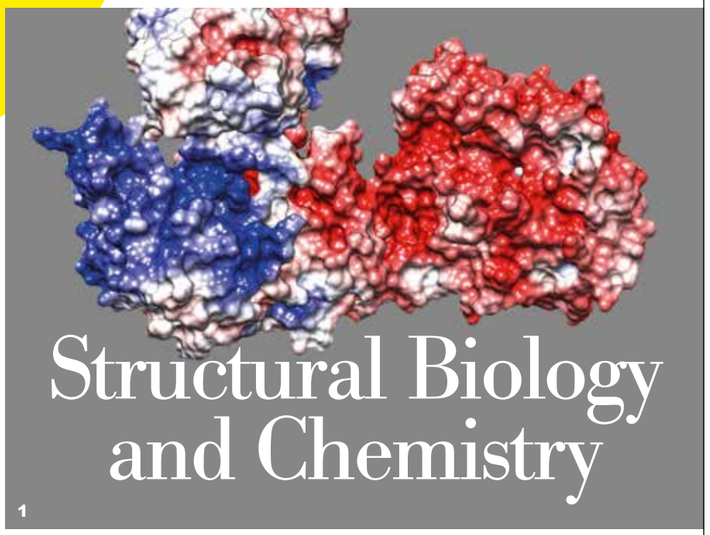
HOW TISSUES ARE SHAPED DURING EMBRYOGENESIS

Using live imaging microscopy of transgenic quail embryos, researchers in the Morphogenesis Regulation In Higher Vertebrates Unit shed new light on how tissues are shaped during embryogenesis. They identified that during early development, cell division powers dramatic cell rearrangements and promotes the relative displacement of cells within embryonic tissues. The resulting tissue fluidization is critical to remodel the simple two-dimensional early embryo into complex three-dimensional tissues. The ability of dividing cells to promote rearrangements depends on interactions with neighboring cells. It is the relatively low activity levels of the molecular engine that generate cellular forces (actin and myosin) in the immediately neighboring cells that enable a dividing cell to deform and displace these neighbors. These findings, which are likely to be relevant to humans, might underlie various developmental, homeostatic or pathological processes.

Source: Dev Cell, *Feb. 2016*

AWARDS FOR SCIENTISTS

- **Elisa Gomez-Perdiguero:** Starting Grant from the European Research Council (ERC) and support from the Schlumberger Foundation for Education and Research (FSER) for her research on the origins of macrophages in adult tissues and their role in tissue regeneration.
- **Laure Bally-Cuif:** Janssen Award from the National Academy of Medicine for her research on neural stem cells in zebrafish.
- **Laure Bally-Cuif and François Spitz:** elected as members of the European Molecular Biology Organization (EMBO).
- **Jérôme Gros:** selected under the EMBO Young Investigator Program.
- **François Schweisguth and Shahragim Tajbakhsh:** elected as members of Academia Europaea.



1

The structure of a molecule is intricately linked to its functions. The Structural Biology and Chemistry Department focuses its research on the three-dimensional organization, properties and synthesis of molecules of biological interest, especially those that play a role in human disease. This information is vital for the development of new therapeutic and vaccine strategies.

The department studies the three-dimensional structure of molecules to improve understanding of their biological functions and their role in the development of infectious diseases, genetic diseases, and cancer. The scientists aim to shed light on the molecular mechanisms involved in the assembly of protein complexes associated with pathological or infectious processes. Their findings are used to develop chemical tools to regulate these mechanisms. A number of cutting-edge techniques and specialist skills are used to study these interactions at a molecular level, including crystallography (3D structure of molecules, drug design); nuclear magnetic resonance, or NMR (structure, movement and interaction of small molecules); electron microscopy (structures of large biological complexes); molecular modeling (determining structures); mass spectrometry (stoichiometry, conformation and dynamics of large protein complexes); chemical and/or chemoenzymatic synthesis for therapeutic, vaccine and diagnostic use; and techniques to design molecular tools that shed light on molecular/cellular interactions and host-pathogen recognition. The department is directed by Michael Nilges.

JOINT EVOLUTIONARY HISTORY OF THE DNA REPLICATION AND DNA TRANSCRIPTION APPARATUS

Archaeal replicative DNA polymerases D (PolD) constitute an atypical class of DNA polymerases made of a proof-reading exonuclease subunit (DP1) and a larger polymerase catalytic subunit (DP2), both with unknown structures. Ludovic Sauguet and Pierre Raia, in the Structural Dynamics of Macromolecules Unit headed by Marc Delarue, have determined the crystal structures of *Pyrococcus abyssi* DP1 and DP2 at 2.5 and 2.2 Å resolution, respectively, revealing a catalytic core strikingly different from all other known DNA polymerases (DNAPs). Rather, the PolD DP2 catalytic core has the same "double-psi β-barrel" architecture seen in the RNA polymerase (RNAP) superfamily, homodimeric RNA silencing pathway RNAPs and atypical viral RNAPs.
This finding brings together DNA transcription and DNA replication within the same protein superfamily. This study suggests that the DNA replication and DNA transcription apparatus share a joint evolutionary history.

Source: Nature Communications, *August 2016*


2

UNDERSTANDING THE ROLE OF BACTERIAL TOXINS

Researchers in Daniel Ladant's unit study nucleotidyl cyclase toxins such as CyaA from *Bordetella pertussis* and ExoY from *Pseudomonas aeruginosa*. The latter's role in pathogenicity and its functionality are less well understood and are the focus of studies in Undine Mechold's group. ExoY is injected by the Type 3 secretion system into host cells. Inside cells, an eukaryotic co-factor activates it to synthesize various cyclic nucleotide monophosphates, most notably cGMP. Since the original discovery of ExoY in 1998, the identity of the co-factor has remained unknown and this has slowed down research in the field. Undine Mechold and colleagues have now identified filamentous actin (F-actin) as said co-factor. Association with actin strongly stimulates ExoY activity *in vitro. In vivo,* ExoY is recruited to actin filaments in transfected cells and alters F-actin turnover. ExoY-like adenylate cyclases are also found in Multifunctional-Autoprocessing Repeats-in-ToXin (MARTX) toxins produced by various Gram-negative pathogens and actin was shown to also activate one of these toxins, namely the ExoY-like adenylate cyclase MARTX effector domain from *Vibrio nigripulchritudo*. These results suggest the existence of a group of actin-activated nucleotidyl cyclase toxins. The identification of actin mutants that no longer activate ExoY by means of a yeast genetic screen strongly confirms this discovery.

Source: Nature Communications, *December 2016*

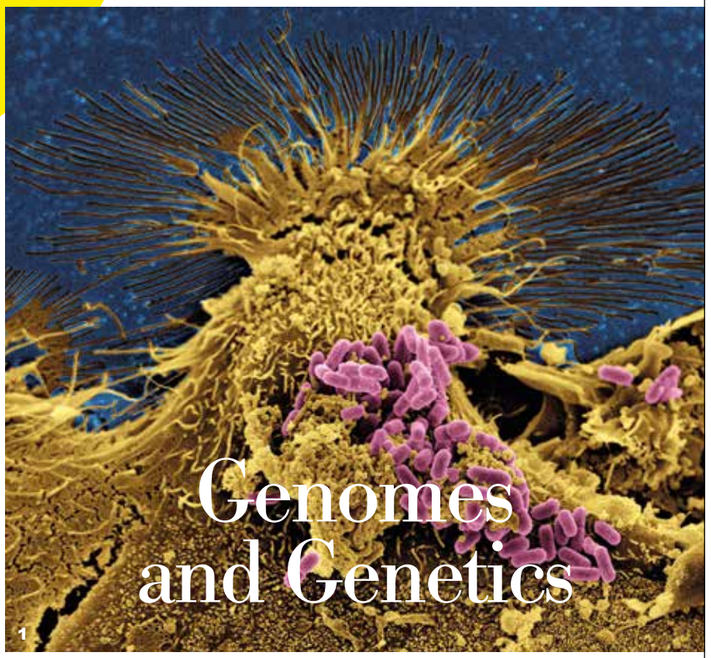
VACCINES DERIVED FROM SYNTHETIC SUGARS

Glycans found at the surface of mammal cells and microorganisms act as recognition signals that are involved in several physiological and pathological processes. An infected host can trigger an immune response targeted at the cell-surface glycans of the responsible pathogenic agent. This is the case for bacillary dysentery, a severe enteric disease caused by *Shigella* bacteria, which is endemic in developing countries. Research is ongoing for a vaccine for this disease. The scientists in the team led by Laurence Mulard in the Chemistry of Biomolecules Unit, working in collaboration with Armelle Phalipon from the Molecular Microbial Pathogenesis Unit, applied their expertise in glycoscience and molecular chemistry to design SF2a-TT15, the first vaccine candidate against endemic bacillary dysentery derived from synthetic sugars.
SF2a-TT15 acts as a perfectly defined functional mimic of the heterogeneous polysaccharides at the surface of the bacterium *S. flexneri 2a*, the most prevalent serotype. A clinical batch of SF2a-TT15 was produced as part of the European project *Stopenterics*; it is currently being tested in humans in a phase I clinical trial sponsored by the Institut Pasteur. This clinical trial, coordinated by Cécile Artaud (from the Clinical Core in the Center for Translational Science, directed by Nathalie Jolly) and carried out in Tel Aviv in cooperation with Dr. Jacob Atsmon, will evaluate tolerance of the vaccine candidate and provide preliminary data on the immunogenicity of SF2a-TT15 in healthy volunteers.

Source: Clinical Trials, *June 2016*


3

1 - First structure of a D-family DNA polymerase. 2 - Observation of Bordetella pertussis *bacteria. 3 - Glassware used in scientific research.*



Genomes and Genetics

1

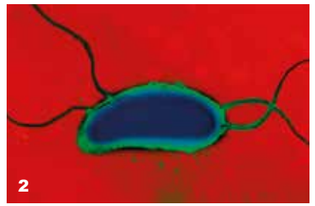
By decoding the content and architecture of genomes, thereby shedding light on new biological functions, genetics raises numerous questions and offers a vast array of research possibilities for the scientists in the Genomes and Genetics Department.

The department explores the genetic information of microorganisms such as yeast and bacteria, as well as that of humans. The genomes of the tuberculosis bacilli, *Streptococcus, Vibrio, Legionella*, and other pathogenic bacteria and models, are studied in depth with the aim of understanding how they live and what determines their pathogenic nature. Yeasts are also studied, both for their own properties and as models to shed light on human genetics. Additionally, the department is investigating the evolution of infectious agents and the selective pressure they have exerted on both human and insect vector genes over time. The progress of these research programs is largely based on new sequencing and genotyping techniques. The department is directed by Didier Mazel.

DISCOVERY ABOUT THE REPLICATION OF THE TWO *VIBRIO CHOLERAE* CHROMOSOMES

Bacterial genomes generally contain a single chromosome. The initiation of bacterial chromosome replication needs to be perfectly regulated to ensure that chromosome duplication occurs only once per cell cycle. The bacterial pathogen responsible for cholera epidemics, *Vibrio cholerae,* is distinctive in that it has two chromosomes. The teams led by Didier Mazel, Romain Koszul and Ole Skovgaard (Roskilde University, Denmark) investigated how coordination of the replication of the two *V. cholerae* chromosomes is controlled, focusing in particular on the mechanism that identifies the ideal moment to trigger Chr2 replication during the cell cycle. They discovered that Chr2 replication depends on the replication of an intergenic sequence of 150 nucleotides located very precisely on Chr1, via a previously unknown mechanism. They demonstrated that this sequence is vital for cell viability – its deletion results in an imbalance in the number of copies of the two chromosomes and high bacterial mortality.

Source: Science Advances, *April 2016*



2

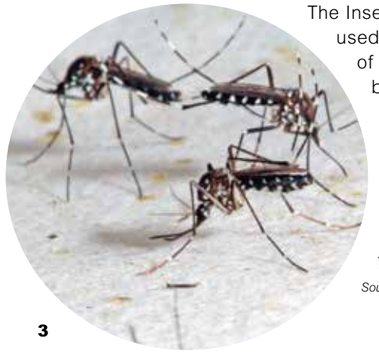
1 - E. coli *O104:H4 bacteria (in purple), a genome sequenced by the Institut Pasteur. 2* - Vibrio cholerae *with its flagellum on the centrosome. Cholera agent. 3* - Aedes albopictus, *the mosquito vector for diseases including dengue and chikungunya. 4 - Intracellular replication of* Legionella pneumophila *(in red/orange) in epithelial lung cells.*

DENGUE VIRUSES DEVELOP IN THE MOSQUITO

Dengue is the most widespread arbovirus in the world, with as many as 400 million people infected every year. Dengue viruses, like all RNA viruses, have an extremely high mutation rate (a million times higher than ours), because they have no correction mechanism for replication errors in their genome. Together with dengue's rapid replication and large population, the high mutation rate creates a "cloud" of related mutants. This quasispecies structure is vital for the replicative success and adaptive potential of RNA viruses.

The Insect-Virus Interactions five-year group, directed by Louis Lambrechts, used a high-throughput sequencing technique to monitor the composition of the cloud of dengue mutants during infection of several genetic backgrounds of their mosquito vector. Their analyses demonstrated that the viral population changes in the mosquito as a result of the combined effect of genetic drift (linked to a significant initial bottleneck) and natural selection. More surprising still, the research revealed that viral genetic diversity was modulated by the mosquito genotype. This indicates that the development of the virus, and therefore its emergence potential, depends on the type of mosquito that transmits it.

Source: PLoS Genetics, *June 2016*

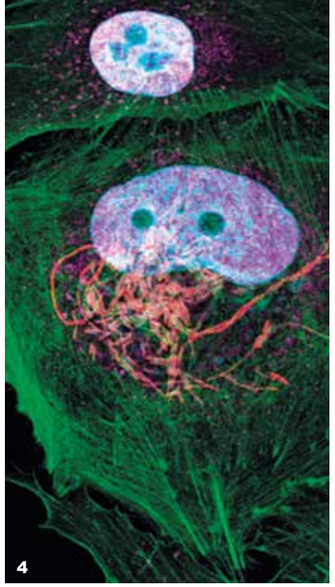


3

RECENT EVOLUTION OF THE MAIN BACTERIAL CLONES RESPONSIBLE FOR LEGIONNAIRES' DISEASE

Legionella pneumophila is a bacterium found in natural water sources across the world, but it can also contaminate water supply systems, leading to severe pneumonia epidemics that can be fatal. The team led by Carmen Buchrieser, working with Julian Parkhill's team from the Wellcome Trust Sanger Institute (Hinxton, UK), sequenced the genomes of 337 isolates of *L. pneumophila* belonging to the five clones responsible for nearly half the cases of Legionnaires' disease in north-western Europe. The scientists analyzed these sequences and compared them with strains that are representative of the biodiversity of this species. Their research suggests that the main clones responsible for the disease have emerged independently in recent decades. They seem to have spread across the world by adapting to human environments. Moreover, the recent emergence and propagation of these clones suggests that people infected with the bacteria actually contribute to their spread, and that the clones are able to adapt to water distribution systems installed by humans.

Source: Genome research, *November 2016*



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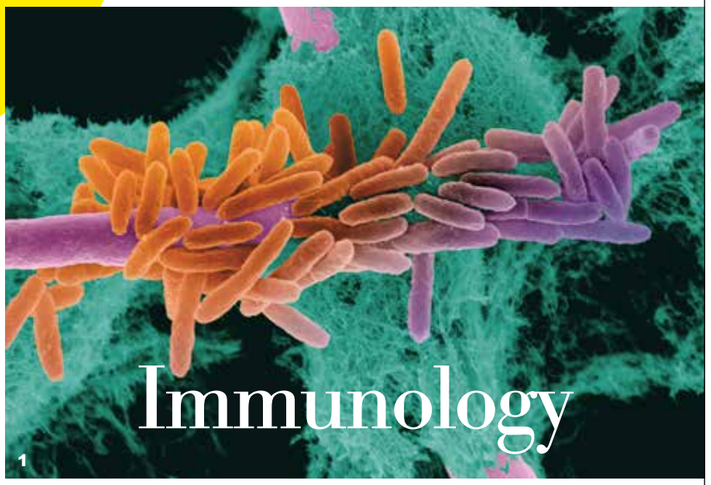
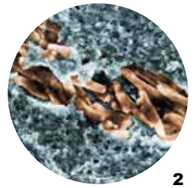


1

Research carried out in the Immunology Department focuses on the development and regulation of the immune system and its protective and pathological immune responses.

The department's three main research areas are the development of the immune system, innate and adaptive immunity, and immune responses and diseases. Within the first area, several teams are working on the differentiation of immune cells and their dynamics during the immune response. Innate (non-specific and immediate) immunity and adaptive (specific and acquired) immunity both contribute to immune responses. Teams are investigating these responses, the cells involved and their interactions. Some teams are studying protective, anti-infectious and anti-cancer immunity; others are focusing on immunological disorders such as allergies and autoimmune diseases. The aim is to strengthen the former and correct the latter. Finally, the LabEx (Laboratories of Excellence) project *"Milieu Intérieur"* is monitoring a cohort of 1,000 healthy donors to determine the genetic and environmental factors contributing to a healthy immune system and its natural variability.



2

MYCOLACTONE, A BACTERIAL TOXIN AND NATURAL IMMUNOSUPPRESSANT

Buruli ulcer is an emerging tropical disease that causes severe skin lesions. The bacterial agent responsible, *Mycobacterium ulcerans*, secretes a toxin called "mycolactone", known for its analgesic and immunosuppressive properties. By combining genetic and proteomic approaches, scientists from the Immunobiology of Infection Unit were able to identify its molecular target as the Sec61 translocon, a complex responsible for translocating newly synthesized proteins to the endoplasmic reticulum and into the secretory pathway. By inhibiting Sec61, mycolactone blocks the production of immune mediators. This discovery pinpoints mycolactone as a natural immunosuppressant and paves the way for new therapeutic approaches to control inflammation and pain.

Source: J. Exp. Med., *Dec. 2016*

AWARDS FOR SCIENTISTS

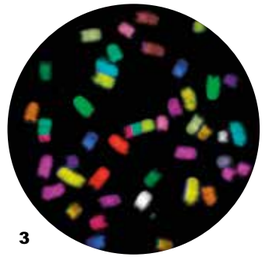
• **Nader Yatim:** the Albert Sezary Award from the National Academy of Medicine, and the University Award from the Val-de-Marne Departmental Council. Nader Yatim completed his PhD thesis, entitled "The simultaneous activation of pathways for cell death and inflammation regulates the adaptive immune response", in the Immunobiology of Dendritic Cells Unit.
• **James Di Santo:** Advanced Grant from the European Research Council (ERC) for his program ILC_REACTIVITY. The aim of this project is to understand the signals that regulate the development and activation of innate lymphoid cells (ILCs). ILCs are involved in the early stage of immune response to infection, in tissue regeneration and metabolic homeostasis.

1 - Interaction between Aspergillus fumigatus *and* Pseudomonas aeruginosa, *two microorganisms in the lung microbiota, observed using scanning electron microscopy. 2 -* Mycobacterium ulcerans, *the bacterial agent of Buruli ulcer, observed using scanning electron microscopy. 3 - Chromosomes of a tumor cell with translocations between VDJ and oncogenic MYC regions.*

PRESERVING THE GENOME DURING V(D)J RECOMBINATION

The adaptive immune system uses a process for the rearrangement of DNA known as "V(D)J recombination". This enables it to create a theoretically infinite immune repertoire in order to recognize and fight all types of infection. But the process is risky because it requires the formation of double-strand DNA breaks, one of the most dangerous lesions for genome stability. Scientists in the Lymphocyte Development and Oncogenesis Laboratory have demonstrated that the RAG1/2 nuclease, which cleaves DNA during this process, is also involved in repairing these breaks. This discovery sheds light on the evolutionary processes that led to the emergence of the adaptive immune system in vertebrates, while keeping the risks of genome instability, and therefore cancer development, to a minimum. These findings are not only important from a fundamental research viewpoint; they will also play a vital role in improving our understanding of lymphoid cancer and diseases associated with immunodeficiency syndromes.

Sources: Cell Rep., *Sept. 2016*, Nat. Commun., *Feb. 2016*

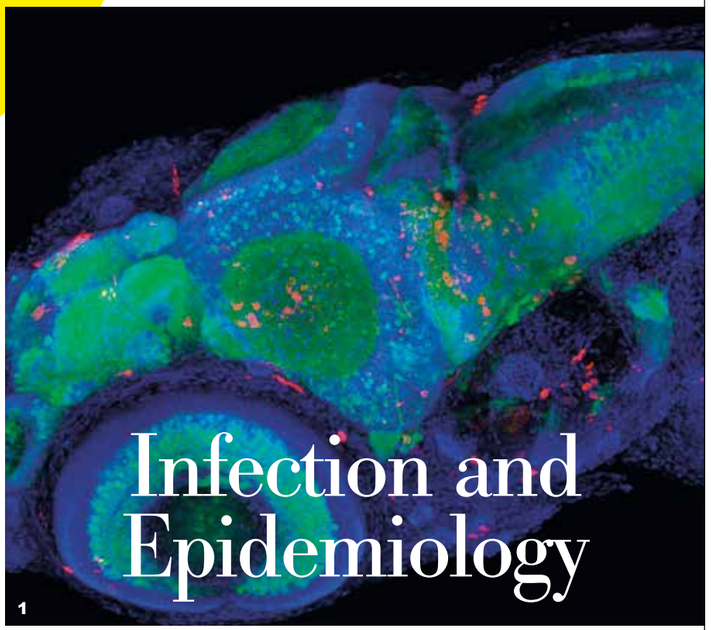


3

A STRATEGY TO DETERMINE RELATIONSHIPS BETWEEN CELLS

Innate lymphoid cells (ILCs), recently discovered in mucosal tissues, play an essential role in the early stages of the immune response. They are classified into three subtypes (ILC1, 2 and 3) on the basis of their effector functions. However, depending on the tissue and its inflammatory state, they can exhibit plasticity that disguises their identity and their relationships. To shed light on this phenomenon, scientists from the Lymphopoiesis Unit developed a single-cell transcriptome analysis technique that enabled them to identify the networks of transcription factors that are vital for the differentiation of these cells. Understanding these networks and the differentiation of ILCs is a first step towards being able to use them in immunotherapy.

Source: Nat. Immunol., *March 2016*



Infection and Epidemiology

The Infection and Epidemiology Department conducts fundamental and translational research in the field of infectious diseases, and is also deeply committed to public health issues.

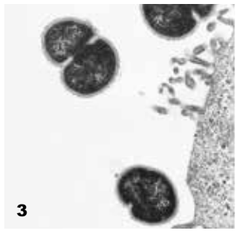
The department studies all aspects of infectious diseases: pathogen reservoirs and transmission mechanisms, virulence factors, host immune response, tissue lesion development and pathophysiological processes, therapeutic strategies, and the impact of vaccination. These challenges are addressed using approaches and tools from a range of disciplines, including epidemiology, microbiology, dynamic imaging, immunology, histopathology, genetics, comparative genomics, cell biology, biochemistry, and bioinformatics. In addition, the department is deeply involved in public health issues, and is on the front line in the fight against emerging infectious diseases, particularly via the activities of six National Reference Centers (CNRs), three World Health Organization Collaborating Centers (WHOCCs), and the Laboratory for Urgent Response to Biological Threats (CIBU). These activities call for close collaboration with the Institut Pasteur International Network. The department is directed by Marie-Lise Gougeon.

THE ZIKA VIRUS AT THE ROOT OF MICROCEPHALY

The Zika outbreak in Latin America coincided with a dramatic increase in the number of suspected cases of microcephaly, a severe neurological defect characterized by fetuses with unusually small heads. However, the data from this outbreak remained unconsolidated for some time, thereby proving hard to interpret. This led the teams of Simon Cauchemez and Arnaud Fontanet to examine the data from a previous Zika outbreak in order to estimate the correlation between Zika and microcephaly. Of the eight cases of microcephaly reported in French Polynesia over a 23-month period, seven (88%) occurred during the four months following the Zika outbreak. Based on mathematical models, the teams concluded that infection during the first trimester of pregnancy was associated with the highest risk of microcephaly. The disorder was seen to occur in 1% of fetuses whose mothers were infected during the first trimester of pregnancy, whereas the risk is normally 0.2%.

Source: Lancet, *May 2016*

1 - The zebrafish as a model for infection by the chikungunya virus. 2 - Female Aedes aegypti, *the vector for Zika. 3 - Interaction between* Neisseria meningitidis *and an epithelial cell (electron microscopy). 4 - The rabies virus.*



MENINGOCOCCUS: A NEW, SEXUALLY TRANSMITTED VARIANT

Meningococcus is transmitted via the respiratory route and can cause severe, invasive infections such as meningitis, particularly in children. In 2013 an outbreak was reported in the MSM (men who have sex with men) community in the USA and Europe. A team led by Muhamed-Kheir Taha studied this outbreak with a multi-omics approach, in collaboration with the University of Würzburg (Germany). The scientists showed that the outbreak was the result of a new variant of meningococcus, which had undergone modifications enabling anaerobic growth. This gave rise to a mechanistic theory as to how adaptation to the urogenital niche may have developed. Possible close links were observed between strains involved in isolated urogenital infections and strains detected in the MSM community. However, the new strain of meningococcus detected in the MSM community has a heightened ability to multiply in the bloodstream, thus increasing its virulence compared to urogenital strains. Vaccinations have been recommended for populations at risk.

Source: PLoS One, *May 2016*

NEW POST-EXPOSURE PROPHYLAXIS AGAINST HUMAN RABIES

The rabies virus is present across the world in a variety of animal reservoirs (dogs, bats, foxes), and sometimes infects non-reservoir hosts – humans in particular. Rabies is always fatal once symptoms have appeared, but it can be controlled in animal reservoirs by mass vaccination, and a fatal outcome can be prevented in humans exposed to the virus via the early administration of appropriate post-exposure prophylaxis (PEP). PEP is based on vaccination and the administration of costly immunoglobulins, the limited supply of which restricts their use in endemic regions. The team led by Hervé Bourhy, in collaboration with the National Reference Center for Rabies of the Instituto Zooprofilattico Sperimentale delle Venezie (Italy) and Humabs BioMed SA (Bellinzona, Switzerland), developed two new human monoclonal antibodies with a strong neutralizing effect on multiple strains of the rabies virus. In addition, their efficacy was demonstrated *in vivo,* with administration to hamsters protecting them from rabies. This cocktail of human antibodies could be used in the PEP regimen and, due to its capacity for low-cost, large-scale production, it would be readily available in endemic regions.

Source: EMBO Mol Med., *April 2016*

A NEW TYPING STRATEGY

Species of pathogenic bacteria are genetically highly diverse, with large numbers of different strains causing a variety of disease outbreaks. Strain typing – which is the “genetic fingerprinting” of the scientific police, is used to trace outbreaks and map their spread. A new typing strategy has been developed, based on analyzing the complete sequence of bacterial genomes. This strategy makes use of new high-throughput DNA sequencing techniques and powerful bioinformatics analysis methods. It brings complete precision to the filiation of bacterial strains, at the same time showing their pathogenic characteristics, for example antibiotic resistance genes. This new strategy is now in place in the Institut Pasteur’s National Reference Centers.

1

Besides their key role in many infectious diseases, bacteria also serve as models to understand fundamental biological mechanisms. The research performed in the Department of Microbiology mainly focuses on the molecular characterization of functions that enable bacteria to interact with their environment and, in some cases, to cause diseases.

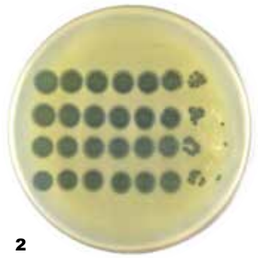
The scientists of the Department of Microbiology study, at the cellular and molecular levels, fundamental biological processes of bacteria and archaea (and their viruses) either alone or in communities and their evolution. They also focus on the mechanisms that render some of these microorganisms virulent and enable them to evade the host immune system, or to develop resistance to antibiotics.

These studies not only improve our understanding of the life cycle of these microorganisms, but also constitute a prerequisite for the development of new therapies or new diagnostic tools that can be used to treat or prevent bacterial infections. The Department of Microbiology is directed by Hilde De Reuse.

A NOVEL STRATEGY OF BACTERIA TO FEND OFF PHAGE ATTACKS

Bacteria are under the constant threat of infection by viruses known as phages. In response, they have developed many defense systems, including the well known CRISPR system. Research carried out by the team of David Bikard (G5 Synthetic Biology) and Bertrand Duclos (CNRS) have enabled the discovery of a novel system allowing Staphylococci to fend off phage attacks.
While studying the CRISPR system of *Staphyloccus epidermidis,* an unexpected observation was made. To defend against phages, bacteria can activate in addition to the CRISPR system another pathway which relies on a kinase (Stk2), whose function had remained mysterious. The team has found that a phage protein (PacK) activates this Stk2 kinase which in turn modifies the activity of several essential pathways. The consequence of this activation results in the suicide of the bacteria infected by the phage thereby preventing the phage from propagating to neighboring bacteria.

Source: Cell Host Microbe, *Oct. 2016*



2

1 - VAPs (virus-associated pyramids) formed by the Sulfolobus islandicus *rod-shaped virus 2 (SIRV2). 2 - Bacteriophages eliminating the bacterium* Staphylococcus aureus *in a petri dish. 3 - The bacterium* Helicobacter pylori *viewed by scanning electron microscopy.*

HOW DOES THE BACTERIUM *HELICOBACTER PYLORI* SURVIVE ACIDITY OF THE STOMACH IT COLONIZES?

3

The bacterium *Helicobacter pylori* colonizes the stomach of half of the human population worldwide. *H. pylori* infection causes gastritis, peptic ulcers and is associated with the development of gastric cancer, which is responsible for 800,000 deaths worldwide every year.
H. pylori and other gastric *Helicobacter* bacteria are the only microorganisms able to persistently colonize the stomach niche despite its acidity. The team headed by Hilde De Reuse (*Helicobacter* pathogenesis unit) has identified in *H. pylori,* a new transporter of nickel that is indispensable to allow this pathogen to infect the stomach and is thus required for *H. pylori's* virulence. Indeed, nickel is an essential co-factor of urease, an enzyme that allows *H. pylori* to resist gastric acidity.
Together with Frédéric Veyrier (Institut Armand-Frappier, Canada), they have discovered that, during evolution, this novel transporter has been specifically acquired by gastric *Helicobacter* bacteria, including *H. pylori*. The acquisition of these proteins during evolution represents a key event in the emergence of one of the most successful bacterial pathogens in the world, *H. pylori.*

Source: PLoS Pathogens, *Dec. 2016*

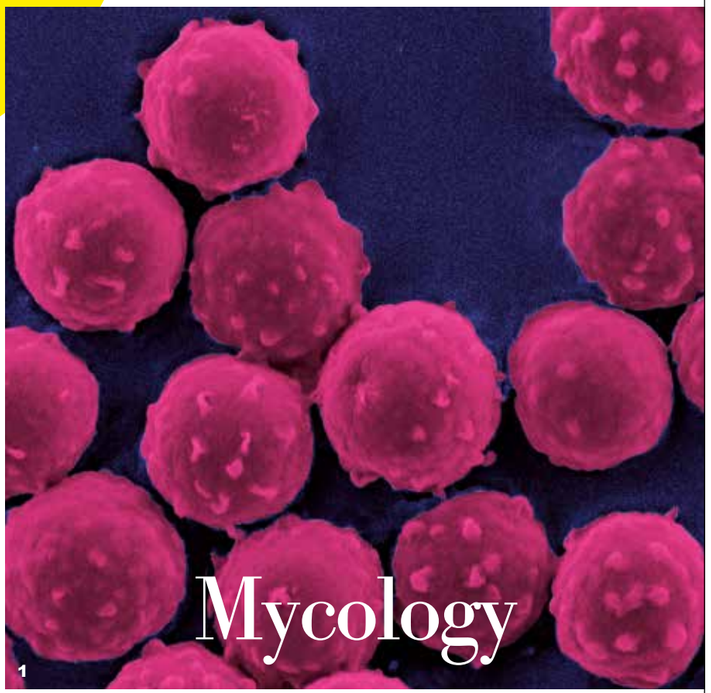
A PHAGE ELEMENT CONTROLS THE FORMATION OF INFECTIOUS SPORES BY THE BACTERIAL PATHOGEN *CLOSTRIDIUM DIFFICILE*

Clostridium difficile is the leading cause of post-antibiotic nosocomial diarrhea. This bacterium produces infectious spores that are highly resistant, facilitating their persistence in hospital. To better understand *C. difficile* transmission, the team of Isabelle Martin-Verstraete (in the Pathogenesis of Bacterial Anaerobes laboratory headed by Bruno Dupuy) has investigated how the mother cell controls the formation of spores. Together with A. Henriques (ITQB, Lisbon), they have identified an original mechanism in which the production of an essential sporulation sigma factor (σK) is prevented by a phage integrated into the corresponding *sigK* gene. The enzyme required for excision of the phage and thus σK synthesis is activated by a small protein that is only synthesized in the mother cell. They have demonstrated that the interplay of these two proteins triggering phage excision promotes the timely production of σK, which in turn switches on sporulation events, cell lysis and spore release thereby favoring *C. difficile* dissemination and infection.

Source: PLoS Genetics, *Sept. 2016*

VALLERY-RADOT PRIZE TO SIMONETTA GRIBALDO

The 2016 Vallery-Radot prize has been awarded to Simonetta Gribaldo for her research accomplishments in the field of Evolutionary Microbiology. Microorganisms were the first forms of life and represent the invisible majority of biological diversity. The group "Microbial Phylogenomics" headed by Simonetta Gribaldo (in the Molecular Biology of Gene in Extremophiles unit headed by Patrick Forterre) uses the information contained in the thousands of available microbial genomes to understand the mechanisms that shaped such diversity, from the very first cell to present-day microbial life, and to increase knowledge on the origin and evolution of fundamental microbial features. Her research highlights the processes that allow microorganisms to adapt to various environments, including the human body. Moreover, it sheds light on the origin and evolutionary history of important cellular processes that are targets of antimicrobials, thereby offering new potential for fighting microbial infection.



1

Fungal infections have been a major and growing public health concern since the early 1980s. The Mycology Department conducts research on the biology of human pathogenic fungi and their virulence mechanisms, with the aim of developing new diagnostic, prevention and treatment strategies for fungal infections.

The Mycology Department's work is focused on the three main fungi responsible for invasive fungal infections in humans: *Aspergillus fumigatus, Candida albicans* and *Cryptococcus neoformans.* The research teams in the department are investigating the genetic diversity of these species, and its link with virulence and resistance to antifungal molecules. Functional genomics approaches are used to identify the virulence factors employed by these fungi in different contexts – formation of biofilms, infection – and to understand how these mechanisms are regulated. The study of host-pathogen interactions, at the level of both individual cells and the organism as a whole, reveals how pathogenic fungi bypass host defenses or how a protective immune response is initiated in the host. The department also provides expertise to partner institutions and hospitals via the National Reference Center for Invasive Mycoses and Antifungals. The department is directed by Christophe d'Enfert.

FUNGAL-BACTERIAL DIALOGS

Pseudomonas aeruginosa and *Aspergillus fumigatus* are two of the microorganisms responsible for serious chronic pulmonary infections in both immunocompromised and immunocompetent patients. Recent studies in the *Aspergillus* Unit show the complex interactions that occur between these two microorganisms either via direct contact or from a distance. During chronic infections *P. aeruginosa* produces quorum-sensing molecules such as phenazines, pyocheline and rhamnolipids. Dirhamnolipids induce the production of an extracellular matrix in *A. fumigatus* and inhibit *A. fumigatus* growth by blocking β1,3 glucan synthase activity, thus altering cell wall architecture. Phenazines and pyocheline can have either stimulatory or inhibitory effects on *A. fumigatus* growth. On the other hand, an unexpected stimulatory effect on the growth of *A. fumigatus* is effected at a distance by *P. aeruginosa.* This effect is mediated via the gas phase, whereby *P. aeruginosa* produces dimethyl sulfide, a volatile compound, which is metabolized as a sulfur source by *A. fumigatus*. This finding establishes a new paradigm in the understanding of interactions among members of the microbiota, with important implications for both the initiation and progression of co-infections by these two pathogens.

Source: mBio, *March 2016*

1 - Conidia of the filamentous fungus Aspergillus fumigatus. *2* - Cryptococcus neoformans. *3* - Candida albicans.

2

ALTERNATIVE SPLICING AND REGULATION OF GENE EXPRESSION IN *C. NEOFORMANS*

Cryptococcus neoformans is a pathogenic basidiomycetous yeast that causes over 600,000 deaths globally each year. Scientists in the RNA Biology of Fungal Pathogens Unit are studying the structure and plasticity of the transcriptomes of this yeast. With the help of RNA-Seq data, they re-annotated the genome of the reference strain of *C. neoformans* var. *neoformans,* and confirmed that the genes of this yeast contain huge numbers of introns. Their analysis showed large numbers of alternative splicing events in *C. neoformans,* with intron retention being the most common. These events are finely and specifically regulated by culture conditions for this yeast. This research also suggests that RNA molecules that retain one or more introns are usually not translated. In *C. neoformans,* and probably in fungi generally, intron retention provides little or no means of diversifying the proteome; rather it would appear to be a strategy for finely regulating the level of gene expression in response to changes in environmental conditions.

Source: Scientific Reports, *August 2016*

CONTROL OF *CANDIDA ALBICANS* GENOME DYNAMICS

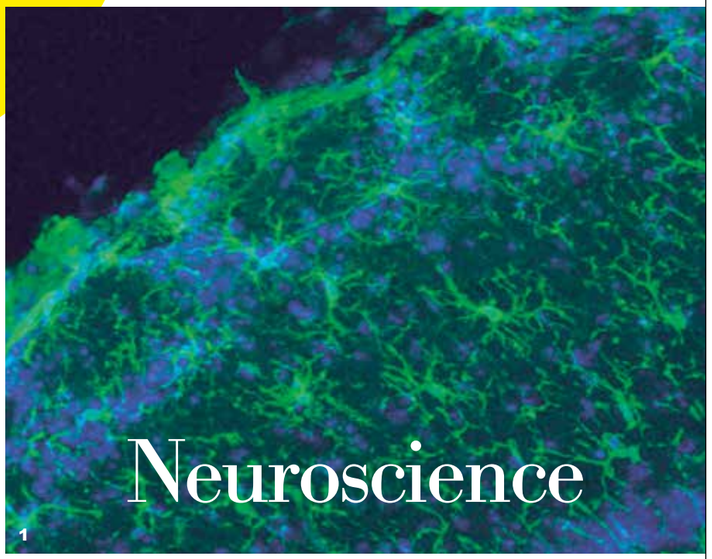
The diploid genome of the pathogenic yeast *Candida albicans* is highly plastic, exhibiting frequent loss-of-heterozygosity (LOH) events. The ability of *C. albicans* to undergo such changes can be critical for its survival upon exposure to antifungal treatments. To provide a deeper understanding of the mechanisms leading to LOH, scientists in the Fungal Biology and Pathogenicity Unit investigated the mechanisms used by *C. albicans* to repair a DNA double-strand break. In addition to revealing that these breaks are predominantly repaired by gene conversion, but also by mitotic crossover or break-induced replication, their work has also unmasked previously suspected, but thus-far unidentified, recessive lethal alleles in the genomes of several *C. albicans* isolates. Recessive lethal and deleterious alleles impose significant constraints on the biology of diploid organisms. Accumulation of such alleles upon clonal reproduction of *C. albicans* could contribute to the maintenance of heterozygosity despite the high frequency of LOH events in this species.

Source: mBio, *October 2016*

3

A NEW DIAGNOSTIC TEST FOR CRYPTOCOCCOSIS

Cryptococcosis is a severe fungal infection. The meningoencephalitic form is always fatal if left untreated. Diagnosis is based on the culture (which involves experienced staff and special equipment) and/or detection of the capsular antigen (CPS) in body fluids. A high level of CPS is a poor prognostic factor, since it is associated with cerebral impairment. A new test, easy to use in the field without special training or skills, was developed by BioSynex – a company specializing in rapid diagnostic techniques – in partnership with the Molecular Mycology Unit. This test both detects CPS (to establish a diagnosis of cryptococcosis) and determines whether the CPS level is high – indicating probable meningoencephalitis and necessary adjustments to the treatment strategy.



1

The Neuroscience Department aims at better understanding how the human brain works, in both its normal and pathological states. As a result of their broad expertise in fundamental neuroscience and genetic and clinical aspects, the neuroscientists achieve innovative medical advances that are amply demonstrated in ongoing clinical trials. The department is also committed to academic training programs.

The Neuroscience Department comprises eight research units. It seeks to shed light on the cellular, molecular and genetic mechanisms underlying the development, plasticity, and pathogenesis of sensory circuits as well as cognitive functions in the mammalian brain. The department has adopted a multiscale approach, covering the structure and function of synaptic proteins, intraneuronal and interneuronal information processing, and the identification of the genetic and epigenetic factors that influence cognitive functions (learning, memory, sensory perception) and defects in these functions (neurological and psychiatric disorders). The theoretical and experimental skills of the scientists in the department serve to develop new pharmacological and genetic tools for the prevention, attenuation and treatment of nerve circuit disorders. There is also a focus on deciphering mental functions from the point of view of computational neuroscience. In addition, the department is trying to gain an understanding of the rules governing the complex interactions between the microbiota, the immune system and the functioning of the nervous system. The department is directed by Prof. Pierre-Marie Lledo.

TRANSFORMATIONS OF DENDRITE SIGNALS ALLOW DYNAMISM IN NEURONAL COMPUTATIONS

The brain is a fantastically powerful computational machine that is thought to rely heavily on massive parallel computing. Even single neurons can act as individual computing devices by transforming electrical information from synaptic inputs contacting its dendrites, according to specific mathematical functions, into a series of output impulses. It is thought that the dendritic operations determining chemical transformations by the same synapses are similar. Members of the Unit of Dynamic Neuronal Imaging recently published a study in the journal *Neuron* that used subcellular voltage and calcium imaging to show that the dendritic operations of electrical and chemical signal scan are very different. These differing transformations were then shown to contribute to the dynamic regulation of a neuron's computation depending on the spatial and temporal pattern of synaptic activity. This work shows that even at the level of a single neuron, chemical and electrical computations are more diverse than previously thought, and thus contribute to the diversity of neuronal circuit function.

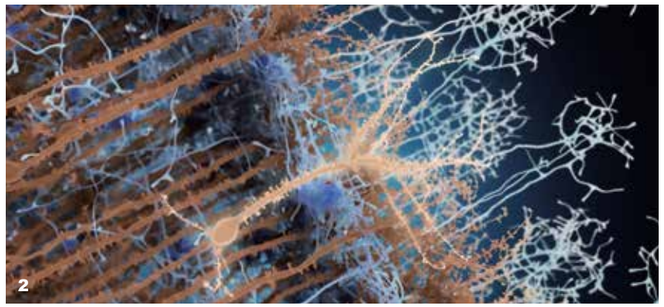
Source: Neuron, *August 2016*

1 - Microglia in the mouse olfactory bulb. 2 - Adult-born neurons. 3 - Rat cortical neurons in culture.

NERVOUS CIRCUITS REARRANGED BY THE ARRIVAL OF ADULT-BORN NEURONS

Although most neurons are produced in the embryo, some regions of the mature brain retain the capacity for continual renewal of neurons into adulthood. The impact of this recruitment on the activity of preexisting circuits is not yet understood. Pierre-Marie Lledo's team revealed the highly dynamic nature of the changes produced by new neurons on host circuits. The development of adult-born neurons was monitored over several months by two-photon imaging. In the mouse olfactory bulb, the scientists observed first-hand the development of arborization, which becomes highly stable after three weeks, and then the formation of connections and their stabilization or elimination. By studying newly-formed contacts, the scientists observed that 10% of connections are modified on a daily basis. This is a highly unusual dynamic, found both in adult-born neurons and the neurons to which they are connected. This study reveals a new mechanism enabling learning and memory via the use of latent connections.

Source: Neuron, *July 2016*



2

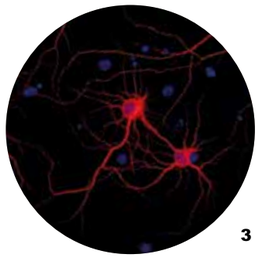
AWARDS FOR SCIENTISTS

- **Jean-Pierre Changeux:** Olav Thon Foundation Prize (Norway), appointed Doctor Honoris Causa by the University of Santiago (Chile) and the Weizmann Institute (Israel).
- **Christine Petit:** Hugh Knowles Prize (USA), for her research on hearing disorders.
- **Nicolas Michalski:** *"Agir pour l'audition"* Early Career Scientific Prize.
- **David DiGregorio:** Pasteur Vallery-Radot Prize.
- **Thomas Bourgeron:** member of Academia Europaea.
- **Roberto Toro:** Open Science Prize for his Open Neuroimaging Laboratory project, a large-scale compilation of human cerebral imaging data.
- **Pierre-Marie Lledo:** Roger de Spoelberch Foundation Prize.

AUTISM: MUTATIONS CAUSE VULNERABILITY TO SENSORY IMPAIRMENT

Early involvement of the contactin 6 gene in neuronal migration and synaptogenesis plays a crucial role in establishing the neural networks that determine the sensory and motor aspects associated with autism. The fact that expression of contactin 6 is confined to the cerebral cortex, the cerebellum and the structures of the auditory and visual system, led scientists in the Human Genetics and Cognitive Functions Laboratory to identify genomic variations and occasional harmful mutations in large cohorts of autistic patients. They focused in particular on analyzing the functional impact: neuron growth modified *in vitro* and local impairments of the 3D structure of contactin 6 following mutation. This research led to the identification of vulnerability genes as significant factors in sensory impairment associated with autism, such as hyperacusis.

Source: Molecular Psychiatry, *May 2016*



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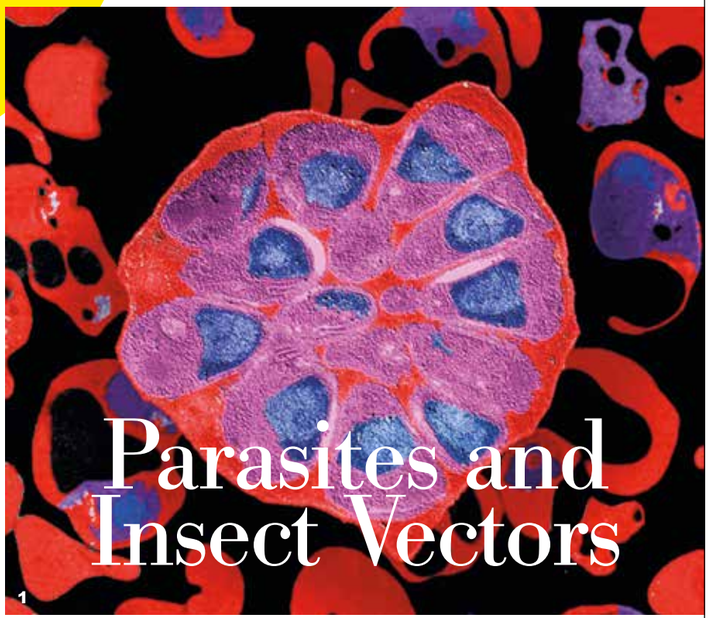


Parasites and Insect Vectors

1

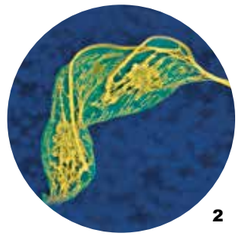
The Department of Parasites and Insect Vectors investigates the biology of parasites and their vectors. Its research program addresses global public health concerns in terms of disease prevention, control and antiparasitic treatment.

With seven research units and the Center for the Production and Infection of Anopheles (CEPIA), the department focuses its research on three key eukaryotic pathogens responsible for severe parasitic diseases that have a significant health and economic impact and affect most of the world's population: *Plasmodium* – the causative agent of malaria, *Leishmania* – the agent of leishmaniasis, and *Trypanosoma brucei* – responsible for sleeping sickness. The *Anopheles* mosquito, which is the vector of *Plasmodium* and a number of arboviruses, is being studied along with the tsetse fly, the vector of African trypanosomiasis. The department combines fundamental research on *in vitro* and *in vivo* models – including field work in Africa and Asia – with applied research on resistance to antimalarial drugs and on the discovery of new antiparasitic drugs. Original models and new experimental tools are developed to help understand the dynamic interactions between these microorganisms and their hosts, identify the fundamental bases of parasitism and transmission by vectors, reveal host invasion mechanisms, and determine parasite factors underlying virulence and pathology of these organisms. The department is directed by Gérald Spaeth.

SLEEPING SICKNESS: PARASITES FOUND HIDING IN THE SKIN

The role of skin in harboring arthropod-borne parasites has been overlooked for decades as these organisms have been regarded primarily as blood-dwelling pathogens. Intriguingly, infections with low or undetected blood parasites are common, particularly in the case of Human African Trypanosomiasis caused by *Trypanosoma brucei gambiense*. We therefore hypothesized that the skin may represent an anatomic reservoir of infection. In a recent study, we have definitively shown that substantial quantities of trypanosomes exist within the skin following experimental infection, which can be transmitted to the tsetse vector, even in the absence of detectable parasites in the blood. Importantly, we have also demonstrated the presence of extravascular parasites in human skin biopsies from undiagnosed individuals. The identification of this novel anatomical reservoir requires a re-evaluation of current diagnostic methods and control policies.

Source: eLife, *September 2016*

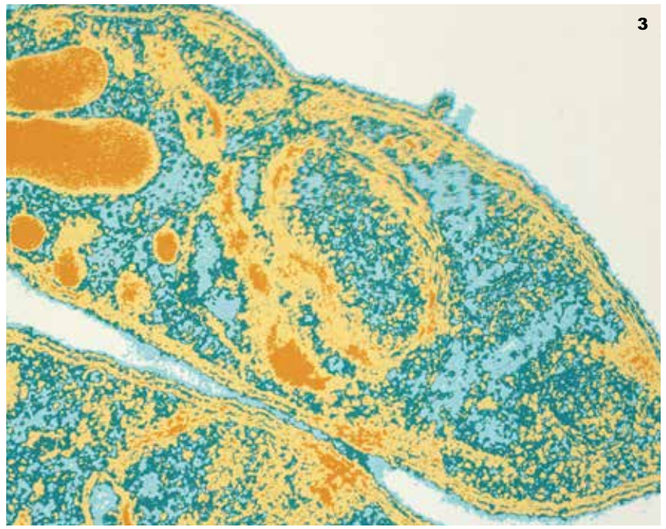


2

MALARIA: A MUTANT PARASITE WHICH PROMOTES A HIGHLY EFFICIENT AND LONG-LASTING PROTECTIVE IMMUNITY

Despite increased prevention and eradication efforts over the past fifteen years, malaria remains the most deadly parasitic disease. An effective vaccine is needed to combat this disease, but the many strategies the parasite has evolved to outmaneuver the host immune response mean that developing a malaria vaccine is a difficult task. Our team has taken an original approach to attenuate parasite virulence for effective vaccine development in a murine model of malaria disease. We genetically modified strains of the *Plasmodium* parasite by deleting the gene that codes for the HRF (histamine-releasing factor) protein. The resulting mutants proved to be highly effective in triggering a potent immune response and conferred mice with protection from any reintroduction of the *Plasmodium* parasite, including highly virulent strains. Finally, this vaccine strain not only induced a cellular response but also triggered high levels of specific antibodies that recognized parasite antigens known to be vaccine targets.

Source: J. Exp. Med., *July 2016*



3

LEISHMANIASIS: TARGETING HOST/PATHOGEN INTERACTION AS A NOVEL STRATEGY TO TREAT THE DISEASE

Leishmaniasis is an emerging tropical disease caused by *Leishmania*, which colonize and control macrophages of host organisms, thus subverting the immune system. Current treatments are inefficient to cure the disease due to their toxic side effects and the emergence of resistant parasites.
To discover more effective treatments, we validated and exploited the parasite protein kinase LmCK1.2 as a therapeutic target, which is secreted to manipulate the host macrophage. We established a four-step pipeline for the discovery of LmCK1.2 inhibitors with anti-leishmanial activity. From over 5,000 kinase-biased compounds screened on LmCK1.2 and its mammalian ortholog*, we identified 88 hit compounds that could efficiently inhibit the parasite kinase. Evaluation of the potency of these compounds against host-free and intra-macrophagic parasites revealed 75 hits with high anti-leishmanial activity. However, most of the compounds displayed a strong toxicity towards macrophages and various human cell lines. Four molecules that showed strong anti-leishmanial activity, but no toxicity towards mammalian cells, were used in a target deconvolution assay that confirmed endogenous CK1.2 as the primary cellular target for two of our hits. Our data further confirm LmCK1.2 as a highly promising therapeutic target (Durieu et al., AAC, 2016), and validate our screening pipeline that can fuel the discovery of novel anti-leishmanial compounds with high therapeutic index, low toxicity, and proven target specificity.

** Gene that evolved separately from a common ancestral gene.*
Source: Antimicrob. Agents Chemother, *April 2016*

1 - Red blood cell infected with Plasmodium falciparum. *2* - Trypanosoma brucei. *3* - Plasmodium falciparum.

1

Viruses that are pathogenic for humans are vast in number and they cause chronic or acute infections that often prove fatal. The Virology Department studies all aspects of viruses to improve our defenses against them.

Researchers in its 17 units investigate the mechanisms used by viruses to hijack cells and multiply. They study how viruses spread, pass from one individual to another or one species to another, and how they outmaneuver host defense mechanisms. They also seek to identify the molecular bases of their pathogenicity. The viruses studied include respiratory viruses (influenza, etc.), cancer-causing viruses (papillomaviruses and hepatitis B and C viruses), retroviruses (HIV or HTLV), insect-borne viruses that are responsible for severe diseases (dengue, chikungunya, Zika, yellow fever and Rift Valley fever), and viruses causing hemorrhagic fevers (Lassa fever virus). Virology Department researchers work closely with others on the Paris campus and with members of the Institut Pasteur International Network. The Virology Department is also involved in translational research projects to design vaccine candidates, screen new therapeutic targets and develop diagnostic tools. It houses several National Reference Centers and World Health Organization Collaborating Centers, thereby playing a crucial role in the epidemiological monitoring of viral infections. The department is directed by Monique Lafon.

2

TWO FOR ONE

Zika and dengue are two mosquito-borne flaviviruses that cause different diseases in humans. Zika virus infection generally causes mild flu-like symptoms but can also result in serious complications, like microcephaly in newborns if their mothers were infected during pregnancy, or Guillain-Barré syndrome-type paralysis. The dengue virus exists as four serotypes and causes hemorrhagic fevers that are often fatal. The Structural Virology team had already revealed that some antibodies, developed by a patient infected by the dengue virus, had the rare property of being able to neutralize the four serotypes of this virus. They had also identified which part of the viral protein (epitope) was recognized by these antibodies. This year, while continuing research into these antibodies, they were surprised to find that one of them could also neutralize the Zika virus and that the two viruses shared a common epitope. This discovery should make it possible to create a single vaccine, capable of fighting both Zika and dengue.

Source: Nature, *August 2016*

1 - Cell undergoing apoptosis (cell death). Formation of apoptotic bodies. 2 - Magnification of the head of a mosquito able to spread viral infections (dengue, Zika, chikungunya, etc.).

A NEW COURSE IN MEDICAL ENTOMOLOGY

The *Insectes vecteurs & transmission d'agents pathogènes* (Insect Vectors and Transmission of Pathogenic Agents) course was held at the Institut Pasteur in Paris for the first time. This course, focusing on research into diseases spread by certain arthropods, is co-led by Anna-Bella Failloux from the Arboviruses and Insect Vectors Unit (Institut Pasteur) and by Vincent Robert from the Research Institute for Development (IRD). It will be held every two years. Next year, it will be supplemented by a knowledge enhancement workshop, run in another Institut Pasteur International Network member institute, and a MOOC devoted to medical entomology, organized in partnership with the CNAM.

ANTIBODIES CAPABLE OF ELIMINATING HIV-INFECTED CELLS

Despite their efficacy in containing HIV infection, antiviral treatments cannot cure patients of the infection caused by this virus because infected cells remain in the body. Researchers from the Virus and Immunity Unit have shown that broadly neutralizing antibodies – rare antibodies capable of neutralizing several HIV strains – were not only able to block the spread of the virus from cell to cell, but some of them were also capable of destroying HIV-infected cells by recruiting Natural Killer (NK)-type cells. These discoveries deepen our understanding of the action mechanisms of broadly neutralizing antibodies. They open up new therapeutic possibilities, particularly if, when injected alongside antiviral drugs, these antibodies can be used to cure patients infected with HIV.

Source: Nat. Commun., *March 2016*

MICHAELA MÜLLER-TRUTWIN WON THE 2016 PUYOO AWARD

In healthy patients, bone marrow cells produce macrophages, dendritic cells and neutrophils, which help to combat infection. In the event of inflammation or chronic infection, as is the case with HIV infection, the development of bone marrow cells is impaired and they produce suppressive myeloid cells. These cells alter lymphocyte function and lower the patient's defense mechanisms.
Michaela Müller-Trutwin, Head of the HIV, Inflammation and Persistence Unit, received the Puyoo Award from the Association for Research and Health for All, for her work on the role of suppressive myeloid cells in the pathology of HIV infection.

Medicine, clinical research and public health

The Institut Pasteur and its international network are putting their scientific expertise to work for the health of populations and individuals. This mission is conducted by the centers of expertise, which are recognized in France and abroad, as well as the Institut Pasteur Medical Center and the Center for Translational Science.

PASTEURIANS

"Strengthening links between researchers and clinicians."

"I've worked in the world of translational science for a long time and have always borne in mind the virtuous loop between researchers and clinicians. Back when I was head of clinical research at Lyon University Teaching Hospital, I helped to bring doctors and researchers together. At the Institut Pasteur today, we are trying to incorporate clinical aspects into the research conducted on campus. Public health is a long-standing mission at the Institut Pasteur and it links research to prevention, diagnosis and treatment. It is an honor for each and every one of us to turn scientific progress into medical progress for the benefit of patients."

ODILE GELPI
Vice-President Medical Affairs and Public Health

PASTEURIAN EMBLEMS

"For me, this photo perfectly reflects the Institut Pasteur's work."

Odile Gelpi bought this photograph to decorate her office when she arrived at the Institut Pasteur in 2014. It shows India, the banks of the Ganges, a throng of people happily taking part in ritual bathing and, almost certainly, an underlying fear of contracting infectious and communicable diseases from the water. For the Vice-President of Medical Affairs and Public Health, this scene depicts "a story about public health" and also a colorful, lively and optimistic view of care provided to individuals and populations across the world.

Center for Translational Science

The aim of the Institut Pasteur Center for Translational Science (CRT) is to facilitate the transfer of knowledge from fundamental research to the clinical field, and vice versa, in order to enhance patient care and improve our understanding of disease.

The Center for Translational Science (CRT) is composed of various research structures and complementary activities:
• a Clinical Core that instigates and coordinates clinical research activities, oversees the ethical and regulatory authorization process, and monitors project advancement;
• a Technical Core, in association with the Citech *(see p. 22)*, which provides access to state-of-the-art technologies selected to meet the needs of translational science;
• sampling activities, including securing informed consent and collecting samples, mostly from healthy volunteers (ICAReB, *"Milieu intérieur"* LabEx) but also from patients;
• patient care within the Institut Pasteur Medical Center. Links are established with medical teams in other care structures, including affiliated hospitals, hospitals with partnership contracts and joint units;
• scientific and communications activities, both within the Institut Pasteur and externally.

Weekly "Open Desk" sessions

Every Thursday afternoon, the CRT holds Open Desk sessions to address the needs of biomedical research teams. Scientists come and present their projects, as early in the planning stages as possible, to a group of experts with all the skills needed to assess them and help get them off the ground (methodological, regulatory, ethical, legal and technological expertise and access to biological resources). This gives the scientists a comprehensive, coordinated understanding of the procedures involved and the feasibility of the project.

New technologies for scientists

The aim of the CRT's technical core is to provide scientists with all the technologies they need to discover new biomarkers. In 2016, a next-generation cytometer and new protein-analysis equipment were added to its extensive facilities. It has also set up an online bioinformatics course on analyzing mRNA sequences.

Clinical research at the international level

Fabien Taïeb, a physician specializing in infectiology, joined the CRT to develop clinical research within the Institut Pasteur International Network. A kick-off meeting for this project, known as INCREASE, was held in May 2016 with seven pilot institutes in the network (Cambodia, Cameroon, Ivory Coast, Dakar, French Guiana, Madagascar and Tunisia). The first initiatives included producing an electronic case report form (eCRF) and a needs inventory, and setting up teams to apply for European & Developing Countries Clinical Trials Partnership (EDCTP) grants. The teams also tested a collaborative website, "Together", developed by the Information Systems Department and the International Group for Data Analysis.

FORGING LINKS WITH PATIENTS AND HEALTHY VOLUNTEERS

In June 2016, the CRT organized the first conference targeting the Institut Pasteur's healthy volunteers. During the morning session, eleven scientists who use biological resources from these healthy volunteers presented the results they had obtained thanks to their samples. In the afternoon, a round table discussion explored the role of participants in biomedical research. A final session provided an overview of current research into hidradenitis suppurativa and was attended by patients who have this disease, many of whom are being treated at the Institut Pasteur Medical Center.

Scientific events

The CRT organizes a range of events with the aim of boosting the medical component of the Institut Pasteur's activities and facilitating knowledge transfer from scientists in the International Network to healthcare facilities. Research Director, James Di Santo, joined the CRT as Deputy Director with the role of identifying priority areas and coordinating scientists' initiatives.
This led to the CRT's involvement in running working groups on aging, vaccination, cancer (especially liver cancer) and snake bites.
The Pasteur-Medicine Quarter Hour – short talks given by clinicians – has become a popular monthly event for Institut Pasteur scientists.
In the same vein, the CRT continues to invite scientists to present their research findings to hospital departments in Pasteur-Science Quarter Hour sessions.
The annual "Translational Science Day" presents the research carried out in a wide range of fields by leading translational scientists at an international level.
This is an opportunity to find out about new developments and share thoughts on cross-cutting topics such as genome editing.

The CRT also organizes specific events geared towards physicians and scientists on subjects related to translational science, such as neuroscience and cancer research.

Boosting the Institut Pasteur's medical dimension

The CRT has set up a 12-member medical committee tasked with creating the status of Institut Pasteur "affiliated physician" in 2017.
Around a hundred affiliated physicians will share their medical network with Institut Pasteur scientists. The CRT is also continuing its efforts to attract physicians to the Institut Pasteur, with a second-year Master's program, guest researcher posts, partnership contracts, Institut Pasteur and AP-HP joint units, affiliated hospitals, etc.

TWO PROJECTS WITH SCIENTISTS BASED ON PARTNERSHIP CONTRACTS

• **Bipolar disorder project.** Chantal Henry was recruited to Pierre-Marie Lledo's unit under a partnership contract. She is working on several projects that explore the dynamic relationship between the olfactory system and emotions as a prognostic tool for bipolar disorder. She is also developing an application to monitor bipolar patients.

• **Spondyloarthritis project.** This project is led by Corinne Miceli, who secured a partnership contract last year in Lars Rogge's unit. The aim of the project is to set up a cohort of patients with severe forms of spondyloarthritis and to determine the effect of anti-TNF therapy and IL-17 pathway inhibitors on the immune cells of these patients.

CNR and PIBnet

The Institut Pasteur manages 15 National Reference Centers (CNRs) in mainland France and four associated CNR laboratories at the Institut Pasteur in French Guiana. In keeping with the Institut Pasteur model, these structures are designed to focus on public health and work closely with the research units that host them.

2016 was the final year of the five-year term for which the National Reference Centers (CNRs) were established by decree. Preparations for the renewal of this term for the 2017-2021 period were made via a call for applications by the Ministry of Health. Seven of these CNRs are also World Health Organization Collaborating Centers (WHOCCs). The Institut Pasteur also houses a WHOCC for enteroviruses (in particular the poliovirus) and a WHOCC for surveillance of resistance to antimalarial drugs at the Institut Pasteur in French Guiana.
The CNRs provide support to the health authorities* and work in association with their host research units to fulfill four key roles that play a part in the Institut Pasteur's public health mission: the provision of microbiological expertise, consultancy services to health professionals or authorities, contributions to epidemiological surveillance, and contributions to health alerts.

MONITORING MENINGOCOCCUS

In France, the incidence of invasive meningococcal infections is low (0.9 to 1.6 cases per 100,000), has been relatively stable for ten years, and has a death rate of between 8 and 10%. Monitoring meningococcal infections (mandatory declaration to Regional Health Authorities) remains essential in view of their epidemic potential. Between 2011 and 2016, the National Reference Center for Meningococci confirmed that 2,248 cases had been detected. A number of clusters and/or outbreaks were studied, following the emergence of the C/cc11 strain within the MSM (men who have sex with men) community. In addition, the CNR started using a whole genome sequencing approach in epidemiological surveillance. Lastly, it used the new Meningococcal Antigen Typing System (MATS) to assess the coverage of Meningococcus B by the new recombinant vaccine Bexsero®, meeting vaccination requirements for clusters of cases in line with the recommendations of the French High Council for Public Health.

1 - Mucor indicus *is a filamentous fungus in the mucorales order that causes zygomycosis.*

PIBnet – the collaborative microbiology platform

The CNRs are supported by the shared facility for microbial characterization (P2M), which is part of the Pasteur International Bioresources network (PIBnet) project and focuses exclusively on innovative techniques in public health. P2M was set up in 2015 as a single, new channel for receiving requests from all the CNRs. Nearly 16,000 pathogen sequences (bacteria, viruses or fungi) were processed in 2016. Automation ensures rapid results at optimal cost. This activity, which is unique in France, proves that it is possible to transfer innovative techniques to public health as a matter of course. The value-add is undeniable for decision-makers, who benefit from more precise information: the discovery of clustered cases, rapid proof of their existence and demonstration of absence of links (avoiding the need for investigations).

A crisis situation relating to *Bacillus cereus* emerged in the summer of 2016, with the deaths of premature babies in a number of different hospitals, who had all received breast milk from the Necker Hospital milk bank. The health authorities called in PIBnet and its P2M facility, and the effectiveness of this model and its organization was amply demonstrated:
• rapid first response (Sanger sequencing), with the Laboratory for Urgent Response to Biological Threats (CIBU);
• confirmation of the presence of different strains (whole genome sequencing) by P2M within a very short time frame.
P2M and its dedicated team of bioinformaticians provide a basis for planning cross-disciplinary projects, deliberating on a variety of future organizational methods, facilitating management of regulatory requirements using specific skills (MOT, BSL-3 environment), and training health professionals (in particular via technology transfer).

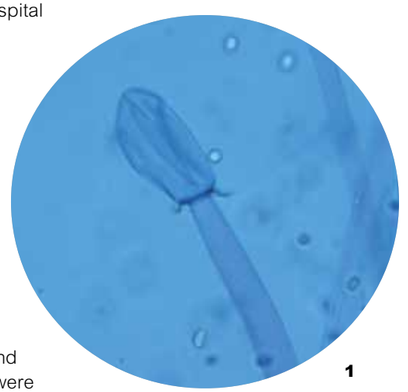
PIBnet on the international stage

One of the aims of PIBnet is to facilitate biobank establishment and management within the Institut Pasteur International Network (IPIN), in order to optimize samples. A group comprising eight IPIN members was formed and met twice in 2016. Two 3-day seminars allowed the key points of biobank creation to be discussed: tools, scientific objectives, the security of samples and data, and legal and regulatory aspects. There was a particular focus on the Nagoya Protocol, which concerns some of the IPIN countries. Feedback sessions helped set highly ambitious targets for this group of eight.

** In 2016, the Institute for Public Health Surveillance, the traditional contact authority for the CNRs, became Santé Publique France (SPF).*

AN INVESTIGATION IN THE FIELD OF PEDIATRIC HEMATOLOGY

The National Reference Center for Invasive Mycoses and Antifungals was contacted in 2016 following the rare instance of the isolation of a mold in clinical practice affecting immunosuppressed children. *Mucor indicus* is a fungus regarded as non-pathogenic and used in the food industry.
The fear arose that we were facing an outbreak originating from the same potentially food-borne source. Following a national investigation by the CNR in association with Santé publique France (SPF) and a number of mycologist colleagues, nine cases were identified in seven university hospitals (five colonizations and four serious infections), mostly in the context of a malignant disease in hospitalized patients.
Following the epidemiological study by SPF to determine the origin of these infections, hospital care was not found to be at fault, although a common cause could not be ruled out.
Investigations of clusters of cases are difficult due to insufficient knowledge about fungi and fungal infections.
In parallel, the CNR carried out whole genome sequencing of strains of *M. indicus* (clinical and historical strains and strains from collections) with the P2M facility. Analysis by P2M bioinformaticians led to the conclusion that there was a probable common origin, although the source of the infection was not found. The expertise of the CNR and P2M and its value to the health authorities were amply demonstrated during this episode.



1

Medical Center

The Institut Pasteur Medical Center (CMIP) is the Paris-based entity in direct contact with patients, providing a range of services including a vaccination center; consultations for infectious and tropical diseases, travel medicine, and allergies; and an anti-rabies center.

The Institut Pasteur International Vaccination Center (CVI) is a reference center for travelers to countries where the environment, and health and hygiene conditions, are not the same as those usually encountered in France. Its reputation attracts a high number of people seeking vaccinations and specific information relating to their planned trips abroad.

Vaccination and travel medicine

In 2016 over 72,000 vaccines were administered at the Vaccination Center and in travel medicine consultations. There are two patient categories: those who attend the center privately, prior to family holidays or leisure trips, and those who attend in connection with their business trips. In this second category, it is interesting to note that companies themselves – and NGOs, which are also concerned – send their employees to the Medical Center under health monitoring contracts drawn up with the Institut Pasteur. These travelers are examined before departure, and very often also when they return to France. This activity falls within the scope of travel medicine consultations, for which the expertise of the Medical Center is universally recognized. As a result of this expertise, the Center is often in the news, and is consulted in cases of emerging infectious diseases. This was once more the case in 2016 with the emergence of the Zika virus in South America and the West Indies. The Center's doctors treated people returning from affected countries – in particular pregnant women anxious for their unborn babies – and provided expert and appropriate prevention advice to travelers to these regions.

Consultations and medical treatment

In addition to vaccinations and advice for adult and child travelers, vulnerable patients (i.e. those with HIV, organ transplants or other immune deficiencies), and humanitarian travelers, the Medical Center plays a key role in treating diseases imported by returning travelers (malaria, arbovirus infections such as dengue, rickettsial infections, intestinal parasitic infections, leishmaniasis, cutaneous larva migrans, etc.), HIV infection, and widespread infectious diseases such as Lyme disease.
Some of these diseases are monitored in collaboration with Necker University Children's Hospital, via the Necker-Pasteur Infectiology Center (CINP). Eleven doctors from the Infectious and Tropical Diseases Department at Necker Hospital hold clinics at the Medical Center, alongside nineteen doctors from the Institut Pasteur. Together these doctors manage and monitor a large number of patients infected with HIV or viral hepatitis.

Over 72,000
vaccines administered in the international vaccination center and travel medicine clinics

These consultations give rise to a significant amount of clinical research, mainly with the French National Agency for AIDS and Viral Hepatitis Research (ANRS).

There are also dermatology consultations, particularly to treat patients with *hidradenitis suppurativa*, which have led to remission in a number of patients via an innovative therapeutic strategy that specifically targets this disease.
The Medical Center monitors a large caseload of patients, and is consulted on a regular basis to provide advice to organizations abroad.

The Anti-Rabies Center (CAR) provides care and treatment for patients who have been exposed to rabies via a bite, scratch or the licking of a wound or mucous membranes. Although there have been no cases of infection reported in France for a great many years, there are still occasional deaths in people who have been infected abroad. Two types of risk have been reported: exposure during foreign travel, or a bite from an animal imported from abroad.
Anti-rabies treatment should be started as soon as possible following exposure. Treatment consists of several vaccine doses generally combined with serotherapy. Current vaccines are highly effective and well tolerated.

The multidisciplinary team providing consultations for allergies has the capability to treat allergies of all types, including rhinitis, asthma, conjunctivitis and allergic dermatosis.

Clinical research

The Medical Center also undertakes clinical research in its specialist medical areas, with cohorts for conditions such as HIV infection, the pathophysiology of *hidradenitis suppurativa* (microbiology, genetics and immunology, in collaboration with Necker Hospital, the ICAReB platform and the Institut Pasteur campus units), vaccinology (interaction of the yellow fever and measles vaccines in children), and sociology (the study of traveler perceptions and practices relating to vaccination to improve understanding of their reasoning and concerns).

2016 saw the publication of new data on the efficacy of the antibiotic therapeutic strategy used by the Medical Center in severe forms of *hidradenitis suppurativa*. These data are based on microbiological and therapeutic findings from previous years, and should be confirmed with a large-scale therapeutic trial in the next few years.

The new insights offered by these projects demonstrate the support available to clinicians in response to their questions, and fully justify the Medical Center's place in the Center for Translational Science *(see p. 48)*.

THE MEDICAL CENTER ON THE PASTEUR.FR WEBSITE

The Medical Center section is the most frequently visited section on the pasteur.fr website. It is a highly important source of information for the general public in terms of travel health recommendations, and provides vaccination schedules and disease fact sheets.

Innovation

The Institut Pasteur promotes innovation development and technology transfer through its multidisciplinary and transversal approach to research. To turn discoveries into medical progress, the Institut Pasteur has two departments – one develops innovation by supporting new research projects (DDGO) and the other promotes technology transfer (DARRI).

PASTEURIANS

"Playing the innovation game together."

"I developed an arboviral testing method based on blood tests", explains the researcher Jessica Vanhomwegen. *"It was the subject of my doctoral thesis in 2011."* An invention disclosure (ID) was filed in 2012 and then clinical proof was needed. Jessica set to the task with the help of Nancy Geffroy, an expert in legal matters: *"We receive the IDs, check the discovery applications with the researcher, identify the 'objects' that can be patented, try to obtain the rights, and then defend these rights."* Thanks to this patent engineer's expertise, the researcher was pointed in the right direction regarding further research and required findings. The teamwork continues as the future of the patent – finally granted in 2016 – needs to be monitored.

NANCY GEFFROY
Patent engineer (right in the photo) in the Research Applications and Industrial Relations Department (DARRI)

JESSICA VANHOMWEGEN
Postdoctoral researcher (left in the photo) in the Environment and Infectious Risks Unit

PASTEURIAN EMBLEMS

"A patent, the result of several years' work."

Once the invention disclosure had been filed, it took four years to obtain the patent and protect the arboviral testing method. It was a long-term process that involved evaluating the technique, and providing clinical proof of the concept. and assessing it in hospitals, the Institut Pasteur International Network member institutes, and partner institutes (in French Polynesia, Brazil, Bangladesh, etc.).
An industrial partnership was also formed when the patent was granted.


The Director of the United States Patent and Trademark Office

The United States of America

United States Patent

Developing innovation via support for new research projects

The Department of Development and the Grants Office (DDGO) continued to support Pasteurian research throughout 2016, and increased its initiatives to foster new scientific or research funding partnerships.

The results achieved by the DDGO are the fruit of a combined effort involving the scientific community and the four DDGO sub-divisions:
• Mapping and Scientific Communications;
• Partnerships and Incentive Research Programs;
• Grants Office;
• Representation and Information on Europe.

Pasteurian research with a global vision

A new impetus was created in 2016, with the compilation of an exhaustive directory of the activities covered by over 130 research units. This global vision of the scientific projects in progress and those envisaged over the medium term is based on the implementation of the Magellan database – a powerful tool for scientific mapping that was developed specifically for the Institut Pasteur.
The desire to document the entire range of activities carried out by the Institut Pasteur International Network (IPIN) led to the organization of DDGO missions in five of the network's institutes in 2016. The detailed nature of the definitions reveals the diversity of the scientific approaches and the full potential of the transversal research activities that are now essential for building ambitious new programs.

Funding Pasteurian research via calls for proposals

A reduction in national credits for funding research and innovation has forced the Institut Pasteur to diversify its funding base. 2016 saw the development of a new international monitoring tool to enable each and every scientist to find appropriate funding. In parallel, a targeted activity was developed for monitoring international calls for proposals, and scientists now receive emails to inform them of funding possibilities that correspond to their specific fields of activity.
In association with the French Ministry of Research and the French National Alliance for Life Sciences and Health (Aviesan), the DDGO has involved Institut Pasteur experts in the development of future European calls for proposals, in particular those to be launched as part of the Horizon 2020 Work Program 2018-2020.
A key element of our strategy in 2016 involved the identification of new funding bodies and support for researchers in setting up large-scale funding applications coordinated by the Institut Pasteur, in response to calls for proposals by a wide range of funding bodies. There were a number of notable successes:
• INCEPTION *("Instituts Convergences" for the study of emergence of pathology through individuals and populations)*: €12m funding over ten years, within the framework of the Investing in the Future program (Directorate-General of Research and Innovation/French National Research Agency). The project combines integrative biology, social sciences and data science to give insight into the emergence of disease in populations and individuals.
• Infravec 2 (H2020 INFRAIA): €10m funding over four years. The Institut Pasteur is coordinating the work of 24 partners in order to promote excellence in research on the biology of insect vectors, facilitate access to major equipment for scientists, and develop new anti-vector strategies to fight the greatest threats to human health and to livestock industries.
• SAFE-Aqua (H2020 MSCA-RISE): €1m funding over four years. The Institut Pasteur is coordinating a consortium of four partners, who are to implement international and cross-sector scientific collaborations through secondments, with the aim of finding solutions to manage diseases in aquaculture.

Internal investments and the quest for financial partners

In 2016, the DDGO strengthened initiatives to foster partnership agreements, which included self-financed incentive programs, the establishment of industrial partnerships and targeted initiatives around sponsorship and donations, in conjunction with the relevant departments.

Ninety-six incentive projects, including 27 new initiatives, received such support in 2016. These included 17 projects within the framework of the Major Federative Programs (GPFs) "Vaccinology" and "Microbes and Brain", the Ebola Task Force, 22 Transversal Research Projects (PTRs), 16 Concerted Incentive Actions (AICs) and 19 projects to bring innovations to maturity.
The 27 new programs involved 40 research entities on the Paris campus and 16 within the International Network.
Two calls for proposals in a new format were also launched in 2016: the GPF "Inflammation, nutrition, metabolism and cancer", and the first call for proposals in connection with the "Grand Challenges Africa" scheme in collaboration with the European Food Safety Authority (EFSA) and the Bill and Melinda Gates Foundation.
In support of the Research Applications and Industrial Relations Department *(see p. 58)*, the DDGO was instrumental in detecting innovations and bringing them to maturation, optimizing the patent portfolio and creating opportunities for collaborative projects with companies.
In close collaboration with the Department of Communications and Fundraising, the DDGO was also very active in identifying ongoing projects likely to meet sponsorship criteria (with foundations, for example) or to respond to requests from major donors, and in defining the topics to be given prominence in fundraising efforts.

Research applications and technology transfer

The Research Applications and Industrial Relations Department (DARRI) works with industry partners in France and abroad to detect, promote, support, protect, and transfer inventions arising from research efforts by Institut Pasteur scientists. Its aims are to ensure that patients and public health can benefit from the discoveries made in the Institut Pasteur's laboratories, and to yield a fair financial return for the Institut Pasteur and its research units.

Technology protection and transfer relating to research applications are essential sources of revenue for the Institut Pasteur. Innovative projects conducted with academic and industrial partners, in particular translational research with hospitals and the Institut Pasteur International Network, bring concrete medical solutions right to patients' bedsides. The development and transfer of innovations have proved essential for responding to global public health challenges, and finding new diagnostic tests, antibiotics, and vaccine approaches or breakthrough technologies in gene or cell therapy. In 2016, the DARRI redefined the way in which the Institut Pasteur can meet the requirements of its industrial partners and bring added value to innovation. It saw a 40% increase in the number of new R&D cooperation contracts, in service provision and in MTAs (Material Transfer Agreements) with industrial partners.

Continual developments in intellectual property

Innovation on the campus was ramped up in 2016, with 71 invention disclosures registered. In other words a 22% increase in relation to the average for the previous three years, resulting in 32 new priority patents being filed and 16 provisional applications (software, expertise and biological material). The invention disclosure to patent conversion rate was around 49% (remaining stable in relation to 2015). These included the filing of a patent on a drug candidate using immunotherapy to mimic defenses discovered in a highly specific population of HIV patients who control the disease naturally; the protection of an adjuvant (a substance administered along with other active substances) for the treatment of cancer and developed in conjunction with an industrial partner; protection of an effective vaccine candidate against dengue and Zika viruses, resulting from a joint project between the Institut Pasteur and Imperial College; using the measles vector platform, protection of a new vaccine against Zika, which immediately entered the clinical trial phase thanks to our partnerships. Over and above this increase in invention disclosures, the selectiveness and quality of patent applications and their content is central to the Institut Pasteur's industrial property strategy.

Developing partnerships

2016 saw a major agreement with the NIH and the Roche Group, based on new HIV-1 patents obtained in 2012 and 2013 in the field of diagnostics and viral security for blood banks. This agreement stands to generate significant income for the Institut Pasteur up to 2024. Other highlights included:

- strengthening of the partnership with Themis Bio, with a new licensing agreement and excellent prospects for the clinical development of vaccine candidates;
- development, in association with an industrial partner, of an immunology multiplex assay, patent protected since 2012-2013, to detect a number of arbovirus infections (dengue, chikungunya, Zika, etc.) – an innovation that could improve patient care in hospitals throughout the world.

The maturation of inventions has become crucial

In 2016, the Institut Pasteur demonstrated strong resilience in the face of the dual challenges of the progressive expiry of historical patents and the legal context of the "Myriad decision" in the USA. It is now mandatory to achieve further development for innovations within specific industrial applications before filing a patent. The maturation of inventions is a key priority, and the Institut Pasteur has strengthened its links with industrial partners and stepped up collaborative R&D initiatives that encourage innovation and the funding of research. In addition to increasing invention disclosures and collaborative R&D initiatives, financial investments will be necessary in 2017 to accelerate and strengthen the maturation of high-potential innovations on campus. In the short term, the objective is to develop innovative projects that encourage collaborative initiatives; the medium-term goal is to renew the patent portfolio; and over the long term, we need to provide public health solutions by making use of our patents through licensing agreements.

71 invention disclosures

32 new priority patents and

16 provisional applications

166 industrial contracts signed

255 industrial contracts in place

RENEWAL OF THE PASTEUR MICROBES AND HEALTH CARNOT INSTITUTE

The Carnot designation aims to recognize the ability of research institutions to collaborate with companies, thereby enhancing their visibility. On July 6, 2016, the French government rewarded the Pasteur Microbes and Health Carnot Institute under the "Carnot 3" call for proposals. The aim of Pasteur Microbes and Health, led by Jean-Christophe Olivo-Marin and his deputy, Daniel Larzul, is to understand the complexity of microbe-host interactions and, more generally, the implications of the microbial world for human health, as well as to offer diagnostic, therapeutic and vaccination solutions.

FORWARD STRIDES FOR BIOASTER

Bioaster is a technology research institute specializing in technological innovations in microbiology, and has the support of high-profile academic and industrial partners. It was created in April 2012 on the initiative of the French government by the Institut Pasteur and the Lyonbiopôle competitiveness health cluster. Highlights for 2016 included an immunology publication with Richard Lo Man's group, new Ebola diagnostic projects, a collaborative initiative with the ICAReB (Clinical Investigation and Access to Biological Resources) platform, a project with Axenis (an Institut Pasteur spin-off), advances in interactions between Bioaster and the Imagopole and installation of a stereomicroscope for small animal surgery at the Institut Pasteur.

Education

Knowledge transfer is one of the Institut Pasteur's core missions, reflecting its commitment to society. Talented young scientists and professionals in science and medicine from all over the world are drawn to its high-quality courses taught by top-level experts.

PASTEURIANS

"Helping students become researchers."

"You need to be curious and dedicated to become a researcher", agree Fani and Deshmukh. Fani Koukouli came from Greece to attend the PPU* international doctoral program for four years and is today a postdoctoral fellow at the Institut Pasteur. *"My studies here have been an education both in terms of career and personal development, as I have gained in self-confidence."* Deshmukh Gopaul, who supervises iGEM** project students every year, adds: *"Transferring knowledge also means checking that students really aspire to become researchers. Because you need to be determined to do this job and constantly challenge yourself."*

DESHMUKH GOPAUL
Project coordinator, Design for Biology

FANI KOUKOULI
Postdoctoral fellow, Integrative Neurobiology of Cholinergic Systems Unit

** Pasteur-Paris University.*
*** Synthetic biology project.*

PASTEURIAN EMBLEMS

"The lab coat, a symbol of knowledge transfer."

At the Institut Pasteur, knowledge transfer is halfway between education and research. Supported in their quest to become researchers, and to gain the required qualities and abilities, students acquire *"the knowledge and self-assurance they need to don their lab coat and embark on a career as a scientist on completion of their education"*, according to Deshmukh Gopaul. The young graduate Fani Koukouli acquired this self-assurance and has subsequently demonstrated it by publishing two scientific papers, one on the subject of fundamental neuroscience* and the other about schizophrenia**.

* PNAS, *Dec. 2016.*
** Nature Medicine, *Feb. 2017.*

Relaying knowledge

Education and training are at the heart of the Institut Pasteur's activities, continuing the legacy of its founder, Louis Pasteur. For over 125 years, since the first microbiology course taught by Émile Roux in 1889, the Institut Pasteur has played a key role in science teaching.

Each year, over 1,200 students, PhD students and healthcare professionals from 68 countries, attend one of the 60 courses and workshops provided at the Institut Pasteur in Paris or at one of the 33 institutes in the Institut Pasteur International Network. Over 600 young scientists are also hosted by laboratories on the Paris campus to train as scientists and complete their undergraduate, Master's and PhD research projects.

A unique setting for science and research training

The Institut Pasteur, renowned for the excellence of its research, provides young scientists from France and abroad with a unique setting for training through experience in its laboratories, where they can complete internships for their undergraduate, Master's and PhD studies. Alongside this practical training, the Institut Pasteur runs high-level Master's and PhD courses, as well as vocational science courses leading to recognized university diplomas. Courses in Paris are run by scientists on campus, with valuable input from lecturers based at partner institutions in France (such as Paris Descartes, Pierre & Marie Curie, Paris Diderot and Paris-Sud universities, the Institut Curie, the CNRS and Inserm) and abroad.
The fact that renowned scientists are involved in Institut Pasteur courses on a daily basis is pivotal to the success of our teaching, providing students with continual access to the latest developments in research. The focus on laboratory testing and practical work is a key strength and one of the distinctive characteristics of education at the Institut Pasteur. Teaching has also been considerably influenced by the development of the Institut Pasteur International Network, in terms of both the scientific subjects taught and the countries of origin of the students.

To maintain its leading position, the Institut Pasteur is extending its teaching activities by placing greater emphasis on online courses (MOOCs and SPOCs), opening up courses for younger students, encouraging multidisciplinarity and links with medicine, as well as promoting entrepreneurship and business development.

900 **students each year**

300 **PhD students** on the Institut Pasteur campus

PHD GRADUATION CEREMONY

The fourth graduation ceremony for PhD students on campus who defended their thesis during the 2015-2016 academic year was held on December 16, 2016. This year's speaker, Prof. Alim-Louis Benabid, winner of the 2014 Lasker Award and the 2015 Breakthrough Prize, gave an address on the practice of scientific research and discovery. Four talented researchers from the Institut Pasteur International Network were also honored at this event: N. Arsentieva (Institut Pasteur in Saint Petersburg), C. Ngoagouni (Institut Pasteur in French Guiana), M. Rohani (Institut Pasteur in Iran) and J-A. Tangena (Institut Pasteur in Laos).
The ceremony was attended by Institut Pasteur staff, representatives from partner organizations, and figures from political, diplomatic and business circles with links to the Institut Pasteur. Launched in 2013, the annual graduation ceremony has become a major event on the campus calendar, serving as a showcase for the professional excellence produced by the Institut Pasteur's research and training. The next ceremony will be held on December 15, 2017, with guest speaker Sir Paul Nurse (laureate of the 2001 Nobel Prize in Physiology or Medicine for his contribution to knowledge of the cell cycle).

New courses in 2016

In 2016, for the first time in the history of the Institut Pasteur in Paris, three first-year Master's courses in English were introduced: Molecular Cancer Genetics, Basic Immunology, and Cell Biology. These courses are run in partnership with the Institut Curie and the École Normale Supérieure (ENS).
Two new courses with an international focus were launched on the subject of virology and its public health implications: Retroviruses and Viruses and Cancer. They are geared towards research professionals and include lectures by internationally renowned speakers such as our Nobel Prize laureate Françoise Barré-Sinoussi.
The Institut Pasteur is continuing to develop its online teaching activities, with the aim of making the courses taught at the Education Center, or at institutes in the International Network, available to as many people as possible. In 2016, just a year after they were launched, the Institut Pasteur MOOCs were already highly successful in terms of numbers (3,000 to 5,000 students enrolled for MOOCs) and international visibility.
The Institut Pasteur represents nearly 20% of the MOOCs in health available on the platform FUN (France Université numérique). The MOOCs developed in 2016:
• Medical Entomology MOOC (broadcast in 2017), with nearly 3,000 registered, 20% of the audience passed the final test, compared to an average of 6 and 10% for scientific MOOCs;
• Innate Immunity MOOC (broadcast in 2017);
• Diagnosis and prognosis biomarkers in global health MOOC (broadcast in 2017);
• In the footsteps of Zika… Approaching the unknown MOOC (broadcast in 2016), in partnership with the University of Geneva;
• Global Health at the Human-Animal-Ecosystem Interface MOOC (broadcast in 2017), in partnership with the University of Geneva.
And two courses made in previous years and broadcast again in 2016:
• Concepts and methods in epidemiology MOOC (3rd broadcast, over 3,800 learners);
• Vaccinology MOOC (2nd broadcast, slightly more than 2,000 learners).

Predoctoral programs

The Institut Pasteur is keen to step up its training for students at earlier stages in their academic career. Several predoctoral programs have therefore been developed at undergraduate and Master's level for students from all over the world. The *Amgen Scholars* Program, for example, enables around 20 students from European universities and higher education institutions to come and work on a research topic for eight weeks in one of the Institut Pasteur's laboratories. This international program is run entirely in English and culminates in a conference in Cambridge, UK.
The Institut Pasteur also hosts students under the EU's Erasmus+ program, thanks to its partnerships with several European universities. A program run by the Pasteur Foundation also provides the opportunity for five or six undergraduate students from the US to complete training through research at the Institut Pasteur.

In an effort to vary its predoctoral courses and consolidate its position at the forefront of innovation in synthetic biology, the Institut Pasteur set up its own iGEM (International Genetically Engineered Machine) team in 2015. Since MIT launched the iGEM competition in 2004, teams from all over the world have competed to develop the most innovative synthetic biology project. The 2016 Institut

Pasteur team was composed of around 20 undergraduate and Master's students from a variety of disciplines (biology, physics, chemistry, mathematics, political science, law and industrial design). The Institut Pasteur's participation in this program was boosted by new partnerships with ESPCI ParisTech engineering school, ENSCI-Les Ateliers design school and the Faculty of Law at Paris-Sud University, as well as by its long-standing partnership with Pierre & Marie Curie and Paris Diderot universities. In the 2016 iGEM competition, the Institut Pasteur team won a gold medal and three first prizes for best diagnostics project, best applied design project and best supporting entrepreneurship project.

PhDs: training through research

With almost 130 research units in Paris and a network of 33 institutes worldwide, the Institut Pasteur is truly a higher-education hotspot for many young scientists. Each year, around 70 PhD students complete their studies in the laboratories on the Paris campus. The students may be eligible for various types of funding – from their university, via the laboratories' own resources obtained through regional, national or European themed programs, from non-governmental organizations or through the Institut Pasteur's international doctoral program *(see inset on opposite page)*. The Institut Pasteur also offers scientific supervision for PhD students with its thesis committees and offers personal support via a program that provides individual tutoring and career guidance.

The Institut Pasteur in Paris runs specific PhD programs, such as the Pasteur-Paris University (PPU) international doctoral program, open to students with a Master's degree (or equivalent) from a foreign university who wish to carry out their PhD research in an Institut Pasteur laboratory. This high-level program, launched in 2008, is run in close partnership with Paris-Descartes, Pierre & Marie Curie and Paris-Diderot universities, and, since 2015, the University of Paris-Saclay. Led by Susanna Celli since November 2015, the three-year program results in a PhD from a French university.

In 2016, to improve mobility for health and environment researchers between Latin American and Caribbean countries and Europe, the Institut Pasteur launched the Pasteur-Paris University – Enhancing Mobility in Health and Environment (PPU-EMHE) program. This program is run in partnership with research funding bodies in Argentina, Mexico, Costa Rica, Peru and Uruguay. In 2016, three PhD students on the PPU-EMHE program joined the "Élie Wollman" PPU year group.

Each year, the Institut Pasteur Department of International Affairs also awards doctoral grants for the completion of PhDs at one of the institutes in the International Network (outside mainland France). The research topic can be related to any subject under study in the International Network, ranging from infectious diseases (infectious pathophysiology, immunology, microbiology, epidemiology, virology and parasitology) to public health activities (diagnosis, surveillance, resistance, etc.). Applicants must hold a Master's or equivalent degree and be enrolled at a doctoral school based at a French or foreign university.

To keep up with the major changes in medical practice and biomedical research brought about by scientific breakthroughs and recent technological advances, the Institut Pasteur, the Institut Curie and the École Normale Supérieure are continuing their "Médecine-Sciences" (MS) program.
This program, set up in 2015, offers a top-level dual medical and scientific curriculum. It includes an early introduction to research, with the aim of training up a body of professionals with both scientific and medical expertise. Students are recruited through a competitive examination at the end of their second year of medical or pharmaceutical studies. The program offers comprehensive interdisciplinary training and provides students with an outstanding range of top quality teaching, lectures and internship possibilities. The many advantages include guaranteed funding for the first three years, effective scientific and medical tutoring, a prestigious ENS qualification and a PhD in Science. Graduates of the "Médecine-Sciences" program can enjoy excellent career prospects in either academia or the healthcare industry, in France or abroad.

Training in business development and entrepreneurship in science

The Institut Pasteur is strongly committed to finding business applications for its research, and its teaching activities clearly reflect this approach. Throughout 2016, several initiatives were developed and pursued in this field, especially the "Creating your own company" series – informal monthly events for Institut Pasteur scientists interested in business development, featuring guest speakers who have enjoyed entrepreneurial success in biotechnology – and the summer school held in July 2016 in partnership with Medicen.

To conclude, the Institut Pasteur has developed well-structured, effectively organized teaching activities at local, national and international levels, bolstered by the involvement of leading experts and professionals. The courses and initial and continuing training on offer at the Institut Pasteur have earned an outstanding international reputation, attracting promising young scientists from across the world and helping to build an international network of researchers.

PPU – THE "ÉLIE WOLLMAN" CLASS

The PPU "Élie Wollman" class of 2016 included 15 students from Europe (Spain, Italy, Portugal and Ukraine), Central and South America (Brazil and Mexico) and Asia (China, India, Malaysia and Pakistan). Each year, a new set of students specializing in a wide variety of different fields are given the chance to work together during joint activities run by the PPU organizing committee, as well as literature seminars and the international doctoral program annual retreat. In May 2016, this retreat was held in Morzine. All current PhD students attended a conference where they discussed the progress of their research in a focused but informal setting with the aim of providing constructive suggestions to improve their projects.

International

PASTEURIANS

"Constant learning to remain at the forefront of knowledge."

"I was a doctor in a hospital near Yaoundé before I joined the Pasteur Center in Cameroon. As soon as I arrived in 2001, I got involved in the first Cameroonian project for reducing mother-to-child transmission of HIV. The results had a significant impact on the rollout of this operation in the rest of the country. We extended our research to appropriate care for HIV-infected children. So this has been the basis of my training in epidemiology and clinical research over the years. Working, while constantly learning, to remain at the forefront of knowledge – that is my vision of a career path for an Institut Pasteur scientist."*

MATHURIN CYRILLE TEJIOKEM
Head of the Epidemiology and Public Health Department at the Pasteur Center in Cameroon

** DIU-CESAM (inter-university degree in statistics applied to medicine and medical biology), Paris VI, Paris VII, and Aix-Marseille II universities. Second year Master's program, ISPED (Institute of Public Health, Epidemiology and Development), University of Bordeaux II. PhD in Epidemiology and Public Health Response, Paris-Sud University.*

PASTEURIAN EMBLEMS

"It reminds me of the topic I've been working on for 16 years."

Mathurin Tejiokem sees this triptych photo on his desk every day. It was produced by the Total Foundation as part of a program for helping HIV-positive mothers and their children, and for improving childcare conditions. This program – which was overseen by Mathurin Cyrille Tejiokem – included healthcare courses that were partly designed to assess the feasibility of early antiretroviral multitherapy in infants infected with HIV in Cameroon (ANRS-Pediacam study). The pictures evoke the health of the mother and child. They highlight the importance of cooperation between healthcare facilities and research institutions, including the Pasteur Center in Cameroon.

The Institut Pasteur has an ambitious international policy. Its Department of International Affairs is responsible for running and promoting the Institut Pasteur International Network, but also for developing new institutional and/or scientific partnerships to address global challenges in human health and research.

2016 international highlights

January

THE INSTITUT PASTEUR IN FRENCH GUIANA PUBLISHES THE FIRST COMPLETE GENOME SEQUENCE OF THE ZIKA VIRUS CIRCULATING IN THE AMERICAS

❶ After confirming the first cases of infection in Suriname and French Guiana in November 2015, the Institut Pasteur in French Guiana publishes an article in the journal *The Lancet* reporting the complete genome sequence of the Zika virus, responsible for the unprecedented epidemic sweeping through the Americas. The findings demonstrate almost complete homology between this virus and the strains that caused the epidemic in the Pacific in 2013 and 2014.

PASTEUR INTERNATIONAL NETWORK ASSOCIATION BECOMES AN NGO IN OFFICIAL RELATIONS WITH WHO

❷ The admission of the Pasteur International Network Association into official relations with the World Health Organization (WHO) in January 2016 will strengthen cooperation between the Institut Pasteur International Network and the United Nations health agency.

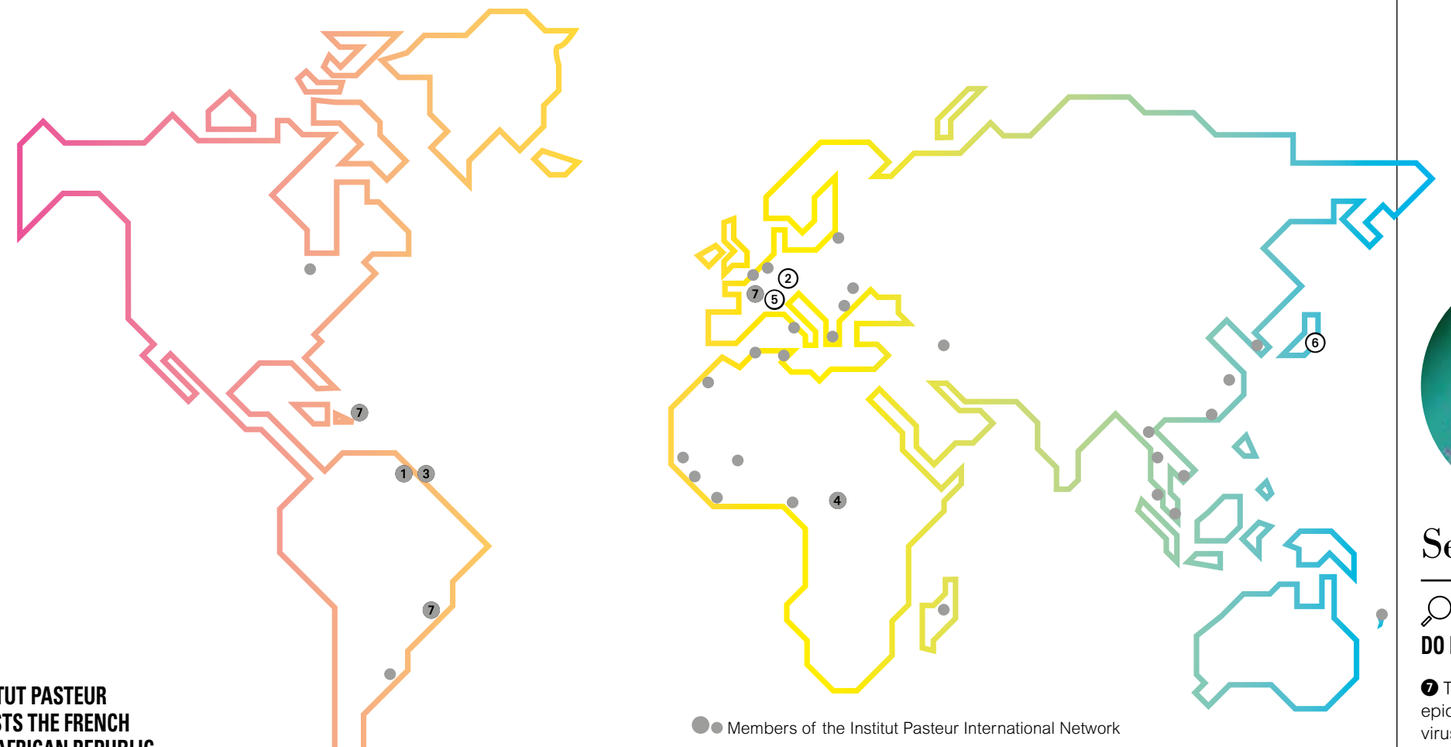
May

THE INSTITUT PASTEUR IN BANGUI HOSTS THE FRENCH AND CENTRAL AFRICAN REPUBLIC PRESIDENTS

❹ On a visit to the Central African Republic capital on May 13, French President François Hollande visits the Institut Pasteur in Bangui with his Central African counterpart, President Faustin-Archange Touadéra. Despite the successive political crises and civil wars that have gripped the country, the Institut Pasteur in Bangui has successfully fulfilled its role among the Central African population.

FRAMEWORK COOPERATION AGREEMENT BETWEEN CNES AND THE INSTITUT PASTEUR

❸ The Institut Pasteur and CNES sign a five-year framework cooperation agreement to encourage the development of projects using space technologies in biomedical research, especially in French Guiana.



Members of the Institut Pasteur International Network

June

COUNCIL OF DIRECTORS OF THE INSTITUT PASTEUR INTERNATIONAL NETWORK

❺ The directors of every member institute of the Institut Pasteur International Network meet at the Château des Ravatys from June 22 to 24, to discuss the major areas for network development.

CREATION OF THE PASTEUR JAPAN FOUNDATION

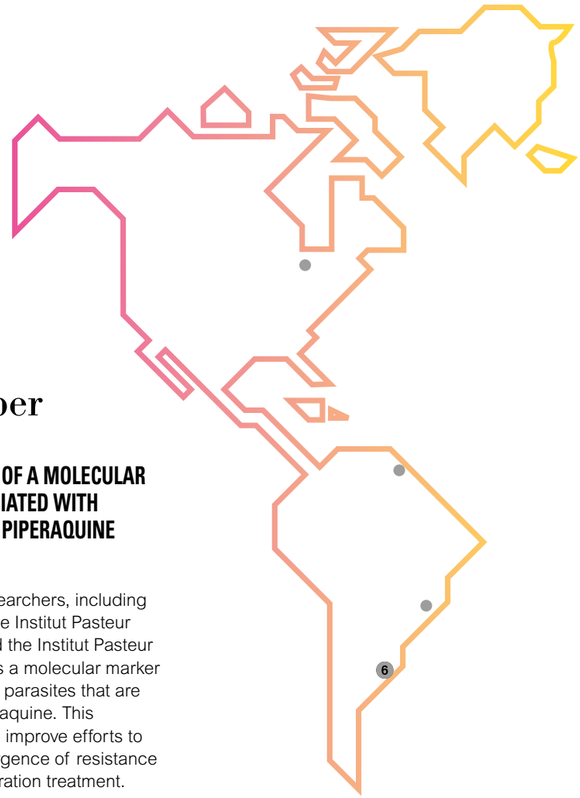
❻ On June 15, the Pasteur Japan Foundation is officially set up, replacing the Association Pasteur-Japon. The aim of this new Tokyo-based foundation is to support research and exchange programs for scientists with the aim of boosting cooperation between the Japanese scientific community and the Institut Pasteur International Network.

September

CULEX MOSQUITOES DO NOT SPREAD THE ZIKA VIRUS

❼ To explain the scale of the Zika epidemic and the speed at which the virus invaded the American continent, scientists put forward the theory that it might be transmitted by other mosquitoes than those from the *Aedes* genus. A study carried out by the Institut Pasteur, the Institut Pasteur in Guadeloupe and FioCruz rules out mosquitoes from the *Culex* genus – widespread in human environments – by demonstrating that these mosquitoes are incapable of spreading the Zika virus.

Discovery | Institutional | Award/Appointment | Event | Scientific event | Anniversary



Members of the Institut Pasteur International Network

October

AVELIN FOBANG AGHOKENG RECEIVES THE DEDONDER CLAYTON AWARD

❶ Dr. Avelin Fobang Aghokeng, a scientist at the Research Institute for Development (IRD) in Cameroon, wins the 2015 Dedonder Clayton Award for his research on a "Test & Treat" approach to deal with HIV infection. This annual award is given by the Institut Pasteur to scientists in Africa and Asia in recognition of the quality of their research in the field of HIV/AIDS and related diseases.

November

DISCOVERY OF A MOLECULAR MARKER ASSOCIATED WITH RESISTANCE TO PIPERAQUINE TREATMENT

❷ A team of researchers, including scientists from the Institut Pasteur in Cambodia and the Institut Pasteur in Paris, identifies a molecular marker to detect malaria parasites that are resistant to piperaquine. This discovery should improve efforts to monitor the emergence of resistance to this next-generation treatment.

AGREEMENT WITH KYOTO UNIVERSITY TO SET UP AN INTERNATIONAL JOINT UNIT

❸ The first international joint research unit is set up between the Institut Pasteur in Paris and Kyoto University. The scientists involved in the unit will work on immune response to the influenza vaccine.

2016 INTERNATIONAL NETWORK SYMPOSIUM

❹ The third Symposium of the Institut Pasteur International Network, this year focusing on biomarkers, is held from November 29 to December 2 on the Institut Pasteur campus. The Symposium attracts more than 350 participants. Seventy speakers take to the floor and more than 150 posters are presented, demonstrating the dynamism of the International Network and the quality of the research it produces.

FIRST STONE LAID FOR THE INSTITUT PASTEUR IN GUINEA

❺ On November 11, the President of the Republic of Guinea lays the first stone of the Institut Pasteur in Guinea. This event marks the official start of construction work, with the new building scheduled for completion in 2018. The mission of the Institut Pasteur in Guinea, set up in October 2015, will be to respond to epidemic emergencies and contribute to monitoring and research on infectious diseases in association with laboratories across the region.

December

10TH ANNIVERSARY OF THE INSTITUT PASTEUR IN MONTEVIDEO

❻ The Institut Pasteur in Montevideo celebrates its 10th anniversary. With around a hundred researchers, this institute has become a leading regional center for research and technology.

CREATION OF THREE NEW INTERNATIONAL JOINT UNITS IN THE INTERNATIONAL NETWORK

❼ To promote research cooperation within the network, three international joint research units are set up with: the Institut Pasteur in Cambodia on malaria, the Institut Pasteur in Montevideo on leptospirosis and the Institut Pasteur of Shanghai on leishmaniasis.

Discovery Institutional Award/Appointment Event Scientific event Anniversary

PASTEURIANS

"For us, being Pasteurian runs in the family!"

Georges Canetti dedicated his life to his tuberculosis research at the Institut Pasteur. His brothers were Elias Canetti, laureate of the Nobel Prize in Literature, and Jacques Canetti, the famous artistic director who devoted his work to French *chanson*. *"Our uncle, Georges, was always the first to read Elias' work and the first to listen to Jacques' music"*, explains Jacques' daughter Françoise Canetti. *"He maintained the bond among the three brothers."* Elias' daughter, Johanna, points out that *"the brothers were all involved in research in one way or another, whether it was through fighting disease, searching for new singing talents or seeking to encapsulate the era and society in literature."* So for Johanna, Françoise and her brother, Bernard, it seemed only logical to come together as a family to support research. As Bernard concludes, *"What better way for our family to keep the bond between our parents and our uncle alive than by supporting the Institut Pasteur?"*

JOHANNA CANETTI
(on the left), daughter of Elias Canetti, writer and laureate of the Nobel Prize in Literature

FRANÇOISE AND BERNARD CANETTI
(on the right), children of Jacques Canetti, music producer, director and founder of the Trois Baudets theater

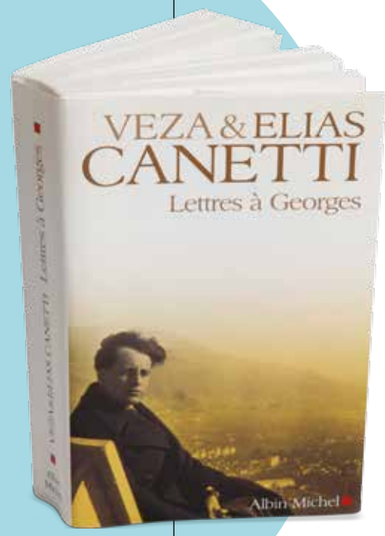
Our resources

As a foundation officially recognized for charitable status, the Institut Pasteur enjoys a unique economic balance that enables it to adopt an independent, open and responsive approach in its research. The Institut Pasteur is only able to accomplish its mission and keep fighting against global threats to human health thanks to the concerted efforts and long-standing commitment of the Pasteurian community – employees, donors, patients, teaching staff and students.

PASTEURIAN EMBLEMS

"This correspondence among the Canetti brothers was what inspired us to support the Institut Pasteur."

The Georges, Jacques and Elias Canetti Award was set up in 2006 after Françoise Canetti discovered 158 letters exchanged by the three brothers, which were donated to the Institut Pasteur. This correspondence was reproduced in the book *Lettres à Georges* (Letters to Georges), published by Albin Michel in 2009 and translated into more than 30 languages. The book pays tribute to a great Pasteurian, Prof. Georges Canetti, and illustrates the close bonds among the three brothers, each of whom enjoyed an outstanding career in his field. It inspired the children of Elias and Jacques *(see photo opposite)* to set up this prize, entirely funded by their family and friends, which for the past 12 years has rewarded the work of scientists involved in research on infectious diseases, especially tuberculosis*.



** 2016 Laureate: Laleh Majlessi, for her research on tuberculosis.*
See all laureates at www.pasteur.fr

Financing structure

€319.5 M
Current income in 2016

€87.5 M
Research contracts and agreements **27.5%**
€55.5 M
Annual income
€32.0 M
Carry-over of unused income from previous years

€35.6 M
Industrial revenue **11.2%**
€32.1 M
Royalties
€3.5 M
R&D contracts, expert assessments and consulting contracts

€16.5 M
Sales and services **5.2%**
€4.9 M
Medical Center
€5.0 M
Activities for network institutes
€6.6 M
Sales, services and other products

€139.6 M
Revenue from own activities

43.7%[1]

€75.3 M
Public gifts & donations **23.6%**
€43.2 M
Donations and sponsorship
€0.7 M
Apprenticeship tax
€31.4 M
Legacies

€39.6 M
Revenues from assets **12.4%**
€6.9 M
Revenues from assets
€32.7 M
Financial revenue

€114.9 M
Public gifts & donations and revenues from assets

36.0%[1]

€54.0 M
French Ministry of Research

€3.3 M
Santé Publique France

€57.3 M
Government contributions

17.9%

€7.7 M

€7.7 M
Other current revenue (including a €0.7 M contribution from institutions outside mainland France)

2.4%

1. The values and percentages include the carry-over of unused income from previous years.

REVENUE FROM OWN ACTIVITIES

Research contracts and agreements
Overall, research contracts and agreements (accounting for €87.5 M and 27.5% of income) rose by €5.4 M in relation to 2015. This rise was due to both French public research contracts and other French or foreign (non-EU) private contracts. We witnessed a rise in funding from both French and international private funding bodies, and from prestigious ERC (European Research Council) contracts won in 2015, despite a decline in European contracts in general.

Industrial revenue
The variation in royalties recorded is entirely due to the fall in revenue from patent license agreements, which amounted to €21.3 M, compared with €27.5 M in 2015. The details of the main revenue per license family is as follows:
- Diagnostics (€17.3 M / -€0.6 M): this license category which accounts for 81% of patent royalties, was stable compared with 2015. The marked decline for a license with one industrialist was offset by an adjustment to 2015 revenue thanks to a license with the NIH;
- Therapeutics: this license category, with revenue of €1.5 M (-€2.6 M), recorded a significant fall in two major contracts;
- Vaccines (€1.9 M / -€2.5 M): this license category recorded a loss due to the end of the resolution of a litigation matter with an industrialist in 2015.
Revenue from brand license agreements was stable at €10.8 M.

Contracts signed with industrialists
(€3.5 M), related to research & development or expert assessments by scientists, were down €2.7 M in relation to 2015. This fall, amounting to €2.1 M, resulted from a decline in the carry-over of income from future commitments.

Sales and services
Sales and services (€16.5 M, accounting for 5.2% of income) include public health activities conducted at the Medical Center, services provided to network institutes, scientific services and other various products derived notably from operation of our infrastructures.

PUBLIC GIFTS & DONATIONS AND REVENUES FROM ASSETS

Public gifts & donations (€75.3 M, accounting for 23.6% of income) include all donations and legacies recorded as operating income, and apprenticeship tax. The contribution of public gifts and donations to the Institut Pasteur's current income is generally up by €11.7 M in relation to 2015 (+ €6.6 M for legacies and + €5.1 M for donations, whereas apprenticeship tax is down €0.7 M).
Revenues from assets (€39.6 M, accounting for 12.4% of income) include current financial revenue, gross rent and dividends from income property, and agricultural revenue from estates registered among the Institut Pasteur's assets. Rent received for all income property showed a slight decrease (-€0.5 M), whereas financial revenue rose by €4.6 M.

GOVERNMENT CONTRIBUTIONS

These are made up of the grants from the French Ministry of Research and Santé Publique France, which contribute to National Reference Center activity funding.

OTHER INCOME

This item includes recovery of provisions and transfer of charges.

Financial statements

€319.6 M
Current expenses in 2016

€140.3 M
Staff expenses

€99.0 M
Operating costs

€26.8 M
Depreciation

€52.8 M
Provisions and commitments to be achieved

€0.7 M
Financial costs

In 2016, the operating deficit grew by €5.0 M compared with 2016, reaching -€32.1 M. The financial result (€32.0 M), comprising income from short- and long-term investments, enabled us to balance the current result for the financial year. Exceptional items bring the Institut Pasteur's net result to €7.4 M.

Current operations
Current revenue increased by 2.0% compared with 2015. The highest rises were recorded on research contracts and support from our donors.
On the other hand, government contributions, which remain key to balancing the Institut Pasteur's current result, and industrial income, were down.
Current expenditure was up by 2.1% from 2015, owing to the implementation of the 2014-2018 strategic plan. This plan is designed to increase the Institut Pasteur's attractiveness by strengthening and developing its technological platforms, its bioinformatics activities, cooperation with the 33 institutes in the Institut Pasteur International Network and with clinicians, and business development. As in 2015, the Institut Pasteur's social assignments account for 82.3% of total employment for the financial year reported in the profit-and-loss account (*Use of resources* statement presented in the *Accounts – Institut Pasteur Financial Report* appendix), with the remaining 17.7% earmarked for fundraising to the general public and operating expenditure.

Exceptional items
Exceptional operations comprise both a gift component (donations and legacies for the share exceeding €300,000) and a financial component (net valuation of financial assets resulting from capital gains or losses, realized or latent, based on the performance of the portfolio, with the balance of capital gains generated always exceeding the capital losses realized).
In 2016, the donations and legacies recorded as exceptional income amounted to €10.7 M. The financial component showed a negative balance of €1.6 M, affected by the poor performance of financial investments over the year.
In addition to these two recurring items, exceptional income for 2016 also includes €2.8 M linked to a contribution (due to actuarial impacts) to provisions for pension liabilities.

Net result
The Institut Pasteur's net result at year-end 2016 was €7.4 M.

Sustainable development

Preserving the environment

The Institut Pasteur has adopted a new strategy for managing its green spaces to promote biodiversity in Paris, and has drawn up an action plan to reduce energy consumption.

Managing green spaces

The Institut Pasteur selected the company Vertdéco to manage its natural heritage. Vertdéco is one of just two landscaping companies in France to have been recognized as “Exemplary”, the highest level of certification awarded under AFAQ 26000, which measures companies’ contributions to sustainable development. Since 2013, Vertdéco has also been recognized by the French government for its use of gardening methods that develop biodiversity, under the national biodiversity strategy. The Institut Pasteur and Vertdéco have been working together to reduce environmental impact and disturbances for local residents.

• **The introduction of a range of electrical gardening equipment** including hedge trimmers and pruners (soon also: lawn mowers) has significantly reduced noise pollution for local residents. Using an electric leaf blower instead of a gas-powered model, for example, reduces the noise generated by 20dB.

• **Turning natural heritage into “living” areas.** The Institut Pasteur’s green spaces have been divided into different types, with the aim of providing the campus community with pleasant outdoor areas and also initiating a process of natural soil enrichment without using chemical pest control solutions. Most of the organic waste generated (from pruning, for example) is reused in flower beds as mulch or ground cover.

• **The Institut Pasteur has installed its first bird box,** known as a “lifebox”, on campus. Lifeboxes are a concept developed by Vertdéco to encourage wildlife in cities and gardens. Developed with the Greater Paris Ornithological Center (CORIF), these nest boxes are a natural way of introducing wildlife into gardens. By making a small effort to provide a home for nesting birds, the Institut Pasteur can greatly benefit the ecosystem. A small group of staff members have received training at the Institut Pasteur to learn how to manage this nest box and find out about the ecology of urban birds.

Energy consumption

Following the energy audit of the Institut Pasteur’s buildings that was launched in 2015, it has drawn up an initial action plan to optimize its energy consumption. The plan will lead to investments in 2017, to optimize the configuration of its air handling units, especially at times when the premises are unoccupied. Estimates suggest that this will save 144MWh in electricity consumption and 1,044MWh in steam, resulting in total savings of around 2%. Other solutions are being investigated to continue optimizing the Institut Pasteur’s energy consumption.

138.26 t
of materials recycled

Recycling

0.87 t
of aluminum cans

71.59 t
of paper and cardboard

2.46 t
of glass

14.19 t
of plastic bottles and tip boxes[1]

9.51 t
of polystyrene

1 - Tip boxes are part of a pilot scheme involving around forty units that will be extended to the entire campus if successful.

Reuse

36.34 t
of pallets

22.42 t
sold for reuse after inspection

13.92 t
sold for grinding and energy production

Other recovery

3.3 t
of dried organic waste

A MEMBER OF THE “RESPONSIBLE CAMPUS” NETWORK

Since 2016, the Institut Pasteur has been a member of “Responsible Campuses”, the first French network of universities and higher education institutions committed to sustainable development, set up by the agency “Graines de Changement” in 2006. All members contribute to a national platform for dialog where they can exchange best practices, coordinate their efforts and communicate about effective strategies for environmentally responsible campuses. The first major event for the Institut Pasteur as a member of this network was in November 2016, when it contributed to a discussion on waste by sharing the success of some of the procedures introduced on campus (e.g. separating organic waste).

Human resources

Providing support and career guidance for Institut Pasteur staff

In 2016, the Human Resources Department continued to restructure its activities and particularly strengthened its role in career development, a vital part of the Institut Pasteur's strategic plan.

Following the initiatives launched in connection with the Institut Pasteur's strategic plan, this year the Human Resources Department implemented and consolidated a number of projects with the aim of modernizing and simplifying HR practices and offering new services to the Institut Pasteur community.

• **A new Jobs and Skills Guide,** developed following negotiations with management and unions, has now been incorporated into the Institut Pasteur's company agreement. This guide reflects the discussions on forward-looking management of jobs and skills (GPEC) launched in 2015 to strengthen career development. Since June 1, 2016, each staff member has been positioned within a category and professional sector, and been assigned a general job profile.

• **The new annual appraisal system** for all Institut Pasteur staff members put this guide into practice, and it also served as a basis for career reviews. This new approach provided a framework for discussions between managers and employees, giving them the opportunity to make training and career development requests and review tasks and skills. This year, the appraisal campaign went digital following the rollout of the first Career Portal module. The online solution reflects the department's efforts to simplify and modernize its activities to better meet the needs of the campus community. Institut Pasteur staff can use the tool to prepare their annual appraisals and career development reviews, consult the training catalog, make training requests and sign up for training sessions, browse the Jobs and Skills Guide and find out about the many job profiles at the Institut Pasteur.

• **The HR Department set up operational HR teams** for each department to optimize its organizational and working procedures. These teams, led by the local HR contacts, are composed of a specific HR contact for each field (administrative management, training and recruitment) and are designed to meet staff needs.

• **The MAASCC, who provide welcome sessions, support and career development structure for scientists,** set up a personalized career guidance program geared towards scientists. In 2016, 172 scientists were given a career interview: 106 PhD students and postdoctoral fellows, and 66 state-employed scientists and engineers in connection with the Careers Committee (in cooperation with the Scientific Careers Department). The Careers Committee also facilitated training for 20 scientists and engineers, internal transfers for 13, and a change of career for three.

The Institut Pasteur alumni community went from strength to strength in 2016. The first meeting, held on June 28, was attended by more than 80 participants, who discussed how to lay the foundations of the community.
On another note, the Institut Pasteur also maintained its commitment to employee health, especially the prevention of musculoskeletal disorders (MSDs), holding sessions on the day-to-day task of pipetting.

Finally, this year for the first time, recognition of the collective and individual efforts of Institut Pasteur staff led to the payment of an individual profit-sharing bonus in respect of the financial year 2015 to those employees concerned. This scheme rewards staff commitment to the scientific and economic development of the Institut Pasteur.

On campus

2,110 *IP employees*

470 *OREX employees* from external research organizations

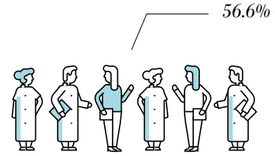
179 *interns*

Of the **2,580** *people working on campus* (excluding interns):

- *58.1% senior scientists and health officers*
- *29.9% non-managerial staff*
- *12% administrative and technical managers*

Recruitment

401 *people hired in 2016*



56.6% women

18% under the age of 25

49.1% scientists (researchers and engineers)

Diversity

59.4% *of the IP staff are women*

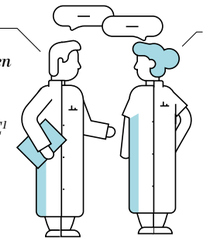
43 *the average age of IP employees*

68 *nationalities on campus*

Career support and development

68% *of scientists on fixed-term contracts, who received guidance, found a job*

355 *scientists given support and guidance by the MAASCC[1] since 2014*

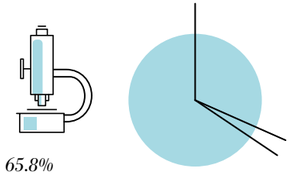


- *58% in the private sector*
- *42% in academia*

1 - Welcome, support and career development structure for scientists

Professional categories at the Institut Pasteur

Of the 2,110 IP employees:



65.8% in the Research category (research, research engineering, clinical research)

31.4% in the Administrative and Technical category

2.8% in the Health category (Institut Pasteur Medical Center, occupational health)

Source: 2016 Social data report

Donations, sponsorship and legacies
A big thank you

In 2016, nearly a third of the Institut Pasteur's resources came directly from individual and corporate donations and legacies.
This support keeps the Institut Pasteur at the cutting edge.

"Thank you for your season's greetings at the start of the year. I remain firmly committed to the Institut Pasteur and its research. You can count on my continued support in 2017, and my loyalty to your outstanding institution. Many thanks."
CD, donor

In 2016, the Institut Pasteur received financial support from almost 220,000 individuals. The funds raised through the generosity of these individuals, as well as our partner companies and foundations, will enable the Institut Pasteur's scientists to continue their vital work and explore new avenues for research. In 2016, we received €29.9M in legacies and donations.

24,000 of our supporters chose to set up direct debits, enabling them to spread their donations over the entire year; 2016 attracted over 57,000 new Institut Pasteur donors.

In 2016, the Institut Pasteur celebrated ten years of Pasteurdon with a strong media campaign, which included a launch event, campus open days, social media, DTTV channels and radio stations, the Pasteur.fr website, posters, press coverage, a special short telephone number, mailshots and email campaigns.

Donations from companies and foundations

For the first time, and in honor of this tenth edition of Pasteurdon, the climax of the "Vivons Vélo" cycling program was a mass cycle ride that finished at the Institut Pasteur. This event, organized by AG2R La Mondiale, raised €55,280 in aid of the Institut Pasteur.

"Human life is at the heart of the Roch-Les Mousquetaires Foundation's priorities. Supporting research teams, in particular those teams ensuring progress in food safety, is our way of backing actions that contribute to the well-being of each and every one of us."
Marie-Thérèse Le Roch, President

The year was also marked by the third edition of Défi Run Assu 2000, an original obstacle course race organized by Assu 2000 and Move Publishing Events in a number of French cities. Over 10,000 runners took part, with over €40,000 raised for the Institut Pasteur.

The Institut Pasteur has a productive and constantly evolving partnership with pharmaceuticals company, Sanofi. 2016 saw the fifth edition of the Sanofi-Institut Pasteur Awards, which are given to scientists in recognition of innovative projects in life sciences and biomedical research. The Sanofi Group also supports strategic Institut Pasteur programs, such as the INCEPTION project, a new integrative biology program to study the emergence of diseases in the population at large and in individuals.

The Roch-Les Mousquetaires Foundation remains a loyal partner, and stood by its firm commitment to the Institut Pasteur's scientists. It gave generous funding to two research programs on food safety and, as part of Pasteurdon, organized the sale of a range of charity-linked products in two store chains in the Les Mousquetaires group, Intermarché and Bricomarché.

Donations from companies and foundations increase a total of nearly €8 M.
Lastly, efforts to enhance our international visibility continued to bear fruit in 2016, with nearly €2.7 M

raised and donated in both Europe and the United States. This achievement was due to our new, more ambitious international fundraising approach, particularly in the United States. In 2016, a fundraising foundation was set up in Japan and the existing association in Hong Kong was overhauled to facilitate the rollout of fundraising campaigns.

We would like to express our heartfelt thanks to all our sponsors and donors for their generosity and continued support. Their contributions are our most valuable asset as we strive to advance knowledge and make significant progress in biomedical research.

Legacies increasingly shared
2016 saw 123 new legacies and gifts submitted to the Board of Directors, representing a 20% increase, or €43.1m. The Institut Pasteur shares most of the legacies bequeathed to it with other institutions.
Life insurance policies continued to represent a leading source of recurring income, and remained stable in 2016, raising €10m. These policies, like legacies and gifts, offer favorable tax arrangements in that they are exempt from transfer duties.

Quality procedures
Renewal of certification that is one of a kind. The Institut Pasteur's Legacies and Real Estate Assets Management Office is the only department of its kind in France to have applied quality procedures to all its activities. Following its annual audit, AFNOR Certification renewed the Institut Pasteur's ISO 9001 certification for 2016.

Communications activities
An extensive promotional campaign for legacies and gifts was launched in 2016 on radio stations and TV channels, and in the mainstream and legal press, to raise awareness of legacies and donations. These funding methods have played such an important role in the Institut Pasteur's development over the years.
There has been a significant rise in the number of people asking for information about legacies, life insurance and donations, as well as gift notifications. Questions concerning more innovative schemes such as the temporary transfer of usufruct rights and posthumous gifts have also seen an increase. In order to process all these new contracts, the Legacies and Real Estate Assets Management Office currently employs two dedicated staff members in charge of legator relations. Those interested in giving to the Institut Pasteur can contact these staff members for advice and guidance or speak to one of the office's three legal experts.
Our six-monthly "Legacies and gifts newsletter" is our key means of communicating with legators, with each issue covering a specific aspect of gifts, legacies, and life insurance policies. This publication generates substantial feedback and a large number of personal testimonials.

The think tank on philanthropic trusts, which was set up by the Institut Pasteur following the success of its first Conference on Philanthropic Trusts in 2009, developed its activities and issued a series of opinions.
The experts in this think tank include notaries, lawyers, and bankers.
To date, it is the only platform where experts from a variety of disciplines can share their thoughts and ideas on questions relating to generosity and philanthropy.

"Your research into microbiota is of particular interest to me, and I am sure that it will lead to significant and far-reaching progress. Long may this continue!"
FC, donor

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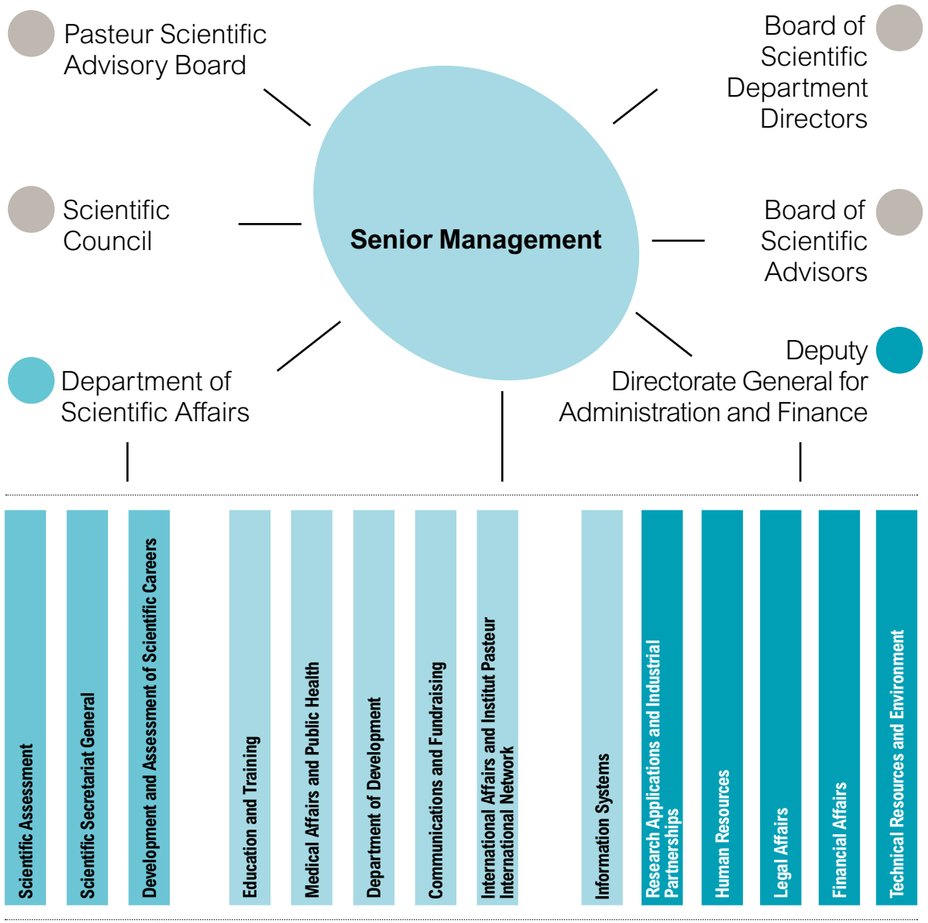

Board of Directors

The Board of Directors makes decisions on all Institut Pasteur matters. It gives its opinion on the strategic policies proposed by the President, votes on budgets, and approves the accounts.

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Head of Research at Inserm and Director of the École Normale Supérieure Institute of Biology

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MARIE-NOËLLE UNGEHEUER
Head of the Clinical Investigation and Access to BioResources Platform (ICAReB)

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Director-General for Health, French Ministry of Social Affairs and Health

Management of the Institut Pasteur

The management team sets the Institut Pasteur's overall strategy. The team is supported in its task by the Scientific Council and the Executive Board to ensure the effective implementation of the strategy.

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President

FRANÇOIS ROMANEIX
Senior Executive Vice-President Administration and Finance

RÉGINE BORGEOT
Vice-President Legal Affairs

ISABELLE BUCKLE
Vice-President Research Applications and Industrial Relations

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PIERRE LEGRAIN
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JEAN-CHRISTOPHE OLIVO-MARIN
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MONICA SALA
Executive Director for Education

PATRICK TRIEU-CUOT
Vice-President Scientific Careers

Scientific Council

The Scientific Council advises the President of the Institut Pasteur and occasionally the Board of Directors on all issues relating to scientific policy, organization, and research and teaching programs.
The Council is consulted on all research and teaching unit creation, closure and merger decisions.

ELECTED PASTEURIAN MEMBERS

ANDRÉS ALCOVER
Head of the Lymphocyte Cell Biology Unit

AZIZ EL AMRAOUI
Secretary
Head of Laboratory in the Genetics and Physiology of Hearing Unit

JEAN-MARC GHIGO
Head of the Genetics of Biofilms Unit

MICHAELA MÜLLER-TRUTWIN
Head of the HIV, Inflammation and Persistence Unit

APPOINTED PASTEURIAN MEMBERS

CARMEN BUCHRIESER
President
Head of the Biology of Intracellular Bacteria Unit

PASCALE COSSART
Head of the Bacteria-Cell Interactions Unit

EXTERNAL MEMBERS

CHRISTOPHE BENOIST
Professor, Harvard Medical School, Department of Microbiology and Immunology, Division of Immunology, Boston, USA

ARTURO CASADEVALL
Professor, Microbiology and Immunology Department, Albert Einstein College of Medicine, New York, USA

VICTOR DE LORENZO
Professor, Centro Nacional de Biotecnologia (CSIC), Systems Biology Program, Madrid, Spain

ANGELA GRONENBORN
Professor, Department of Structural Biology, University of Pittsburgh School of Medicine, Pittsburgh, USA

EVA HARRIS
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JULIAN PARKHILL
Professor, Genomics of Bacterial Pathogens, Sanger Institute, Cambridge, UK

CHRISTOPHE ROGIER
Professor, Val-de-Grâce, Central Management of the French Military Health Service, Paris, France

CLAUDIO D. STERN
Professor, Department of Cell & Developmental Biology, University College of London, UK

Erik Orsenna,
Institut Pasteur ambassador

"Receiving a great honor is a wonderful achievement; being worthy of it is an even better one."

MY ACCOUNT

Ambassadors, like everybody else, must be held to account. I was appointed last year. My primary goal was a book, as writing is my personal method of action, my lab bench and my microscope. I had long held a desire to write about the globalization of health issues, and an idea by our President, Christian Bréchot, sparked my immersion into the geopolitics of mosquitoes, how they invaded the planet and their relationship with parasites and humans.

I managed to confirm what we all knew already – that a *ménage à trois* is intense but often deadly. At the same time, from Cayenne to Maripasoula, Dakar and Kédougou, Phnom Penh and the Mekong Delta, I saw evidence of the strength of our network of institutes, from both a research and treatment pespective. As Françoise Barré-Sinoussi has already said, Paris does not have a monopoly over Institut Pasteur activities. Everywhere I went, I met outstanding professors. As you might suppose, a lowly economist such as myself knows nothing about arthropods, and even less about viruses. I started my mission by returning to school.

On my return to France, I was horrified to find our society consumed by the new trends of "post-truth" and "alternative facts", with direct – and sometimes deadly – consequences, for example a refusal to vaccinate. And so I entered the fray, with Jean François Bach by my side. Those interested in the subject can read about our action during the formal ceremony to mark the academic year of the Institut de France and its five Academies. The subject of our debate was risk. This battle against ignorance is as yet in its infancy. The Institut Pasteur's rightful place is at the forefront of this battle.

The last (or perhaps the first) theater of operations is finance. I would be delighted if everyone took an active part in Pasteurdon. Pasteurdon is a vehicle for creating enthusiasm and belief in something many today profess to criticize – which goes by the name of progress. It also highlights the originality of the Institut Pasteur approach, which, let's not forget, draws strength from partnerships but above all from its freedom of action and innovatory stance.

In a nutshell, your ambassador is continuing the crusade, prouder than ever to be part of your team.

By using Cocoon Silk rather than non-recycled paper, the environmental impact was reduced by:

1,647 kg of landfill	**221 kg** of co_2	**2,213 km** travel in an average European car	**62,302 l** of water	**3,500 kWh** of energy	**2,677 kg** of wood

Sources: Carbon footprint data evaluated by Labelia Conseil. Virgin fiber paper data from latest European BREF data.

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