INSTITUT PASTEUR

ACTIVITY IN 2015

Being a scientist today

How the work of a headstrong, visionary scientist continues to inspire 2,500 men and women.

Institut Pasteur

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Our year

Discover the Institut Pasteur throughout the course of 2015 and learn how our vibrant organization tackles the major health challenges facing the world. International cooperation, scientific breakthroughs and knowledge sharing are just some examples of the many roles played by a key stakeholder in today's research landscape.

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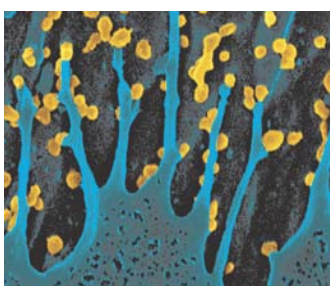
Our missions...

research
health
business development
education
international

On our campus and in our 33 institutes worldwide, there are men and women leading the fight against the diseases that threaten human health.



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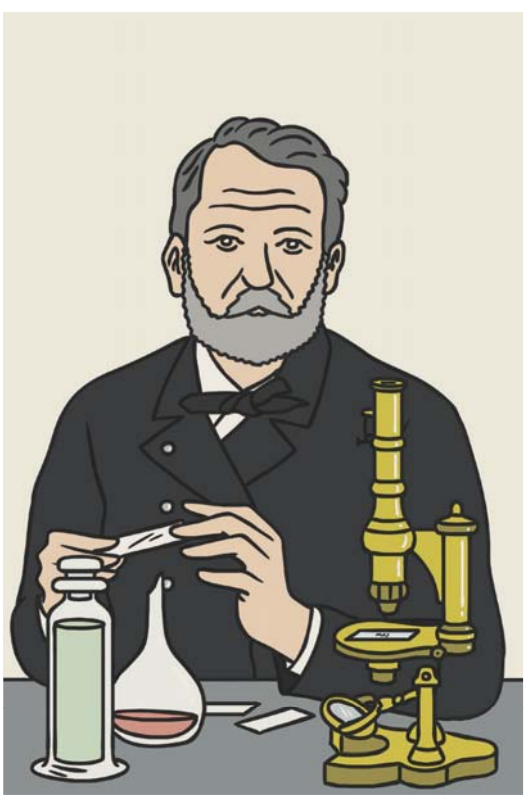
Our resources

The Institut Pasteur's economic model relies on funding from four sources. In 2015 our income amounted to €314 M. Essential activities and services underpin and support the work of our scientists including research applications and industrial relations, partnerships, fundraising and legacies, sustainable development and human resources.



Public gifts and donations help the Institut Pasteur maintain its independence. In 2015, thanks to corporate sponsors, private foundations and individual donors, almost €63.6 M went towards our operating costs.

Being a scientist today

— How the work of a headstrong, visionary scientist continues to inspire 2,500 men and women.


Institut Pasteur

2015 highlights

— Twelve intense months marked by scientific breakthroughs and highlights.

04 June 2015

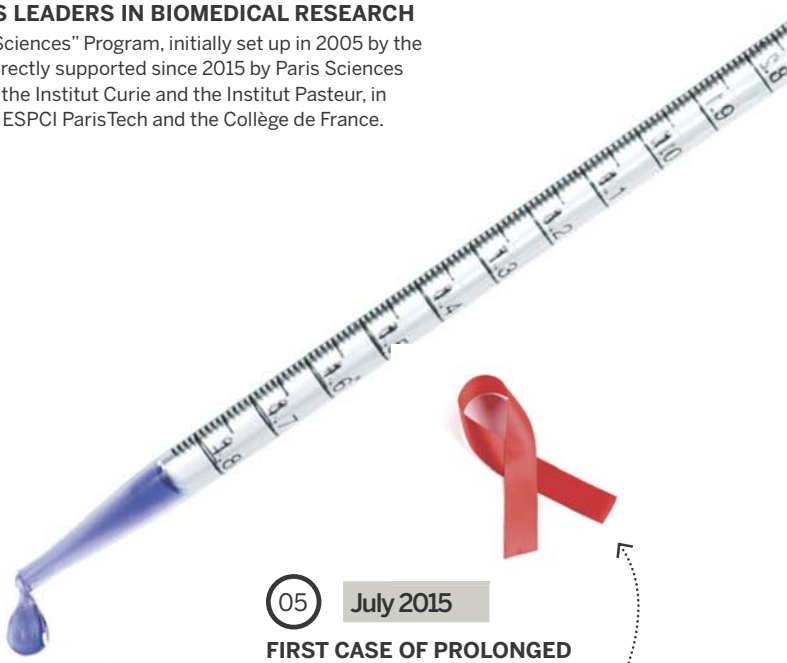
MERS-COV IN SOUTH KOREA: THE INSTITUT PASTEUR SUPPORTS THE RESPONSE

As part of its global health activities, the Institut Pasteur is actively involved in the WHO mission via its Outbreak Investigation Task Force.

03 April 2015

THE INSTITUT PASTEUR TAKES PART IN THE "MÉDECINE-SCIENCES" PROGRAM TO TRAIN TOMORROW'S LEADERS IN BIOMEDICAL RESEARCH

The "Médecine-Sciences" Program, initially set up in 2005 by the ENS, has been directly supported since 2015 by Paris Sciences et Lettres (PSL), the Institut Curie and the Institut Pasteur, in partnership with ESPCI ParisTech and the Collège de France.



02 March 2015

CHAMBÉRY BABIES – *ROUXIELLA CHAMBERIENSIS*, A NEW BACTERIUM IDENTIFIED BY THE INSTITUT PASTEUR

Following the death of three newborns at Chambéry hospital in December 2013, scientists at the Institut Pasteur announce the complete characterization of this previously unknown bacterium.

05 July 2015

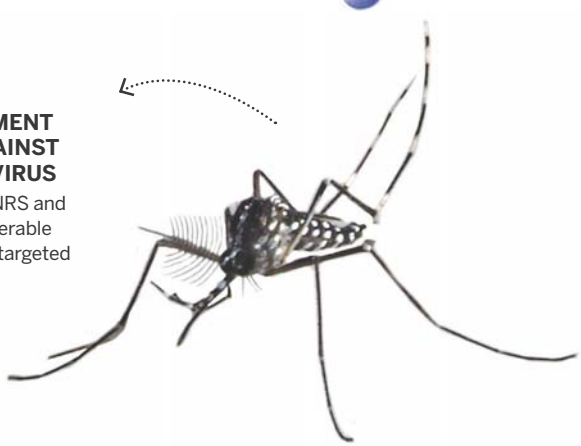
FIRST CASE OF PROLONGED REMISSION (12 YEARS) IN AN HIV-INFECTED CHILD

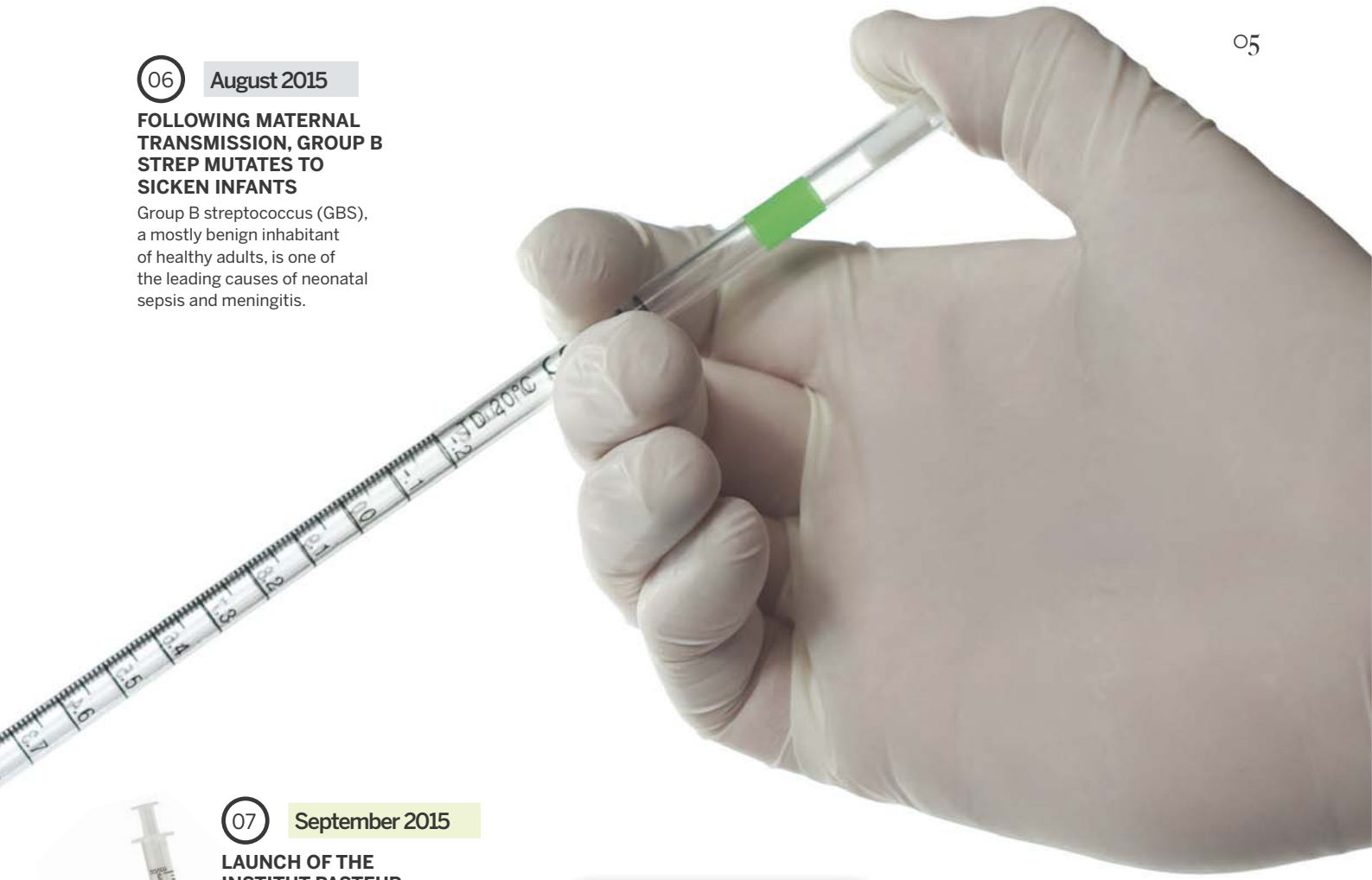
A young woman now aged 18 and a half, who at birth was HIV-infected via mother-to-child transmission, is in virological remission, despite not having taken any antiretroviral therapy for the last 12 years.

01 January 2015

NEW HOPE FOR THE DEVELOPMENT OF AN EFFECTIVE VACCINE AGAINST THE FOUR TYPES OF DENGUE VIRUS

Teams from the Institut Pasteur, the CNRS and Imperial College London identify a vulnerable site on the surface of the dengue virus targeted by broadly neutralizing antibodies.

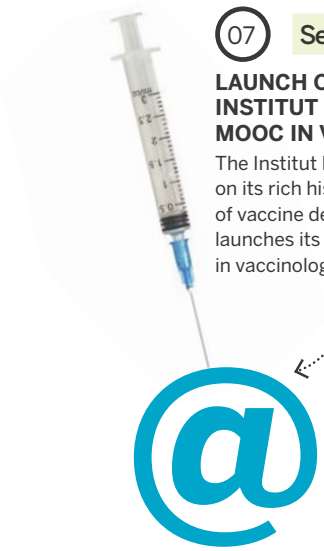




06 August 2015

FOLLOWING MATERNAL TRANSMISSION, GROUP B STREP MUTATES TO SICKEN INFANTS

Group B streptococcus (GBS), a mostly benign inhabitant of healthy adults, is one of the leading causes of neonatal sepsis and meningitis.



07 September 2015

LAUNCH OF THE INSTITUT PASTEUR MOOC IN VACCINOLOGY

The Institut Pasteur, drawing on its rich history in the field of vaccine development, launches its first online course in vaccinology.

08 October 2015

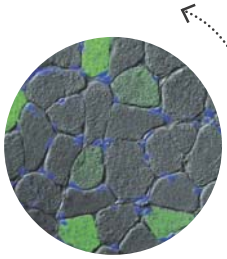
MARISOL TOURAINE OFFICIALLY OPENS ELIGO BIOSCIENCE, A START-UP INCUBATED AT THE INSTITUT PASTEUR

Eligo Bioscience is set up to tackle the major challenge represented by the rise in antibiotic resistance. After raising funds of €2.4 million, the start-up is developing a new generation of smart antibiotics that specifically targets bacteria carrying a resistance or virulence gene.

10 December 2015

SEPSIS: CELL THERAPY TO REPAIR LONG-TERM MUSCLE IMPAIRMENT

Scientists from the Institut Pasteur, Paris Descartes University, Sainte-Anne Hospital, and the CNRS publish a paper proposing a therapeutic approach which has produced initially encouraging results in restoring muscle capacity in animals.



09 November 2015

SAINTE-ANNE HOSPITAL BECOMES THE FIRST INSTITUT PASTEUR AFFILIATED HOSPITAL

An agreement is signed to strengthen relations between the two institutions in the fields of research, training, teaching, and scientific events.

A year spent combating Ebola

— The Ebola epidemic that began in March 2014 in West Africa before spreading throughout Guinea and to Liberia and Sierra Leone infected 28,600 people and claimed 11,300 lives, making it the most severe Ebola outbreak since the virus was first described in 1976. Back in 2014, the Institut Pasteur was already involved in the response, setting up a task force of scientists that was active for the whole of 2015.

From December 2014
For 52 weeks, the Institut Pasteur sends successive teams of volunteers to set up and run the diagnostic laboratory in the Macenta center.

January 23, 2015
Scientists from the Institut Pasteur in Dakar and Paris announce that they have successfully reconstructed the chains of transmission of the Ebola virus, and their context, within the Guinean capital from February to August 2014.

May 22, 2015
The Institut Pasteur and the Institut Pasteur International Network make available the genetic sequences of the virus to support public health efforts to stem the epidemic and to facilitate the development and evaluation of vaccines and diagnostic and therapeutic tools.

June 26, 2015
Sequencing the genome of Ebola virus strains circulating in Guinea allows scientists to retrace the spread of the virus and monitor its evolution in the country where the outbreak started.

September 21, 2015
The memorandum of understanding to set up the Institut Pasteur in Guinea, the 33rd member of the International Network, is signed.

The Institut Pasteur adopted a three-pronged strategy: responding to the emergency epidemic situation in the field by involving teams from the Institut Pasteur in Dakar and setting up a diagnostic laboratory in the Macenta treatment center in the forest region of south-eastern Guinea; improving understanding of the virus by sequencing its genome; and developing new diagnostic tests and vaccine candidates. The first trials of the new diagnostic tests using RT-PCR, including the paper-based test, were carried out at the Macenta center. After 53 weeks working to tackle Ebola, the center officially closed in December 2015. This laboratory was a clear demonstration of the dedication and commitment of the Institut Pasteur and its International Network in the face of this health crisis. During the year in which it was open, 37 volunteers were trained and sent to emergency areas for 4- to 6-week missions. At the first BSL3+ mobile laboratory set up in Guinea, 26 African and 10 European technicians and scientists were also trained in Ebola diagnosis.

Three Ebola virus variants identified in Guinea. In 2015, scientists from the Institut Pasteur in Dakar and Paris, the CNRS, and the University of Sydney sequenced the genome of Ebola virus strains circulating in Guinea. This allowed them to retrace the spread of the virus and monitor its evolution in the country where the outbreak started. This research revealed the co-circulation in Guinea, particularly in the urban regions of the capital and neighboring towns, of three distinct variants of the virus whose mutations were described in an article published in *Nature*. Characterization of the genetic variations of the virus is crucial to ensure the continued efficacy of diagnostic tools and for the development of effective treatments and vaccines.

This research continued with the functional characterization of these variants, particularly their ability to resist treatment and to infect cells in humans or bats, the reservoir for the virus.

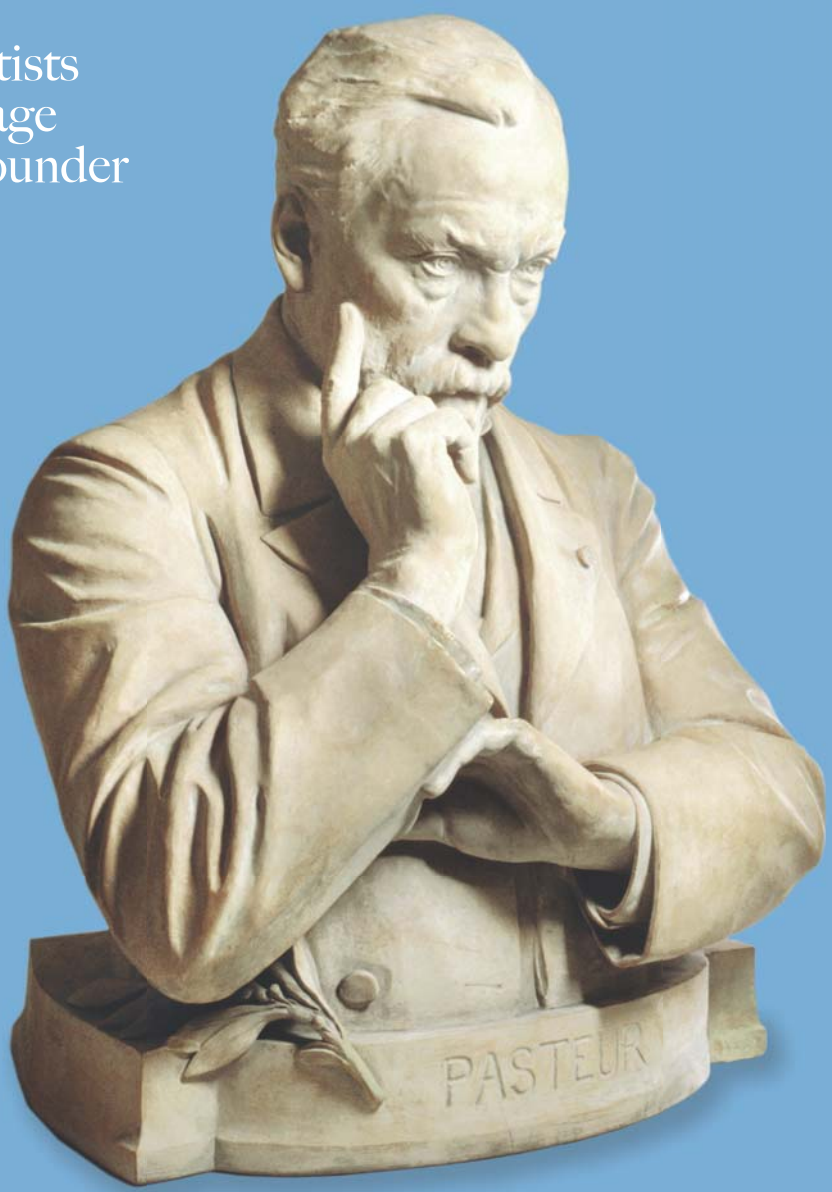
The next-generation sequencing developed for this study is now being used at the Institut Pasteur to research other viruses including dengue, Rift Valley Fever, and Zika.

This laboratory set up in Macenta was a clear demonstration of the dedication and commitment of the Institut Pasteur and its International Network in the face of this health crisis.

A new institute in the International Network. The long-term impact of the Institut Pasteur's work in Guinea will be seen through the activities of the new Institut Pasteur in Guinea, in Conakry. The memorandum of understanding for the new institute was signed in September 2015. This 33rd member of the Institut Pasteur International Network will be closely involved in epidemiological surveillance and emergency response, in research, and in training and supporting Guinean scientists in researching and monitoring infectious diseases.

Awards and appointments

— Our scientists share the heritage and values of founder Louis Pasteur.



People appointed to the rank of professor

Arnaud Fontanet
Head of the Epidemiology of Emerging Diseases Unit, Director of the Center for Global Health

Ana Simoes de Bivar Cumano
Head of the Lymphopoiesis Unit

Chiara Zurzolo
Head of the Membrane Traffic and Pathogenesis Unit

Appointments

Pascale Cossart
Life Secretary of the Science Academy

Chiara Zurzolo
EMBO Member

Noël Tordo
Director of the Institut Pasteur of Guinea

Thomas Bourgeron
Member of the Academia Europaea (Physiology & Medicine Section)

Sandrine Étienne-Manneville
EMBO Member

European Research Council (ERC) Grants

ERC Starting Grants

David Bikard
Head of the Synthetic Biology G5
• CRISPAIR project (Study of the interplay between CRISPR interference and DNA repair pathways towards the development of novel CRISPR tools)

Germano Cerere
Head of the Mechanisms of Epigenetic Inheritance G5
• RNAEPIGEN project (Mechanisms of epigenetic inheritance by short RNAs)

Sven van Teeffelen
Head of the Microbial Morphogenesis and Growth G5
• RCSB project (Regulation of cell size and shape in bacteria)

Nelson Rebola
Dynamic Neuronal Imaging Unit
• SenseNMDA project (Impact of NMDA receptor diversity in sensory information processing)

ERC Consolidator Grants

Jost Enninga
Dynamics of Host-Pathogen Interactions Unit
• EndoSubvert project (Common mechanisms of host membrane trafficking subversion by intracellular pathogens to rupture bacterial containing vacuoles)

Marc Lecuit
Head of the Biology of Infection Unit
• INVADIS project (Microbial invasion and dissemination within the host, mechanisms and effects)

ERC Advanced Grants

Pascale Cossart
Head of the Bacteria-Cell Interactions Unit
• BacCellEpi (Bacterial, cellular and epigenetic factors that control enteropathogenicity)

Artur Scherf
Head of the Biology of Host-Parasite Interactions Unit
• PlasmoSilencing project (Exoribonuclease - mediated degradation of nascent RNA in Malaria Parasites: A Novel Mechanism in Virulence Gene Silencing)

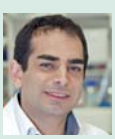
Major scientific awards won by our scientists in 2015

Pierre-Jean Corringer
Head of the Channel Receptors Unit
• Academy of Sciences' Emile Jungfleisch Prize
• Academy of Sciences' biennial Organic Chemistry/ Biochemistry Prize

Lluis Quintana-Murci
Head of the Human Evolutionary Genetics Unit
• Academy of Sciences' Mergier-Bourdeix Prize
• City of Paris' Grand Prix Jean Hamburger

François Schweisguth
Head of the Genetics of Drosophila Development Unit
• Academy of Sciences' Charles-Léopold Mayer Prize

Professor Felix Rey
Head of the Structural Virology Unit
• Pasteur-Weizmann/Servier Prize



Philippe Bousso
Head of the Dynamics of Immune Responses Unit
• French National Academy of Medicine Prize

Mélanie Hamon
Research Associate, Bacteria-Cell Interactions Unit
• Deschiens Prize

Philippe Sansonetti
Head of the Molecular Microbial Pathogenesis Unit
• City of Paris' Grand Prix Claude Bernard

Claude Parsot
Director of Research at the Institut Pasteur, Molecular Microbial Pathogenesis Unit
• Georges, Jacques and Elias Canetti Prize

Arnaud Fontanet
Head of the Epidemiology of Emerging Diseases Unit, Director of the Center for Global Health
• Duquesne Prize

Thomas Bourgeron
Head of the Human Genetics and Cognitive Functions Unit
• Fondation Ipsen Neuronal Plasticity Prize

Marco Vignuzzi
Head of the Viral Populations and Pathogenesis Unit
• Sanofi – Institut Pasteur National Junior Award

Kiri Couchman
Postdoctoral fellow in the Dynamic Neuronal Imaging Unit
• L'Oréal Foundation's L'Oréal-UNESCO For Women in Science Grant

Sandrine Étienne-Manneville
Head of the Cell Polarity, Migration and Cancer Unit
• 2015 Pasteur Vallery-Radot Prize

Fabrice Chrétien
Head of the Human Histopathology and Animal Models Unit
• 2015 Pasteur Vallery-Radot Prize

Sandra Pellegrini
Head of the Cytokine Signaling Unit
• Fondation de France's Thérèse Lebrasseur Prize

Artur Scherf
Head of the Biology of Host-Parasite Interactions Unit
• Fondation de France's George Zermati Prize

Morgane Besson
Integrative Neurobiology of Cholinergic Systems Unit
• Fondation de France's Gilbert Lagrue Prize

Jérôme Gros
Group Leader in the Department of Developmental and Stem Cell Biology
• Human Frontier Science Program winner

Nolwenn Jouvenet
Team Leader in the Viral Genomics and Vaccination Unit
• European Molecular Biology Organization (EMBO) Young Investigator Prize

Romain Koszul
Head of the Spatial Regulation of Genomes G5
• European Molecular Biology Organization (EMBO) Young Investigator Prize

Elisa Gomez Perdiguero
Head of the Macrophages and Endothelial Cells G5
• Claude Paoletti Prize

International Network

Dr Amadou Sall
Institut Pasteur in Dakar
• 2015 UNESCO-Equatorial Guinea International Prize for Research in the Life Sciences

Anne Lavergne
Institut Pasteur in French Guiana
• Robert Deschiens Prize from the Society of Exotic Pathology

Didier Ménard
Institut Pasteur in Cambodia
• Eloi Collery Prize

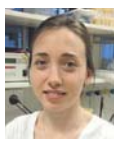
Janin Nouhin
Institut Pasteur in Cambodia
Institut Pasteur International Network's Young Scientist Prize

Dr Hanene Chelbi
Laboratory of Medical Parasitology, Biotechnology and Biomolecules, Institut Pasteur in Tunis
• UNESCO-MARS 3rd Prize for Best African Researcher (Merck Africa Research Summit)

New five-year groups and units

Five-year groups set up in 2015

Jessica Quintin
Immunology of Fungal Infections



Giulia Manina
Microbial Individuality and Infection

Pauline Speder
Brain Plasticity in Response to the Environment

Germano Cecere
Mechanisms of Epigenetic Inheritance

Elisa Gomez Perdiguero
Macrophages and Endothelial Cells

Units set up in 2015

Rogerio Amino
Malaria Infection and Immunity Unit

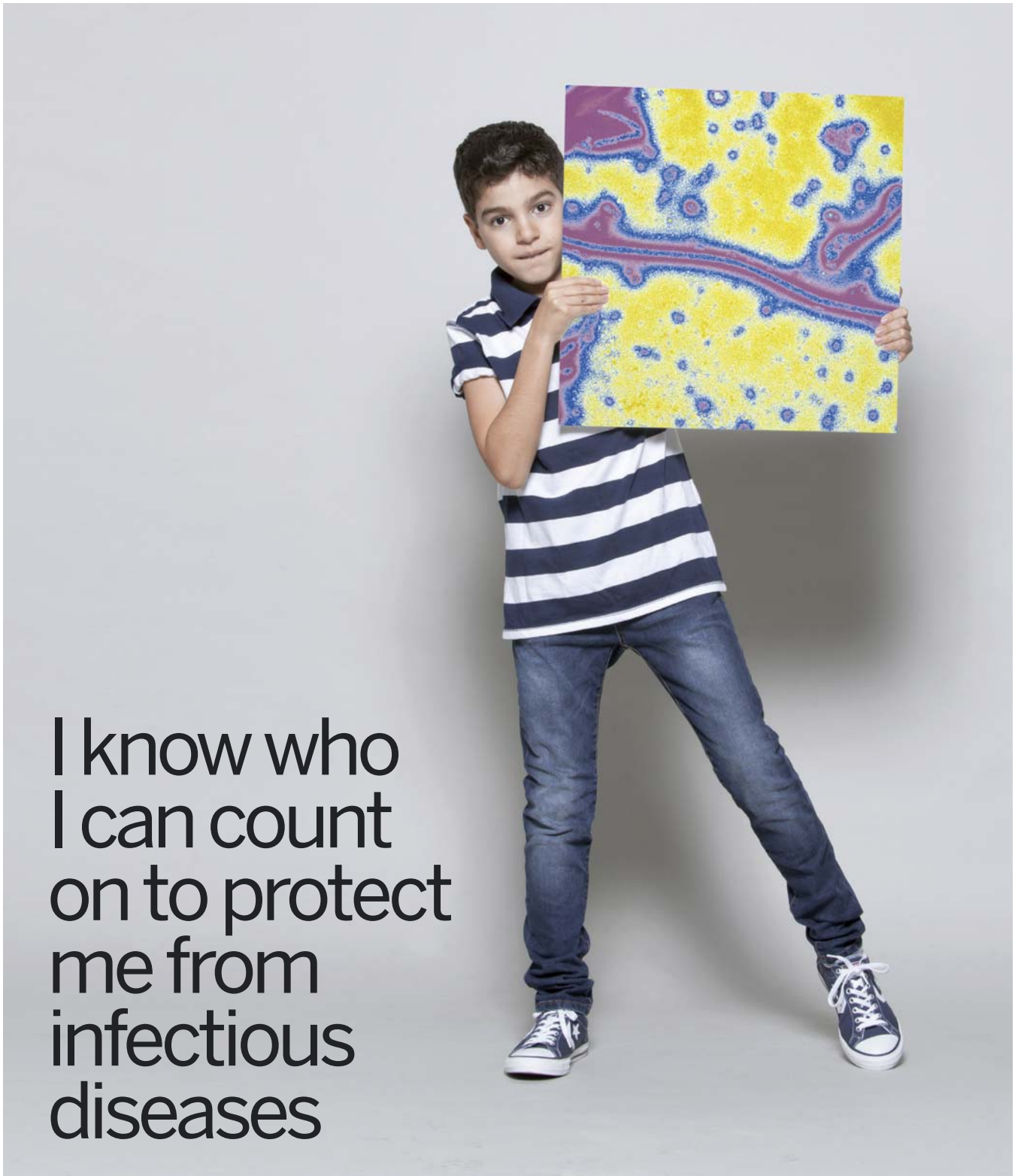
Olivier Gascuel
Evolutionary Bioinformatics Unit

Guillaume Dumenil
Pathogenesis of Vascular Infections Unit

Guilhem Janbon
RNA Biology of Fungal Pathogens Unit

Arnaud Echard
Membrane Traffic and Cell Division Unit

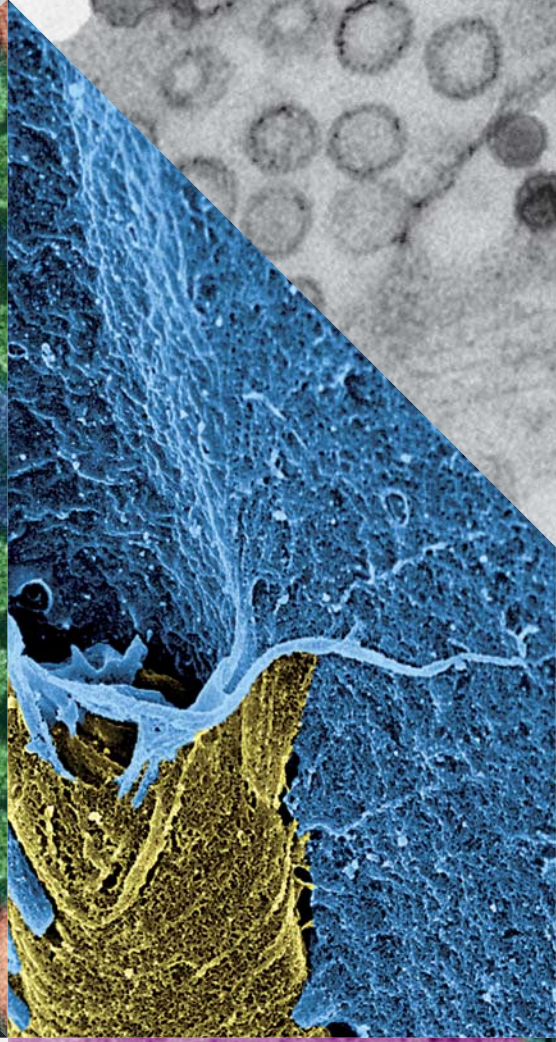
François Spitz
Genomics and Epigenomics of Vertebrate Development Unit



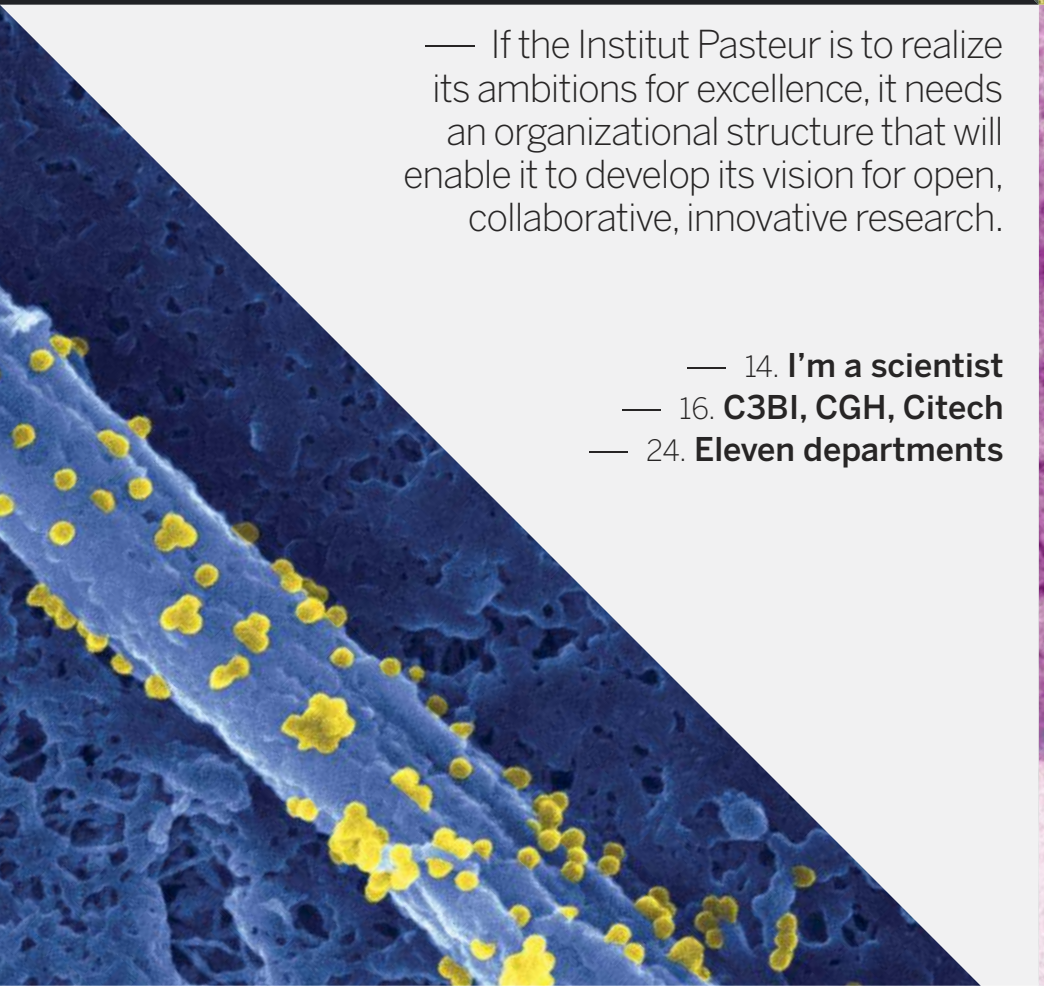
With its unique organizational structure and its interdisciplinary and multidisciplinary approach, the Institut Pasteur is well-placed to tackle viruses. The scientists on its Paris campus and in its International Network are relentless in their determination to combat emerging diseases that represent a threat to global health.

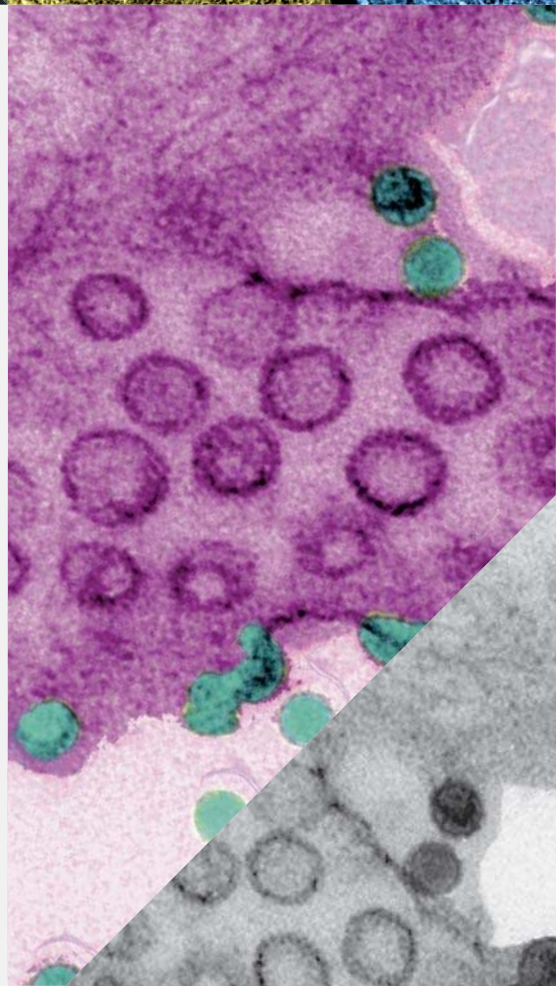
Institut Pasteur

Re-search



— If the Institut Pasteur is to realize its ambitions for excellence, it needs an organizational structure that will enable it to develop its vision for open, collaborative, innovative research.





“I’m a scientist”

— Vocation, passion, tenacity, selflessness, humanism – these are all qualities we associate with scientists. But perhaps the most important of all is an unwavering persistence.

“Like a treasure hunt...”

I initially wanted to be a physicist, but my teenage years and an inspiring biology teacher made me turn instead to life sciences. But I’m still fascinated by the idea of researching the fundamental laws at work behind the seeming chaos that we experience in our day-to-day lives. It’s a bit like a treasure hunt. That’s how I see research, as a long journey towards an unknown horizon which we can’t yet make out but which fills us with hope, and which therefore requires a great amount of determination.

Gérard Eberl,
Microenvironment and Immunity Unit

Research is an amazing human adventure

I was attracted to research by my fascination for the gray areas of knowledge and my desire to shed light on them. Ever since I learned about DNA and the genetic code in my final year of high school, I have been drawn by the idea of unraveling biological mechanisms. I see research as an amazing human adventure, where we constantly have to exchange views with others and share our expertise to make progress.

Sigolène Meilhac,
Heart Morphogenesis five-year group

Michaela Muller-Trutwin,
HIV, Inflammation and Persistence Unit

Retaining a childlike curiosity for the world

Ever since I was little, I've always been fascinated by explorers who braved great danger to discover unknown lands. As I got older, my curiosity for the world around us grew. Being a scientist has meant that I have retained that childlike curiosity for the world, and it is my constant hope that my work will be of use to society. I see scientists a bit like police officers: solving puzzles, proposing new theories based on the clues they find, and looking for proof, while never losing a sense of humility and an ability to challenge their own ideas. Another thing that attracted me to this profession is that scientists are judged on their work, not on their nationality, appearance or gender.

Finding new therapeutic possibilities

I work in the field of morphological sciences such as histology, anatomy, and cytopathology. My activities are based on examining samples under a microscope and describing tissue lesions. The main focus of my work is sepsis, which leads to severe defects in the nervous system and muscle tissue. The research carried out by my team and I ranges from the initial description of lesions to proposals for new therapeutic possibilities, which we always hope to be able to test in humans as quickly as possible thanks to the strong links we have with hospitals.

Fabrice Chrétien,
Human Histopathology and Animal Models Unit

Center for Bioinformatics, Biostatistics and Integrative Biology (C3BI)

— The C3BI is driven by the ambition to become a national and international reference center for all matters related to bioinformatics, associated disciplines and their applications in biology and human health. Preparatory work for the creation of this center, which was one of the goals laid down in the Institut Pasteur's strategic plan, began in 2014.

The field of biology is currently experiencing a major, irreversible revolution. We now have access to vast reams of data – especially genomic data – that contain vital information and have the potential for numerous applications, particularly in the field of health. Biology is following on the heels of other disciplines and developing into a computational science which makes increasing use of mathematical modeling and IT. There is no doubt that techniques for processing new biological data will play an ever greater role in medicine, especially when it comes to diagnostics and personalized treatment. The challenge of processing this exponentially expanding data and the countless questions and objectives it raises are creating tough new problems for the fields of IT and mathematics. This is leading to unparalleled growth in bioinformatics (in the broad sense, including biostatistics and the modeling of living systems). Major bioinformatics centers have been set up all over the world, creating a sufficient critical mass to deal with the complex biological questions raised.

The C3BI was officially launched in March 2015 and has enjoyed considerable support from the Institut Pasteur, particularly in terms of recruitment. This multidisciplinary, transversal center is committed to developing all aspects related to the processing, analysis and modeling of large-scale biological data.

The aims of the C3BI are:

• to promote bioinformatics research, including fundamental research;

• to develop the support offered to research units;

• to set up training courses for a range of audiences;

• to encourage cooperation and dialog among all Institut Pasteur entities and staff on bioinformatics issues;

• to play a structuring role for Paris as a whole, where there are currently few large teams working in this area (except at the Institut Curie);

• to adopt a policy of openness in terms of the services offered (e.g. to the Institut Pasteur International Network) and the research conducted (e.g. temporarily hosting scientists from university laboratories or the CNRS).

The C3BI is divided into two broad sections: the Research Area and the Bioinformatics Platform.

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 those in the process of being set up are primarily affiliated to the C3BI. The C3BI currently has seven units, a G5 and a laboratory:

• Structural Bioinformatics
• Mathematical Modeling of Infectious Diseases
• Imaging and Modeling
• Human Evolutionary Genetics
• Human Genetics and Cognitive Functions
• Microbial Evolutionary Genomics
• Spatial Regulation of Genomes (G5)
• Systems Biology (laboratory)
• Evolutionary Bioinformatics (new unit set up at the end of 2015)

The Bioinformatics Platform comprises all IT, bioinformatics and biostatistics services, including analyses performed in collaboration with research units, the creation of data processing pipelines, and maintenance of databases and bioinformatics software. These services are aimed at various communities ranging from the units on the Paris campus to the international community and the International Network of 33 institutes worldwide. Particular emphasis is placed on bioinformatics and biostatistics training. The platform coordinates and encourages synergy between the activities of three entities:

• The bioinformatics and biostatistics HUB is responsible for analyzing biological data. It provides support for the technological platforms and works on projects carried out by units on campus. More than 80 projects have already been submitted via a permanent call for proposals. The HUB holds an open-door session one morning each week to answer

the many bioinformatics questions from scientists on campus. This service will soon be extended to the entire International Network.

• The International Group for Data Analysis (IGDA) was set up to develop bioinformatics training and activities within the International Network. The IGDA was the driving force behind the Global Genomics Center, a project designed to encourage synergy between the institutes in the International Network in the field of precision medicine. In 2015, it received a major contribution (€1 million) from the Chan Soon-Shiong Institute for Molecular Medicine.

• The Center of Informatics for Biology (CIB, which is primarily attached to the Information Systems Department) is in charge of computational science in general: it administers computer clusters, manages data banks and databases, and introduces and optimizes standard software and bioinformatics Web servers.

In less than a year, the C3BI has already achieved considerable results and has gained national and international visibility:

• The C3BI applied to the CNRS to become a joint service and research unit. This application was analyzed by sections 06 (IT), 21 (genomics), 29 (evolution) and 51 (bioinformatics) and received strong support. The application was accepted by the CNRS management at the end of December, and the C3BI is now attached to the CNRS (USR 3756).

• The C3BI's attractiveness became clear in 2015 when we launched two calls for the recruitment of research engineers for the HUB and for new unit heads. We received 370 and 50 highly qualified international candidates respectively for these two posts, in a field in which recruitment is generally difficult. Twelve engineers joined the HUB at the end of 2015, and a new unit and G5 are due to be set up shortly.

• The Bioinformatics Platform has become a reference center. It is a member of the European ELIXIR network. It hosted the AGM – attended by 200 people – of the French Institute of Bioinformatics (IFB), an umbrella organization for all platforms across France. Of the 16 projects supported by the IFB this year (out of a total of 39 submitted), five involve teams from the C3BI.

• The C3BI has launched a seminar cycle, with the 20 seminars held so far each attended by an average of over 50 scientists. These seminars play a major role in developing interactions and synergies within the C3BI and the Institut Pasteur as a whole.

• New training courses on high-throughput sequencing data analysis have been held in the International Network (in Montevideo, Dakar and São Paulo) and on the Paris campus. These training courses have proved to be hugely successful and will be further developed in 2016.

• The C3BI research units are highly visible in their respective fields, with publications in several leading scientific journals in 2015, including *The Lancet Infectious Diseases, American Journal of Human Genetics, Nature Communications,* and *Algorithmica*. This research touches on wide-ranging fields including the epidemiology of infectious diseases (Ebola, HIV and *Listeria*), human genetics, the modeling of genomes and the cell nucleus, and molecular modeling using ultra-high-resolution NMR. The C3BI's teams share a wide variety of methodological skills, ranging from mathematical modeling to algorithmics, and including all aspects of statistics, from bioanalysis methods to procedures for estimating MCMC or ABC models.

The C3BI, a multidisciplinary, transversal center, is committed to developing all aspects related to the processing, analysis and modeling of large-scale biological data.

Center for Global Health

— The Center for Global Health (CGH), directed by Professor Arnaud Fontanet, was set up in September 2014 with the aim of consolidating the global health activities carried out by Institut Pasteur teams worldwide.

Three lines of action

The CGH has three main lines of action: research to improve human health, training up the scientists of tomorrow, and investigating outbreaks.

Research to improve human health involves promoting multisite, interdisciplinary research projects that target major global health challenges with the aim of developing innovative context-specific preventive, diagnostic, and therapeutic solutions.

Training up future scientists means giving them hands-on experience, knowledge and skills that will enable them to lead ambitious, interdisciplinary, translational research projects, taking into account the "one health" dimension (human, animal and environmental health) and the potential of new tools and big data. Another important aspect is the development of digital teaching and training tools via MOOCs and e-learning modules.

The CGH's outbreak investigation activities have involved the creation of a task force combining the wide-ranging expertise of Institut Pasteur scientists (microbiology, epidemiology, mathematical modeling, etc.) that can be deployed in a matter of days at the request of national authorities and international organizations in the event of an infectious disease outbreak. The aim is to bring the outbreak under control and to develop fundamental and translational research on emerging pathogens.

Launch of the Pasteur Global Health Genomics Center

The international Pasteur Global Health Genomics Center (PGHGC) was set up in October 2015 following the signing of a partnership agreement between the Chan Soon-Shiong Institute for Molecular Medicine and the Institut Pasteur. The aim of the PGHGC, directed by Professor Magnus Fontes, is to strengthen capabilities in genomic research within the Institut Pasteur International Network in order to tackle major global health challenges. Several courses on this subject were run within the International Network in 2015. The PGHGC has a biobank containing patient data and samples for the entire International Network (the Pasteur International Biobank) and provides tools for high-throughput sequencing, bioinformatics analysis and data sharing among the various institutes.

A pilot project: HHGP-Senegal

In connection with the 2020 Pasteur Global Health Initiative, the *Milieu Intérieur* consortium – in collaboration with the Pasteur Global Health Genomics Center, the CGH and the Institut Pasteur International Network – has launched the Healthy Human Global Project (HHGP), an ambitious study which aims to define the genetic and environmental parameters that determine a "healthy" immune system and its natural variability. The initial study (the *Milieu Intérieur* project) will be extended to other continents (Africa, Asia and America) to examine the impact of genetic and environmental variations on the immune response of healthy volunteers.

A pilot study will be launched in October 2016 in Senegal, led by the Institut Pasteur in Dakar in collaboration with the Institut Pasteur in Paris. The HHGP-Senegal project will analyze a group of healthy donors from the populations of the Senegalese villages of Dielmo and Ndiop.

Targeting major global health challenges with the aim of developing innovative, context-specific, preventive, diagnostic, and therapeutic solutions.

The Pan-African Coalition for Training in Research and Public Health (PACT)

Since January 2015, the CGH has been coordinating a program in Africa known as the Pan-African Coalition for Training in Research and Public Health (PACT), which is based on the capabilities of the institutes within the International Network. As of late December 2015, PACT is responsible for five regional pilot projects to introduce or strengthen Master's-level training on the following topics:

- Malariology in Cote d'Ivoire;
- Bioinformatics in Senegal;
- Medical microbiology in Cameroon;
- Human genomics to tackle rare and neglected diseases in Tunisia;
- Preparation and response to disease outbreaks in Guinea.

The PACT program also involves a development strategy for digital teaching methods in public health as part of efforts to consolidate the range of advanced courses offered by the Institut Pasteur International Network.

Each of these pilot projects includes a wide range of activities to achieve the desired outcomes in terms of scientific higher education, training in research methods, and the development of career opportunities for students and young researchers in Africa.

June 25 and 26, 2015: International Workshop on Global Health Education

This event, held on the Institut Pasteur's Paris campus and organized in cooperation with the Department of International Affairs, the International Network and the Education Department, was attended by representatives of several internationally renowned universities and research institutes to identify new challenges in training young researchers and to develop partnerships based on a program that aims to strengthen the capabilities of research and teaching systems in the area of public health. These discussions led to the creation of the PACT program.

A total of 12 institutions took part in the International Workshop on Global Health Education:

- **Universities and research institutes: Chapel Hill, LSHTM, Cambridge, Oxford, Heidelberg, EMBO, Karolinska, University of Texas, EHESP.**
- **Institutional funding bodies: Fogarty-NIH, Wellcome Trust, Global Fund.**

Creation of an Outbreak Investigation Task Force (OITF)

Between January and December 2015, Dr. Maria Van Kerkhove carried out more than 12 missions under the aegis of WHO and/or at the request of national governments, including:

- five missions as a member of the MERS-CoV task force led by the WHO Global Outbreak Alert and Response Network (GOARN) to Saudi Arabia, Jordan and South Korea;
- a mission to Sierra Leone as an Ebola technical consultant for WHO.

At the end of 2015, the Outbreak Investigation Task Force coordinated by Dr. Van Kerkhove was composed of some 50 scientists and members of the Institut Pasteur International Network, from six different regions. The group will meet for the first time in April 2016 during the Infectious Disease Outbreak Investigation course.

CREATION OF A TASK FORCE COMBINING THE WIDE-RANGING EXPERTISE OF INSTITUT PASTEUR SCIENTISTS THAT CAN BE DEPLOYED IN A MATTER OF DAYS IN THE EVENT OF AN INFECTIOUS DISEASE OUTBREAK.

Three recruitments to the CGH in 2015

January: Dr. Maria Van Kerkhove, Coordinator of the Outbreak Investigation Task Force at the CGH. Dr. Van Kerkhove is an epidemiologist specializing in infectious diseases and a consultant for the WHO in the MERS-CoV working group.

July: Dr. Golbahar Pahlavan, Deputy Director of the CGH. Dr. Pahlavan has more than 10 years' experience in managing research and innovation projects in global health, particularly in Sub-Saharan Africa.

July: Jennifer Fatni, Project Manager for education and training projects coordinated jointly by the CGH, the Teaching Center and the Pasteur-CNAM School of Public Health.

Center for Innovation and Technological Research (Citech)

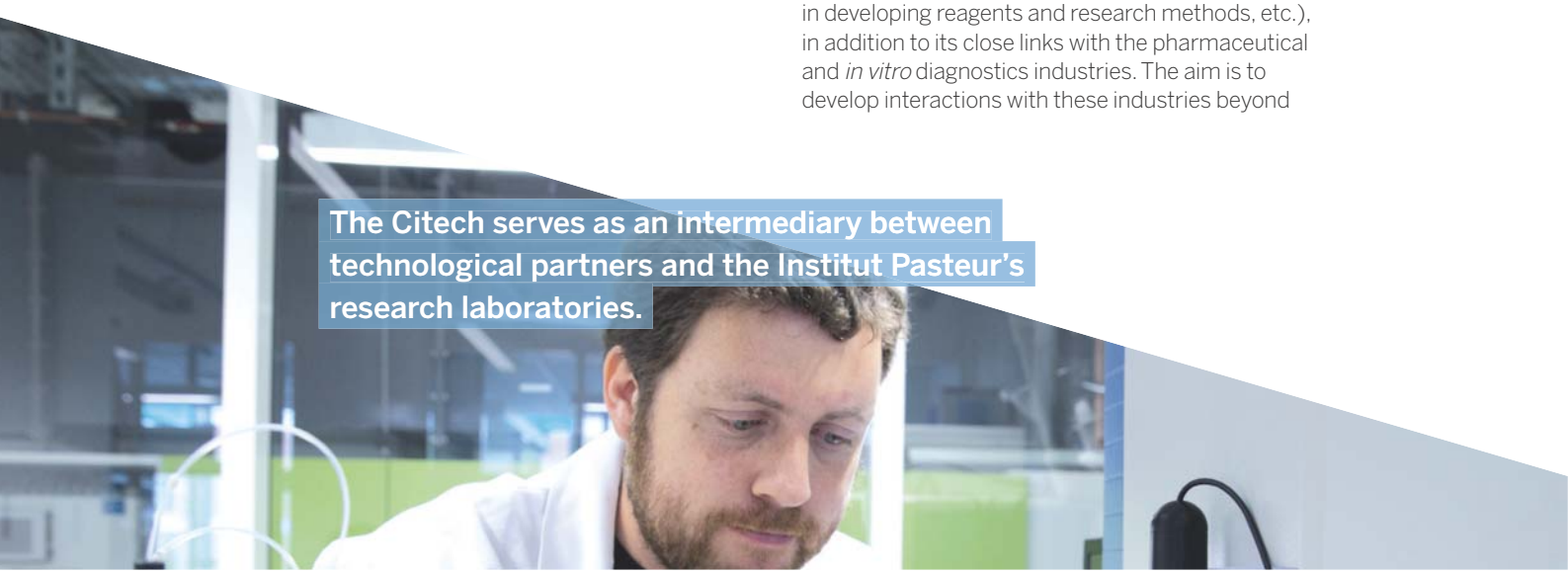
— The Center for Innovation and Technological Research (Citech) is a technological hub with two main objectives: to advance technological innovation and research, and to meet the immediate and future needs of the biological projects developed on campus and within the Institut Pasteur International Network. The Citech was set up in 2014 as a single structure comprising 13 technological platforms, the Central Animal Facility and the newly created Pasteur Tech Lab.

A new organizational structure for the platforms

In 2015, the Citech held discussions to devise a new organizational structure for the Institut Pasteur platforms and Central Animal Facility, with the aim of:
– optimizing the services available on campus and catering for user requirements, particularly by providing the flexibility needed for the rapid implementation of new technologies;
– dealing with requests involving an increasingly wide range of skills and expertise and facilitating synergy between teams;
– enhancing the visibility of technological activities and the staff involved by recognizing directors as leading experts in their fields;
– facilitating the pooling and development of skills and responsibilities;
– providing a new structure for technological R&D activities.
These discussions resulted in a proposed new organizational set-up involving a single leadership and operational structure for all the platforms and the Central Animal Facility, with the aim of gradually harmonizing, optimizing, and implementing procedures during 2016.
The key role played by the departments in setting strategic guidelines has been maintained, with each entity being affiliated to a department and steering committees being set up.

Partnerships with academic and industrial technology developers

In addition to the ongoing technological developments on campus, the Citech aims to strengthen its capabilities by fostering strategic external partnerships with key players in life science technologies, whether in the academic or industrial sphere. One of the main aims of these partnerships is to encourage scientific and/or staff exchanges. In 2015, a first partnership was set up with ESPCI ParisTech. A framework agreement was signed in September, and several collaborative research projects have been launched in the areas of drop- or paper-based microfluidics and super-resolution microscopy.
The Citech also works in conjunction with the Research Applications and Industrial Relations Department (DARRI) to strengthen the Institut Pasteur's links with the life science technology industry (instrument manufacturers, those involved in developing reagents and research methods, etc.), in addition to its close links with the pharmaceutical and *in vitro* diagnostics industries. The aim is to develop interactions with these industries beyond



The Citech serves as an intermediary between technological partners and the Institut Pasteur's research laboratories.

the existing trade links, and to launch more upstream collaborative technological research projects. The Citech has a key role to play in this process, since its platform teams serve as intermediaries between technological partners and the Institut Pasteur's research laboratories. The Citech's technology experts have extensive experience in turning specifications and technical constraints into operational and experimental capabilities for users. They are also ideally placed to receive and provide training in complex technologies.

The Pasteur Tech Lab, an open laboratory at the crossroads of emerging technologies and the Institut Pasteur's biology

In 2015, the Citech opened a center for collaborative technological research projects, the Pasteur Tech Lab. The Citech uses the projects run by the Pasteur Tech Lab, and the start-up funding granted for these projects via calls for proposals, to attract and disseminate emerging technologies. These projects are coordinated by consortia composed of a technology partner (which may be internal or external, academic or industrial), an applications partner (internal), and a Citech entity. The Pasteur Tech Lab is housed in the Tech Lab Central on the first floor of the François Jacob building. The Tech Lab Central site has seven separate modules, each roughly fifteen square meters, which can be assigned to projects for a set period ranging from six to eighteen months. Alternatively, projects can also be conducted on the premises of the research groups or platforms in Tech Lab satellites.

New technologies and services

A new chemogenomic and biological screening platform was opened in April 2015 within the Citech, directed by Fabrice Agou. The main aims of this new platform are to help the research teams develop reliable, innovative trials, to provide compound libraries, and to identify high quality "hits" involving small molecules and peptides in a range of biological fields (virology, microbiology and immunology). The platform will provide the Institut Pasteur's research teams with easy access to a variety of robotics technologies and detection instruments (absorbance, fluorescence, luminescence, fluorescence polarization, TR-FRET, and imaging). A series of new biomaterials and microfluidics services was launched in 2015, directed by Samy Gobaa and housed in the Tech Lab Central. Combining microfluidics approaches with biomaterials enables scientists to conduct experiments at single-cell level in environments that mimic tissues, and also to test several cell culture conditions at the same time. This technique can be used to examine the mechanisms that underpin stem cell differentiation, for example. The specialist team provides basic assistance in microfluidics as well as the equipment required to carry out biological experiments.

IN 2015, THE CITECH OPENED A CENTER FOR COLLABORATIVE TECHNOLOGICAL RESEARCH PROJECTS, THE PASTEUR TECH LAB.

Center for Innovation and Technological Research (Citech)

The Recombinant Proteins Platform

The Recombinant Proteins Platform, part of the Citech, has two teams working on related research areas: the production and purification of proteins in prokaryotic expression systems (*Escherichia coli*) and eukaryotic cells (yeast and *Leishmania tarentolae*) in the team directed by Jacques Bellalou or in eukaryotic expression systems (insect cells and mammalian cells) in the team directed by Stéphane Petres. The latter focuses on protein expression in insect cells, which are placed in 25-liter bioreactors for large-scale culture. The proteins are then purified through affinity chromatography methods or molecular sieving using ÄKTA Avant instruments.

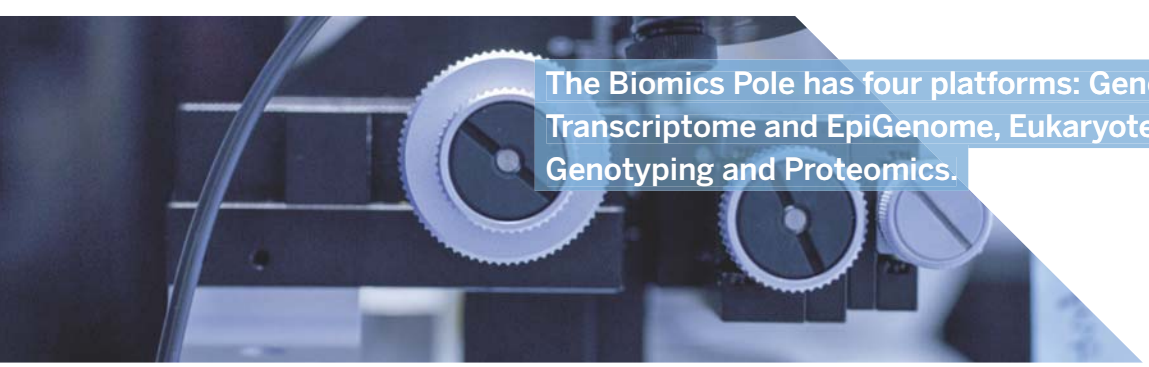
The platform is also closely involved in methodological and technological developments, and it performs an advisory and training role. Jacques Bellalou's team has a TECAN Evo200 robot, which can be used to compare up to 96 culture and analytical purification conditions at any given time and to quickly select the optimal parameters for proteins that are often difficult to obtain in *E. coli*. The purified proteins are analyzed using a Perkin Elmer LabChip GXII capillary electrophoresis system. This automated equipment is reliable, precise and extremely quick, avoiding the need for tedious manual processes and freeing up operators to spend more time on other projects and more demanding experiments.

It is vital to carry out protein quality control after purification, as poor quality samples can lead to costly experiments proving unsuccessful. A new bespoke service has therefore been introduced, directed by Bertrand Raynal, that can be used to check the quality of any sample before embarking on further experiments. Users can fill out a form and ask for tests at a given level to be carried out on their sample the same day. If the sample does not pass the tests, the platform can suggest a more sophisticated solution to improve its quality. This innovative technique for the Institut Pasteur is part of a Europe-wide approach. An appropriate cost-effective pricing strategy is applied to these services. The tests are performed using the Biophysics Platform's Wyatt DynaPro Plate Reader, which can handle up to 1,536 samples at a time.

The Biomics Pole

The Citech's Biomics Pole was set up in 2015 as the successor to the Genopole, with additional proteomics activities. The pole is headed by Sean Kennedy. It has four platforms: Genomics, Transcriptome and EpiGenome, Eukaryote Genotyping, and Proteomics. It also carries out metagenomics studies, in other words sequencing all the organisms in an environmental niche such as the microbiota.

The Biomics Pole also performs single-cell analysis. It has cutting-edge technological equipment such as the Illumina HiSeq 2500 high-throughput sequencing system, which can be



The Biomics Pole has four platforms: Genomics, Transcriptome and EpiGenome, Eukaryote Genotyping and Proteomics.

used for large-scale sequencing of all organisms. This equipment is available to all the Biomics platforms, thereby maximizing its usage potential. The Center for Bioinformatics, Biostatistics and Integrative Biology (C3BI) has freed up some of its bioinformaticians to work together with those in the Biomics Pole in performing bioinformatic and statistical analyses of complex data. During 2015, funding from a range of sources was used to carry out or seed various research projects: Transversal Research Programs, projects funded by the French National Research Agency (ANR) or the European Research Area Network (ERA-NET), as well as an Institut Pasteur Major Federating Program entitled "Microbes & Brain", for which 17 teams in the areas of neuroscience, immunology, and microbiology have joined forces.

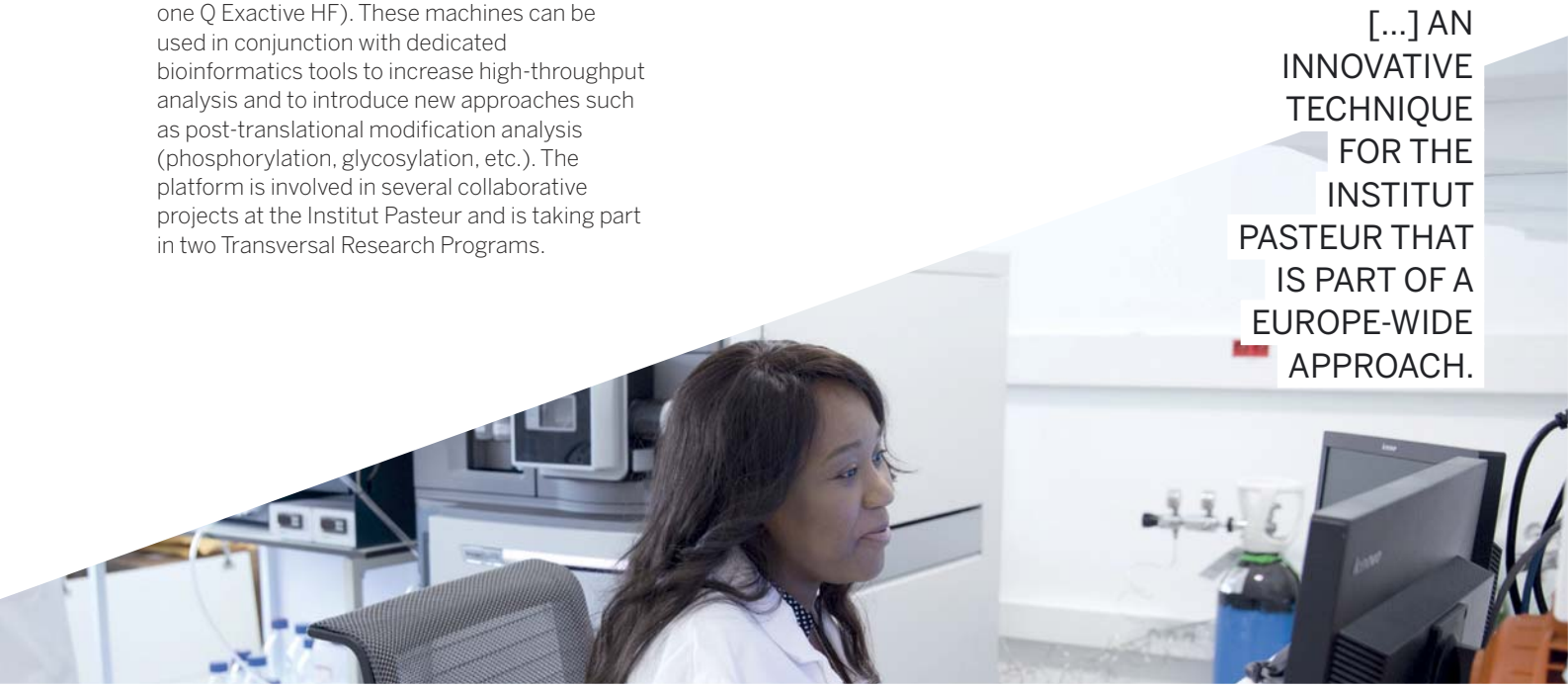
The Proteomics Platform

The aim of the Proteomics Platform, directed by Mariette Matondo, is to introduce and develop innovative proteomics analysis strategies that can be used to identify, characterize, and quantify thousands of proteins (the proteome) in complex samples. These analyses are performed with dedicated mass spectrometers. The platform acquired three next-generation ultra-high resolution Orbitrap mass spectrometers in 2015 (two Q Exactive Plus and one Q Exactive HF). These machines can be used in conjunction with dedicated bioinformatics tools to increase high-throughput analysis and to introduce new approaches such as post-translational modification analysis (phosphorylation, glycosylation, etc.). The platform is involved in several collaborative projects at the Institut Pasteur and is taking part in two Transversal Research Programs.

The Ultrapole

The work of the Citech's Ultrapole, directed since May 2015 by Jacomina Krijnse-Locker, focuses on electron microscopy. The Ultrapole has acquired a Leica EM Cryo CLEM (Correlative Light Electron Microsopy) using joint funding with the Imagopole, directed by Spencer Shorte. This cryo-fluorescence microscope can be used to observe pathogen-infected cells in frozen-hydrated samples, unlike traditional microscopy at room temperature, where samples are fixed using chemicals and water is removed. With the Cryo CLEM, scientists can determine and record the positions of infected cells of interest, which are then automatically recovered with special software and can be observed under high-resolution electron microscopes such as the TECNAI 200 kV. This allows them to visualize a key stage in the induced disease. The Institut Pasteur is the first institute in France to acquire this innovative technology. In 2015, the Ultrapole conducted a project on intercellular communication mechanisms that use long, very thin tubes known as nanotubes. These tubes are involved in transporting pathogens, especially prions, from one cell to another.

[...] AN INNOVATIVE TECHNIQUE FOR THE INSTITUT PASTEUR THAT IS PART OF A EUROPE-WIDE APPROACH.



Cell Biology and Infection

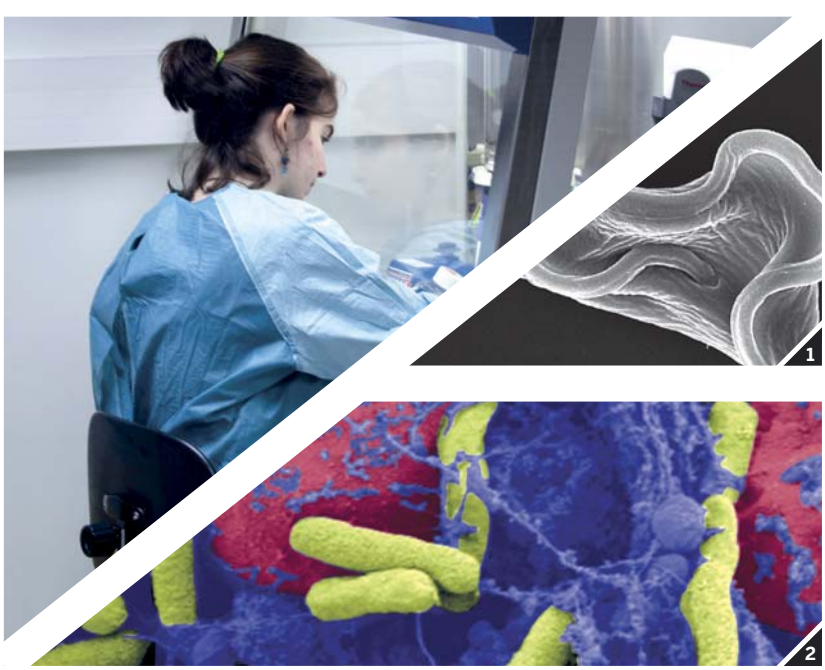
— This department studies the mechanisms regulating normal cell function and the interactions between different types of infectious agents and their targets. It deploys advanced imaging and genomics techniques to shed light on the intricate workings of microbes and cells and to analyze how cells actually function in normal and pathological conditions (e.g. infected, cancerous or aged).

Understanding infectious mechanisms requires a detailed study of cell function during infection. It is also crucial to understand the balance between commensal flora and host. Some teams concentrate on a particular infectious agent. Others focus on gaining a detailed knowledge of the cell, independently of any infectious context. A detailed understanding of cell functions is the only route towards providing an explanation of infection and disease mechanisms. In this context, one of the department's strengths lies in the implementation of new models for host-pathogen interactions. In addition, all departmental activities remain closely in tune with the development of new technologies, including imaging and image analysis, and genomics and postgenomics, and are committed to using a cross-disciplinary and quantitative approach.

1. The bloodstream form of Trypanosoma brucei, *the parasitic flagellate that causes sleeping sickness in Central Africa. Scanning electron microscopy (Jeol 6700F).*

2. Pseudomonas aeruginosa *bacterial biofilm formed on a central catheter.* Pseudomonas aeruginosa *are in yellow and blood cells in red. Research on anti-adhesive strategies to control pathogenic biofilms.*

3. Cytoskeleton of a migrating glioma cell. 3D-SIM image of a migrating glioma cell cytoskeleton. The microtubules are shown in yellow, vimentin in red and actin in cyan blue.

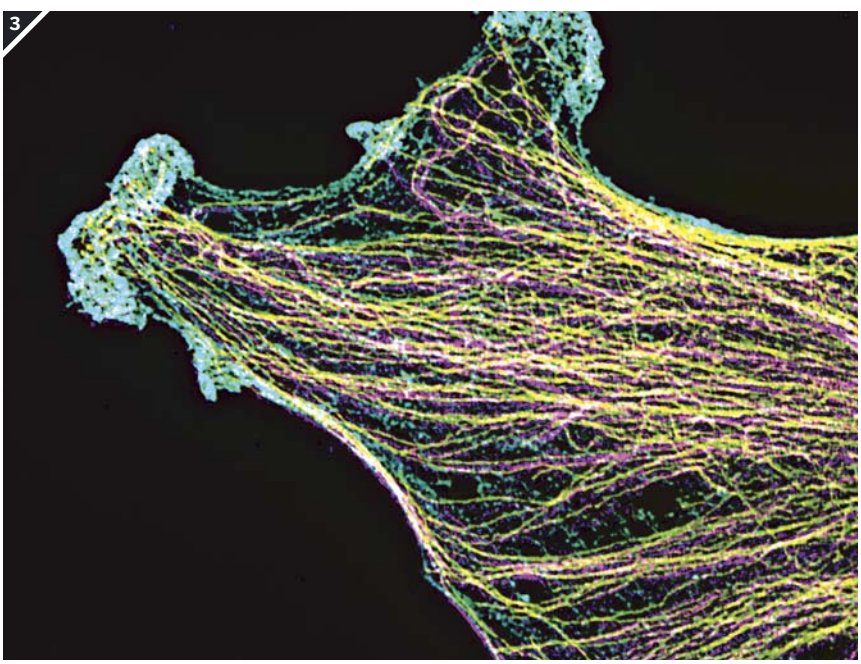


Segmented filamentous bacteria – intestinal symbionts – cultivated *in vitro* for the first time

Segmented filamentous bacteria (SFB) are commensal intestinal bacteria in the Clostridium family, which play a unique role in shaping the immune systems of their hosts. SFB are found in many vertebrates. They are among the first bacteria to colonize the ileum after weaning. Their particular feature is that they adhere to the epithelial cells, and live in a close relationship with their host. This adherence is uncommon in commensal bacteria, and leads to postnatal maturation of the intestinal immune system. Innate and adaptive immune responses are established, which are instrumental in protecting the host against intestinal pathogens and reduce pathological severity in many murine models of autoimmune diseases. SFB therefore make up a key component of the intestinal microbiota, from both a physiological and pathological point of view. However, the mechanisms of these unique interactions with the host remain largely unknown, in particular because it is impossible to cultivate the bacterium *in vitro*. By mimicking the replication conditions of SFB *in vivo*, a scientist in the team led by Philippe Sansonetti, in collaboration with the team led by Nadine Cerf-Bensussan (INSERM, Imagine Institute), has successfully met this challenge for the first time. The production of SFB and intestinal epithelial cells *in vitro* using a co-culture system enables replication of the SFB cell cycle in all its complexity and offers a new perspective on the conditions that this enigmatic bacterium requires in order to grow. The ability to cultivate SFB *in vitro* now gives us the opportunity to study the complex development of this bacterium, elucidate its interactions with its host, both at the cellular and molecular level, and start genetic manipulation.

A crucial protein interaction for tumor development

Cell proteins usually have a number of roles. Scribble is one of these multifunctional proteins. Scribble is present in a large number of animal species, and serves both as a tumor suppressor and a cell polarity regulator, ensuring the correct positioning of the various cell components. In order to fulfill its role, Scribble must itself be in the correct location at the cell cortex. Although, in humans, mislocalization of Scribble is a characteristic sign of the most aggressive tumors, the reasons for such an anomaly are as yet unknown. Scribble is largely similar among the various organisms, but vertebrates and insects show differences in the C-terminal region, which makes up one end of the protein. Batiste Boëda and Sandrine Étienne-Manneville have identified three repeats of a sequence called the SADH motif, which is present in this region of Scribble. These motifs bind to proteins called beta spectrins, which connect the cell's outer membrane to the subjacent cortical cytoskeleton. Some mutations linked to spina bifida and cancer affect the SADH motif. The work of the Cell Polarity, Migration and Cancer laboratory establishes the role of beta-spectrins in Scribble stabilization at the cell cortex and suggests that Scribble-associated diseases might depend on the integrity of the spectrin network.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Prizes and awards

Philippe Sansonetti, Claude Bernard Prize and FRM Grand Prix

Sandrine Étienne-Manneville, Pasteur Vallery-Radot Prize


Sandrine Étienne-Manneville and Chiara Zurzolo, Members of EMBO

A small tag with a major impact on innate immunity

Cells have developed a number of mechanisms to extend the range of functions of the proteins they contain. Proteins, once synthesized, undergo posttranslational modifications, leading to a change in their function. Although most of these modifications occur via the addition of a chemical moiety, the process known as SUMOylation is distinctive because, in this case, tagging is carried out by a small protein itself, called a SUMO protein. There are hundreds of SUMO-tagged proteins and, since SUMOylation is eminently pleiotropic, it regulates most of the biological processes carried out by our cells. Scientists from the laboratory led by Anne Dejean discovered that, in myeloid immune cells, modification by SUMO has a single, unique function: the repression of innate immunity. Thus, the absence of SUMOylation triggers strong inflammatory and antiviral responses in myeloid cells which, in animals, manifest themselves as an increased susceptibility to septic shock and protection against viral infection. SUMO proteins act on chromatin and perform the role of interrupter, preventing an inflammatory response that would be dangerous for the organism when faced with a virus, and preventing an inappropriate antiviral response when faced with a bacterium. Since modification by SUMO is easily manipulated by drugs, this discovery paves the way for new therapeutic approaches for treating infection by pathogens and auto-immune diseases.

Developmental & Stem Cell Biology

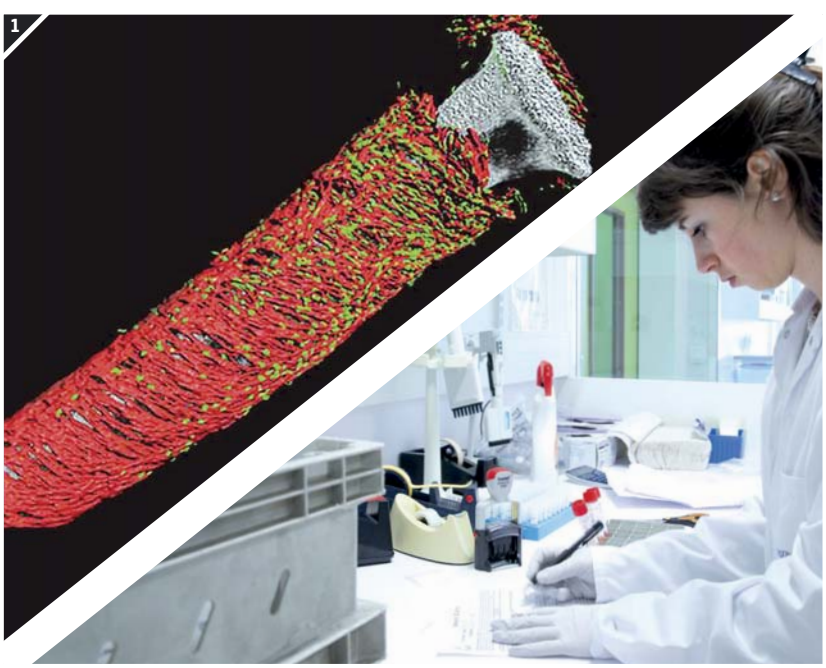
— The Department of Developmental & Stem Cell Biology covers a broad spectrum of multidisciplinary research activities ranging from studies on individual cells to investigations of the organism as a whole. This includes several projects on stem cells and their potential applications in biomedicine.

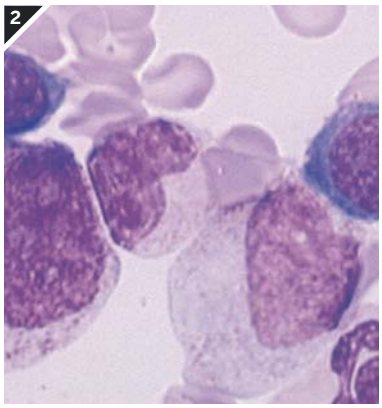
The Department has a unique cutting-edge research environment with a strong tradition in both classical genetics and gene manipulation. Multidisciplinary research focuses on diverse themes from DNA and RNA, to cells and organisms including: 1) how cell identity is established and maintained, with a focus on transcription factors and chromatin dynamics; 2) the establishment of cell lineages in the embryo and adult with a view on the evolutionary context; 3) cell movements and migrations and their roles in organogenesis; 4) roles of (epi-) genetic and non-genetic factors in determining phenotypes, the occurrence of congenital pathologies, and the host's resistance to disease and environmental stress. Cell and organismal aging and metabolism are recent emerging themes that are also being investigated by several laboratories. To understand the formation of tissues and organs from stem cells in the embryo and postnatally, an integrated research program is conducted from the molecular level to live imaging of these processes directly in the organism.

1. Mouse esophagus being colonized by skeletal muscle stem and differentiating cells (green) originating from the head and overlying smooth muscles (red). Understanding this process provides insights into diseases associated with swallowing (Tajbakhsh lab: Gopalakrishnan et al. Developmental Cell, 2015).

2. Normal hematopoietic progenitors.

3. Fruit fly larva.



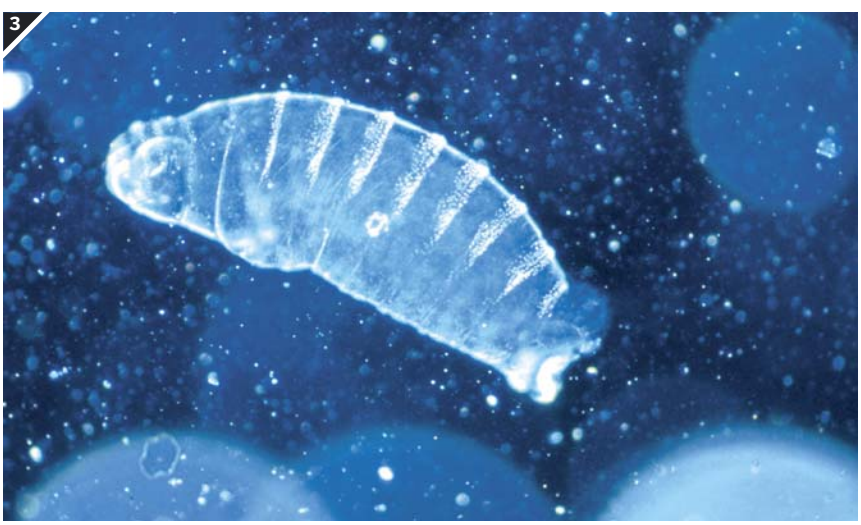


Formation of the initial niche for hematopoietic stem cells

In all vertebrates, hematopoietic stem cells (HSCs) emerge from the embryo's aorta, then migrate to settle in successive niches where they give rise to hematopoiesis - in mammals these niches are the fetal liver then the bone marrow. The genesis of these niches is poorly understood, especially the first one, the only niche where HSCs proliferate. Emi Murayama, in Philippe Herbomel's laboratory, has characterized the first niche to which HSCs home in the transparent zebrafish embryo: the 'caudal hematopoietic tissue'. It is made of a venous plexus and of 'stromal reticular cells' (SRCs). By *in vivo* imaging Emi Murayama was able to follow the assembly of this niche. Unexpectedly, the SRC precursors turned out to originate from the somites, through an epithelial mesenchymal transition (EMT). They accompanied the formation of the venous plexus, and matured into SRCs interconnecting the venous sinusoids. The analysis of a mutant revealed that a molecular chaperone, Naca, was required for the maturation of SRCs, and that the latter were essential for HSC expansion and differentiation. The team now studies these SRCs *in vivo* to understand how they promote HSC expansion and differentiation.

A bacteria manipulates pheromone communication, stem cells and reproduction in flies

The homeostasis of self-renewing tissues depends on the ability of stem cells to properly respond to changes in temperature, diet, hormones, circadian rhythm, aging, stress, microbiota and infection. By studying stem cells in the adult fly testis, Stephanie Pontier in the team of François Schweisguth found that the number of stem and support cells varied in response to social interactions with females. Stéphanie Pontier further identified that endosymbiotic bacteria, known as *Wolbachia,* that are present in 60% of the insect species, inhibited the synthesis of pheromones in infected females. Thus, *Wolbachia* interfered with proper female-to-male communication during development and thereby regulated the number of stem and support cells in developing male gonads. Defective female-to-male communication also affected the ability of sperm to fertilize non-infected eggs. This study revealed an unexpected mechanism whereby *Wolbachia* manipulates fly reproduction to the benefit of its own propagation within insect populations.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Correcting the defects leading to precocious aging diseases

Aging is dramatically accelerated in some rare genetic diseases, like the Cockayne syndrome. It was believed that a DNA repair defect was responsible of the precocious aging of these patients, who are also hypersensitive to sunlight. By studying primary cells from Cockayne syndrome patients, Laurent Chatre (in the team of Miria Ricchetti, Stem Cells and Development lab), in collaboration with Alain Sarasin (Villejuif) and Denis Biard (CEA, DSV), found that these cells are rather defective in mitochondrial function and ATP production. These defects are due to depletion of PolG1, the polymerase that replicates the organelle DNA. PolG1 is degraded by the protease HtrA3, which is expressed at very high levels in Cockayne syndrome patient cells. In turn, overexpression of HtrA3 is promoted by oxidative and nitrosative stress. These findings describe one of the hitherto unknown mechanisms responsible for premature aging. They could also shed light on the normal aging process.

By inhibiting proteases, or reducing oxidative and nitrosative stress, the team restored normal activity in patient cells, paving the way for new therapeutic approaches, which are dramatically missing to date. These findings open new research possibilities in terms of preventive therapies for the pathologies associated with aging.

Creation of three new groups

Germano Cecere leads the **Mechanisms of Epigenetic Inheritance Group** and studies the role of small RNAs in epigenetic inheritance during animal development and upon environmental changes. The group is seeking to understand if small RNAs may constitute an RNA-based epigenetic system for propagating the memory of the transcriptional status of the genome across generations.

Elisa Gomez Perdiguero leads the **Macrophages and Endothelial Cells Group** and studies the development and function of tissue macrophages. The group uses mouse fate mapping models to explore *in vivo* the role of macrophages and their interaction with endothelial cells during development, homeostasis and tissue repair.

Pauline Spéder leads the **Brain Plasticity in Response to the Environment Group** and studies how neural stem cells and their microenvironment adapt to external challenges. The group uses the *in vivo* genetic model Drosophila to understand the dynamics of interactions between the different populations in physiological, tumoral and infectious contexts.

Structural Biology and Chemistry

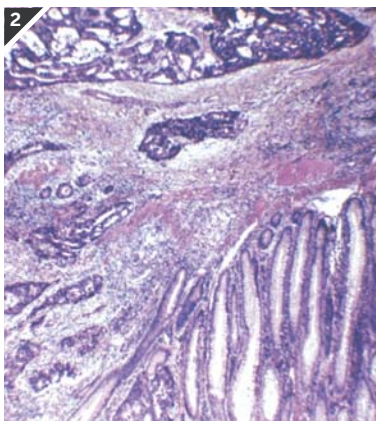
— The structure of a molecule is intricately linked to its function. The units in the Structural Biology and Chemistry Department focus their research on the three-dimensional organization, properties and synthesis of molecules of biological interest, especially those that play a role in human pathology. This research reveals vital information 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 cancers. The scientists aim to shed light on the molecular mechanisms involved in the assembly of protein complexes associated with pathological or infectious processes in order to design chemical tools to block these mechanisms. The department adopts a molecular approach to study these interactions using cutting-edge technologies:
• crystallography, which shows the 3D structure of a molecule and is the tool of choice for designing drugs;
• nuclear magnetic resonance (NMR), which explores the structures of smaller molecules and provides information about their movements and molecular interactions;
• electron microscopy, which provides highly detailed images of the structures of large biological complexes;
• molecular modeling, which is vital for determining structures;
• mass spectrometry, which enables scientists to examine the stoichiometry, conformation, and dynamics of large protein complexes with unparalleled precision;
• chemical synthesis, which is essential for therapeutic and vaccine development.

1. Modulation of the expression of host cell genes infected by Legionella pneumophila *bacteria. Confocal microscopy.*

2. Histological section of epithelioma or cylindrical adenocarcinoma in the rectum, composed of cubic cells arranged in a glandular configuration.

3. Intracellular replication of Legionella pneumophila *(in red) in epithelial lung cells (cell line A549).*



MAG-Tn3 therapeutic cancer vaccine

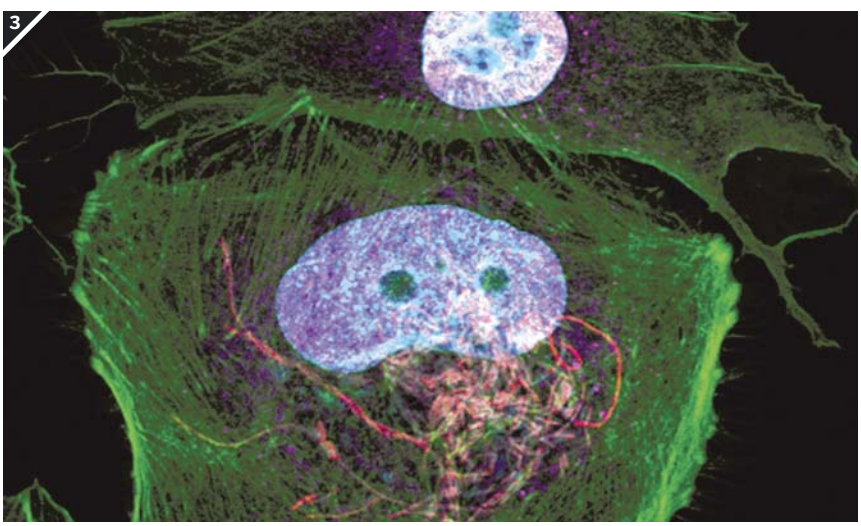
In 2015, one of the Institut Pasteur's flagship vaccine projects, which has received vital support from our donors, reached a major milestone with the first administration to patients of MAG-Tn3, a synthetic cancer vaccine. MAG-Tn3 is the result of collaborative research by Sylvie Bay (from the Chemistry of Biomolecules Unit, directed by Laurence Mulard), Claude Leclerc and Richard Lo-Man (from the Immune Regulation and Vaccinology Unit, directed by Claude Leclerc). It targets adenocarcinoma, particularly in the breasts, lungs, colon, and ovaries. This therapeutic vaccine candidate is designed to treat cancer by stimulating immune responses in patients against their own cancer cells. The scientists worked in cooperation with Cécile Artaud and Annick Dubois (Clinical Core in the Center for Translational Science) to produce a clinical batch of the vaccine, evaluate its effectiveness and absence of toxicity in animals, and secure the required regulatory permission. This work culminated in the launch of a phase I clinical trial in 2015, sponsored by the Institut Pasteur. The main aim of the trial is to assess the tolerance of around 30 breast cancer patients to the MAG-Tn3 vaccine candidate. The vaccination process is currently underway and is being carried out as planned.

Structure of an important part of the bacterial arsenal identified

Scientists from our department have made a major breakthrough in understanding the molecular structure and workings of an important part of the bacterial arsenal. This study, published in the journal *Nature* in 2015, focuses on the assembly mechanism and gives a detailed description of the architecture of a key component in the bacterial type VI secretion system.

This system is used by several pathogenic bacteria to eliminate other competing microbes within their ecological niche. It works like a molecular crossbow which propels a protein arrow into the cytoplasm of the target cell. This crossbow is attached to the bacterial envelope via a membrane complex, which guides its arrow to the target bacterium. In this study, the team led by Rémi Fronzes (Institut Pasteur / CNRS), working closely with the groups led by Eric Cascales and Christian Cambillau (Aix-Marseille University / CNRS), demonstrates that this complex is assembled by the addition of three proteins: TssJ, TssM, and TssL. The scientists present its structure, which was elucidated using electron microscopy.

Their determination of the crystal structure of part of this complex, together with *in vivo* research on bacteria, suggests that a transient pore is formed in the outer bacterial membrane to allow the arrow to pass through and reach its target. The long-term aim is to develop therapeutic strategies which target these stages in the formation of the type VI secretion system so that it can ultimately be blocked.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New research group on the chemistry of nucleic acids

Nucleic acids (DNA and RNA) are fundamental polymers that serve as the carriers of genetic information. They can also be chemically modified to create new nanomaterials, develop gene therapy drugs, and simulate logic functions. It was therefore decided to set up a G5 unit entitled Bioorganic Chemistry of Nucleic Acids, directed by Marcel Hollenstein.
This new entity will focus on two main research areas: the development of synthetic nucleic acids that can bind specific ligands (i.e. aptamers), and the preparation of DNA sequences that can catalyze various chemical transformations. Potential applications include aptamers that can be used as contrast agents in medical imaging, and biocatalysts capable of excising DNA lesions (cancer detection) and of forming and breaking various bonds (amide or glycosidic bonds, etc.), which could have applications in molecular biology.

Molecular gymnastics of a protein that is vital for tuberculosis

The unit led by Pedro Alzari (Structural Microbiology) specializes in research into the 3D structure of proteins using X-ray crystallography. In 2015, the unit's scientists (working closely with Marcelo Guerin's team from the University of the Basque Country in Spain) discovered new characteristics exhibited by the PimA enzyme which could be useful in the fight against tuberculosis. PimA is vital for the growth of the tubercle bacillus and is the main enzyme involved in the synthesis of phosphatidylinositol mannosides, key structural components in the cell wall of the bacillus. This research, published in the journal *Nature Chemical Biology,* was carried out as part of the MM4TB (More Medicines for Tuberculosis) European project, which was set up to identify and develop new drugs to fight tuberculosis. The scientists observed significant changes in the molecular architecture and topology of PimA when it interacts with the cell membrane. These experimental data are the first detailed findings on this type of change observed in an enzyme. They could contribute to the emergence of new enzymology concepts at the water-fat interface. These findings are not only important for fundamental research; gaining a better understanding of the 3D structures and action mechanisms of this family of enzymes could also pave the way for the design of a new class of anti-tuberculosis agents.

Genomes and Genetics

— By unraveling the content and architecture of genomes and 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 humans. The genomes of the tuberculosis bacilli, Streptococci, *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 help us understand human genetics. The department is also thoroughly investigating the evolution of infectious agents and the selective pressure they have exerted on both human genes and insect vectors over time. The progress of these research programs is largely based on new sequencing and genotyping techniques.

1. Larva of Aedes aegypti, *the mosquito vector for dengue, yellow fever, chikungunya, and Zika.*

2. 3D structure of a fragment of deoxyribonucleic acid (DNA) from the Bacillus subtilis *bacteriophage SPO1, showing its double-helix structure.*

A new mechanism for gene amplification in eukaryotes

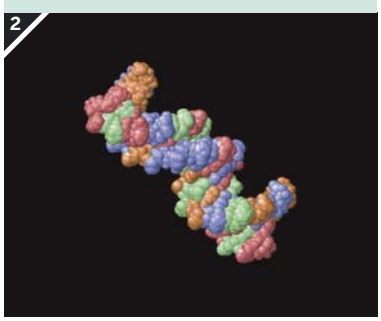
Chromosome aberrations may occur in all eukaryotic organisms (whose cells have a nucleus). Although these aberrations play an important role in evolution, they can also have harmful effects and trigger pathological processes, including cancer, in humans. Little is understood about the mechanisms behind these aberrations. Using yeasts – unicellular fungi that are useful for genetic and genomic research – the team led by Bernard Dujon discovered new types of chromosome aberration, some of which involve massive amplifications of long segments containing dozens of genes, thereby forming "giant" chromosomes known as macrotenes. The scientists obtained these results by using appropriate culture media to grow strains of *Saccharomyces cerevisiae* yeast in which essential genes (those coding for aminoacyl tRNA synthetases) were replaced by their counterparts from a phylogenetically distant yeast, *Yarrowia lipolytica*. The evolutionary divergence between these two species is so great that the resulting strains of *S. cerevisiae* – sick but viable – developed significant cellular stress, facilitating the selection of spontaneous mutants with a better proliferative capacity – a phenomenon that echoes tumor development. An analysis of the macrotene chromosomes showed that they were the result of sudden mutational events, probably brought about by gaps in the DNA template during chromosome replication. These can cause interference between replication loops, leading to rolling circles, which explains the massive amplifications. The genes carried by the amplified segments are overexpressed, and the resulting chromosome structures are stable enough to be maintained for a sufficiently long period to have an impact on evolution or pathological processes. Yeast represents a unique tool for scientists to shed further light on these phenomena.

Quality control of eukaryotic transcription

Transcription is an essential process whereby cells generate RNA copies of genes so that they can be translated into proteins. Alain Jacquier's team showed that in eukaryotic organisms such as yeast, used here as a model organism, this process is much less specific than previously thought. Transcription can begin in "non-coding" genomic sequences, which are not subsequently translated into proteins. This "pervasive" transcription represents a significant proportion of the genome, but it is not readily visible, since the resulting non-coding RNAs are degraded by a series of highly effective quality control mechanisms. Recent findings have also shown that the transcription of more than half of the genes in yeast also generates several aberrant RNAs, which are eliminated by these quality control mechanisms. Overall, a large proportion of transcription events generate "non-standard" RNAs, but this usually goes unnoticed, since these aberrant RNAs are quickly and effectively eliminated by transcript quality control mechanisms.

A young researcher joins the EMBO-YI program

Romain Koszul, who leads the Spatial Regulation of Genomes five-year group, is one of 23 young European researchers who have been chosen to join the prestigious EMBO Young Investigator program. Being in this network will improve visibility for his group and for its research into the role of chromosome organization in microorganisms, bacteria, and yeast. The group recently demonstrated how the genome of the model organism *Bacillus subtilis* uses cohesin proteins during cell division. These proteins induce a change in condensation in *Bacillus subtilis,* which could enable it to disentangle chromosomes during replication, stimulating bacterial growth.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Dengue transmission: doubt cast on an established theory

Every year, some 390 million people worldwide are infected with the dengue virus after being bitten by mosquitoes of the *Aedes* genus. But estimates suggest that 300 million of these people do not present clinical symptoms that are severe enough to be detected by health care systems. It was previously thought that these asymptomatic or mildly symptomatic infections did not produce a high enough concentration of the virus in the blood to infect mosquitoes and perpetuate the spread of the virus. Scientists working on the European project DENFREE, coordinated by Anavaj Sakuntabhai from the Functional Genetics of Infectious Diseases Unit, tested this hypothesis in a study carried out at the Institut Pasteur in Cambodia. People who tested positive for dengue virus in blood tests but did not show any clinical symptoms were then put into contact with healthy laboratory-bred mosquitoes. Subsequent analysis of the mosquitoes confirmed that they had been infected and would be capable of transmitting the virus. According to Louis Lambrechts from the Insect-Virus Interactions five-year group, this finding raises the possibility that people with few or no symptoms – in other words the majority of those infected by dengue – may actually be contributing to the spread of the virus without realizing it. People who are virtually or completely unaffected by the virus are also potentially exposed to more mosquitoes during their daily routines than those who are severely ill, bed-ridden or hospitalized.

Immunology

— The Immunology Department's research focuses on the development and regulation of the immune system, and protective and pathological immune responses in the context of human disease.

The department's work is based on three main research areas:

• development of the immune system: several teams are working on the differentiation of immune cells and cellular dynamics during the immune response;

• innate and acquired immunity: innate, non-specific and immediate immunity, together with adaptive, specific or acquired immunity, contribute to immune responses. Other teams are studying these responses, the cells involved and their interactions;

• immune response and pathology: some teams are studying protective, anti-infectious and anti-cancer immunity; others are focusing on immunologic disorders such as allergies or autoimmune diseases. The aim is to strengthen the former and ameliorate the latter. In addition, teams working on the Laboratories of Excellence (LabEx) project "Milieu Intérieur" ("The environment within") are examining a cohort of 1,000 healthy donors to help identify natural variability in immune responsiveness and pinpoint the genetic and environmental determinants of a healthy immune system.

1. Interaction between a dendritic cell and a lymphocyte.

2. A cluster of type 3 cells (shown in green) in a mouse colon. These cells are induced by the microbiota and block type 2 allergic reactions.

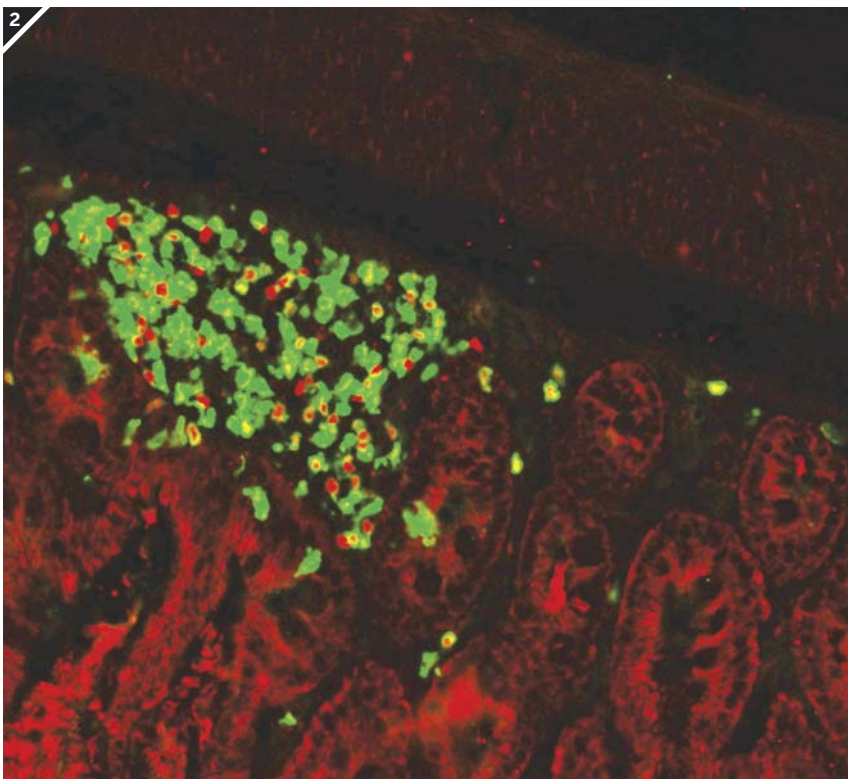
3. The sporozoites drained by the lymphatic vessels are blocked in the proximal lymph node. The popliteal node in mice bitten in their footpad by mosquitoes contains several fluorescent Plasmodium *parasites 1 to 4 hours after the infectious bites.*

AIDS vaccine candidate filmed *in vivo*

Using an innovative non-invasive imaging technique, scientists from the Dynamics of Immune Responses Unit filmed *in vivo* the process by which an AIDS vaccine candidate triggers the immune response. This previously unseen footage shows in real time how cells from the immune system are mobilized to the lymph node in just a few hours. The vaccine starts by inducing the formation in macrophages of the inflammasome, a complex assembly of proteins with a highly specific structure, which releases a signal carried by IL-1β. This signal triggers a chain reaction which assembles several key players of the immune system, including killer cells, which are vital for the elimination of infected cells. These results shed new light on the mode of action of this vaccine, confirming its therapeutic potential.

How dying cells regulate immunity

More than a million cells die every minute in an adult human body. But what actually happens to these cells? How does cell death influence all our living organs and tissues, particularly our immune system? Research into how the different types of cell death influence immunity is vital for the development of therapies based on immune system activation. Scientists from the Immunobiology of Dendritic Cells Unit demonstrated that necroptosis is able to induce a protective immune response against colon cancer. Surprisingly, this process of cell death induces a proinflammatory program in dying cells, which involves the activation of RIPK1. By demonstrating that RIPK1 orchestrates the antitumor immune response through its ability to coordinate the pathways associated with cell death and inflammation simultaneously, this research pinpoints potential new targets in the fight against cancer.

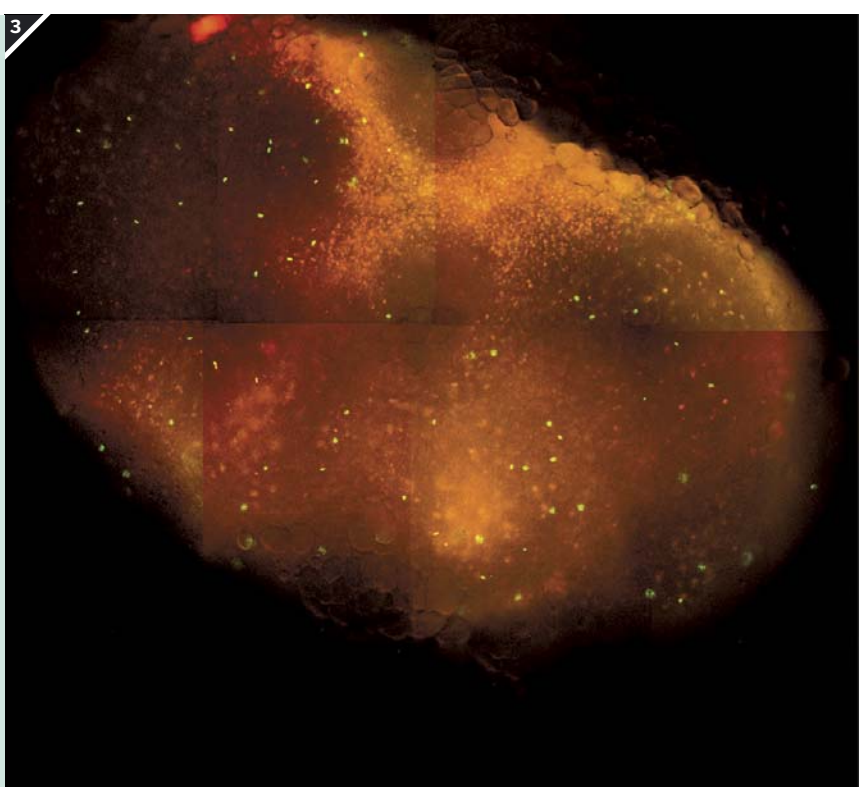


The role of the microbiota in preventing allergies

The human body is inhabited by billions of symbiotic bacteria, carrying a diversity that is unique to each individual. These bacteria are involved in digestion, vitamin synthesis and host defense, and a loss of bacterial symbionts promotes the development of allergies. The hygiene hypothesis suggests a link between the decline in infectious diseases and the increase in allergic diseases in industrialized countries. Scientists from the Microenvironment and Immunity Unit succeeded in explaining this phenomenon, showing how the microbiota affects the balance of the immune system: microbes induce an antibacterial response that specifically blocks the immune cells responsible for triggering allergies. These findings represent an important breakthrough in our understanding of the balance between the immune system's various defense mechanisms, opening up new therapeutic possibilities for treating allergies.

Awards for scientists

Lucie Peduto has been selected for the European Research Council (ERC) Consolidator Award for her research on the mechanisms of fibrosis, a process that leads to several extremely severe inflammatory diseases and is also involved in cancer. This award enabled the scientist, who directs the Stroma, Inflammation and Tissue Repair Unit, to develop an ambitious research program to investigate the cells behind this process. Philippe Bousso, Director of the Dynamics of Immune Responses Unit, was awarded the French National Academy of Medicine's prestigious annual prize for his research on the activation of immune cells in the lymph nodes and the coordination of these cells during the anti-parasite and anti-tumor responses and during graft rejection.



Infection and Epidemiology

— The Infection and Epidemiology Department develops fundamental and translational research in the field of infectious diseases, and remains deeply committed to public health issues.

The department investigates all elements 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 met using tools from a range of disciplines and a transversal approach which includes epidemiology, microbiology, dynamic imaging, immunology, histopathology, genetics, comparative genomics, cell biology, biochemistry and bioinformatics. In addition, the department plays a key role in public health issues, via seven National Reference Centers (CNRs), four WHO 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.

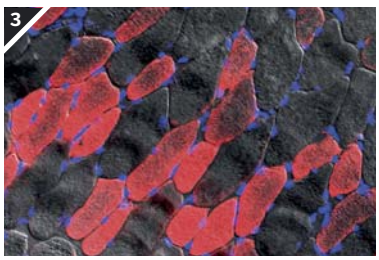
1. Identification of "biofilm" structures formed by the HTLV-1 retrovirus on a lymphocyte surface.

2. Virus of the 2009 A (H1N1) influenza pandemic produced in human muscle cell culture. Colored image.

3. Muscle tissue after sepsis. Muscle fibers are shown in pink. The lighter spaces between the fibers indicate defects in muscle regeneration.

4. Introduction pathway of lineage IV of the dysentery bacillus in Africa.

5. Cells infected by the Zika virus shown using transmission electron microscopy.



Cell therapy: new hope for treating muscle impairment caused by sepsis

Sepsis is a severe generalized inflammatory response to infection. It can cause tissue damage and organ failure that may prove fatal. One of the consequences of this disease, which affects 40% of patients in intensive care, is a loss of muscle capacity, which can lead to functional disability. This is a major public health problem. In normal conditions, skeletal muscle is able to regenerate *ad integrum* after an injury by using stem cells, known as satellite cells. Following sepsis, these satellite cells can no longer perform their regenerative function. The team led by Fabrice Chrétien, Head of the Human Histopathology and Animal Models Unit, working together with the Stem Cells and Development Unit, observed that after a severe case of sepsis, the satellite cells in mice were no longer able to divide and differentiate into muscle cells. They showed that this damage, which occurs at an early stage and has a long-term impact, is the consequence of a drastic loss in mitochondria, which serve as the cell's "powerhouse". These observations explain the persistent muscle impairment seen in patients. The scientists explored the possibility of using stem cell transplantation as a potential avenue for therapy: intramuscular injection of mesenchymal stem cells resulted in a drop in the level of overall inflammation, repaired the mitochondrial dysfunction, and restored the division capability of satellite cells in mice – thereby providing the conditions needed for muscle regeneration. The scientists now hope to validate these encouraging results in a clinical trial, due to take place shortly.

Find out more: Rocheteau P. et al., Nature Communications, 2015, 6:10145.

Shigella dysenteriae, the bacterium that causes bacillary dysentery, traced back to the 18th century

Several teams from the Institut Pasteur in Paris and the Institut Pasteur International Network, working in partnership with a number of international institutions and coordinated by François-Xavier Weill, Head of the Enteric Bacterial Pathogens Unit, have charted the evolutionary history of the bacillus that causes epidemic dysentery (*Shigella dysenteriae* type 1), one of the worst scourges to afflict humans during the 18th and 19th centuries. The scientists analyzed the genomes of more than 330 bacilli isolated in 66 countries between 1915 – in soldiers taking part in the Dardanelles campaign – and 2011. This study enabled them to trace the circulation and evolution of the pathogen during this period for the first time and to pinpoint the origins of the various outbreaks. It revealed that the pathogen was most probably the cause of the massive epidemics of bloody diarrhea reported in Europe in the 18th and 19th centuries, such as the outbreaks that killed more than 200,000 people in France in 1738-1742 and 1779. Between 1890 and 1900, the bacillus spread to America, Africa, and Asia, probably aided by movements of European populations resulting from emigration to America, colonization, and trade. The bacillus remained rife in Europe during the two World Wars – especially in the Dardanelles campaign (1915-1916), when epidemic dysentery was a significant factor in the defeat of the Allied troops – but it died out in Europe in the 1950s. With the exception of the major Central American epidemic in 1969-1972, which saw 500,000 cases, the outbreak in the Indian subcontinent was the most active throughout the 20th century and was the source of several epidemic waves that spread to Africa. This study also highlighted a dramatic increase in antibiotic resistance: 99% of strains developed multiple resistance between 1965 and 1990.

Find out more: Njamkepo E. et al., Nature Microbiology, 2016, 1:16027.

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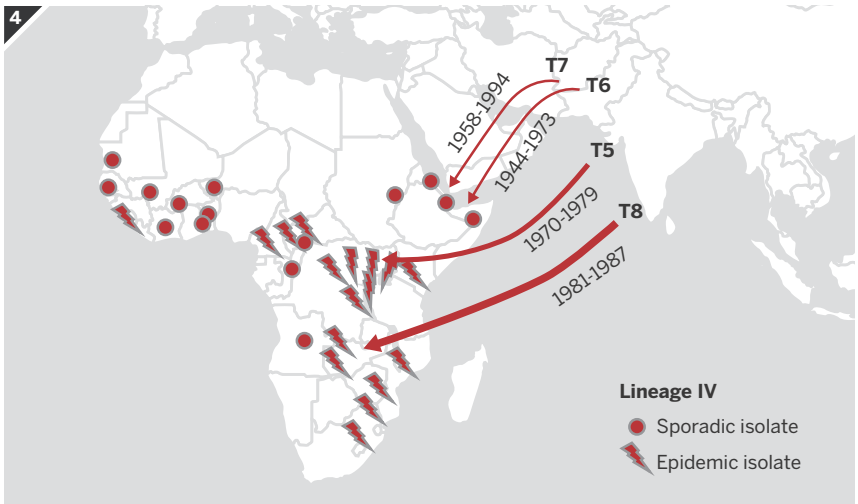

Zika virus behind Guillain-Barré syndrome

Between October 2013 and April 2014, alongside the Zika virus epidemic that hit French Polynesia, there was an increase in the number of cases of Guillain-Barré syndrome, a severe form of limb paralysis often accompanied by respiratory impairment requiring intensive care. More recently, the Zika virus emerged in Latin America, where the number of recorded cases of Guillain-Barré syndrome, as well as infants born with microcephaly, also rose. A multidisciplinary study published in *The Lancet*, coordinated by Arnaud Fontanet, Head of the Epidemiology of Emerging Diseases Unit, in cooperation with scientists from the Institut Louis-Malardé in Papeete, French Polynesia, and the French Polynesia Hospital Center, revealed that 98% of the 42 patients with Guillain-Barré syndrome had recently been infected by the Zika virus. Electrophysiological research demonstrated that the patients had a form of rapidly developing acute motor axonal nerve damage; 29% of patients required respiratory assistance. The risk of developing Guillain-Barré syndrome was estimated at 2.4 for every 10,000 people infected by Zika virus, based on the fact that two-thirds of the population of French Polynesia were infected during the epidemic period in 2013-2014. This work is significant since it confirms for the first time that Zika virus infection is involved in the severe neurological complications that constitute Guillain-Barré syndrome.

Find out more: Cao-Lormeau VM et al., The Lancet, 2016, pii: S0140-6736(16)00562-6.

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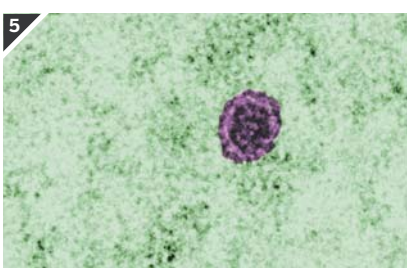


Prizes and awards

Fabrice Chrétien:
Pasteur Vallery-Radot Prize

Arnaud Fontanet :
René & Andrée Duquesne Award

Microbiology

— Besides their major 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.

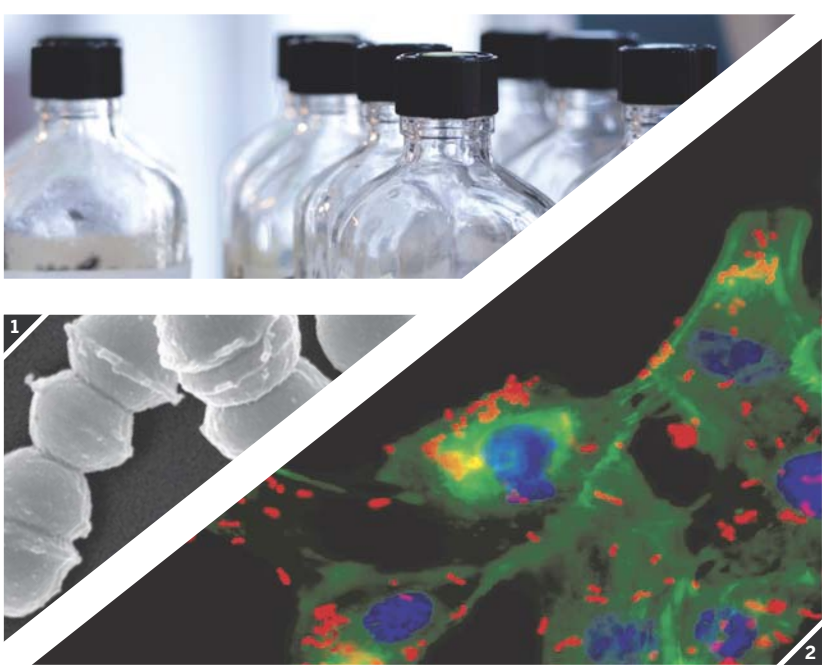
The scientists of the Department of Microbiology study, at the cellular and molecular levels, fundamental biological processes of bacteria and archaea (and their viruses) either alone or in communities and their evolution. They also focus on the mechanisms that render some of these microorganisms virulent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

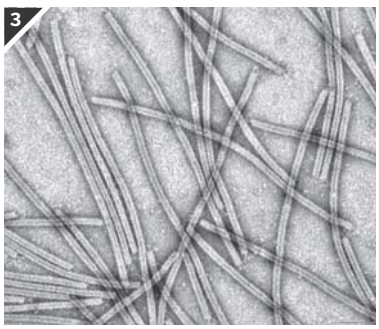
1. Group B streptococcus observed using scanning electron microscopy.

2. Streptococcus agalactiae *(orange dots) at the surface of human pulmonary epithelial cells. Fluorescence microscopy.*

3. Negative contrast electron microscopy of the SIRV2 virus.

4. The Streptococcus gallolyticus *bacterium is located in the colonic mucus layer.*





A microbial virus from extreme environment opens doors to new therapeutic strategies

The rod-shaped virus SIRV2 infects *Sulfolobus islandicus,* an archaeaon hyperthermophilic acidophile microorganism that lives in nearly boiling acidic hot springs. In the research teams of Edward Egelman (University of Virginia) and David Prangishvili (Molecular Biology of Genes in Extremophiles Unit, headed by Patrick Forterre) it was discovered that, in order to survive under extreme conditions, SIRV2 forces its DNA into what is called A-form. The A-form, identified more than half a century ago, was commonly thought not to have any biological relevance. However, this recent study reveals that A-form DNA constitutes a general biological mechanism for protecting DNA in the most adverse conditions.

Moreover, remarkable similarities were found in the strategies used by the virus SIRV2 and by bacterial spores to protect their genomes under adverse environmental conditions. Spores of important bacterial pathogens like *Clostridium difficile* or anthrax-causing *Bacillus anthracis,* present high resilience significantly hindering attempts to fight them. The study of SIRV2 may provide insight into the way bacterial spores work, and help researchers find new ways to destroy them. Finally, this research proves that DNA may be organized in a way that dramatically increases its stability under the harshest conditions imaginable. As such, the capsid protein of the virus SIRV2 can also be used for packaging of DNA molecules that can be used for the development of new therapeutic solutions.

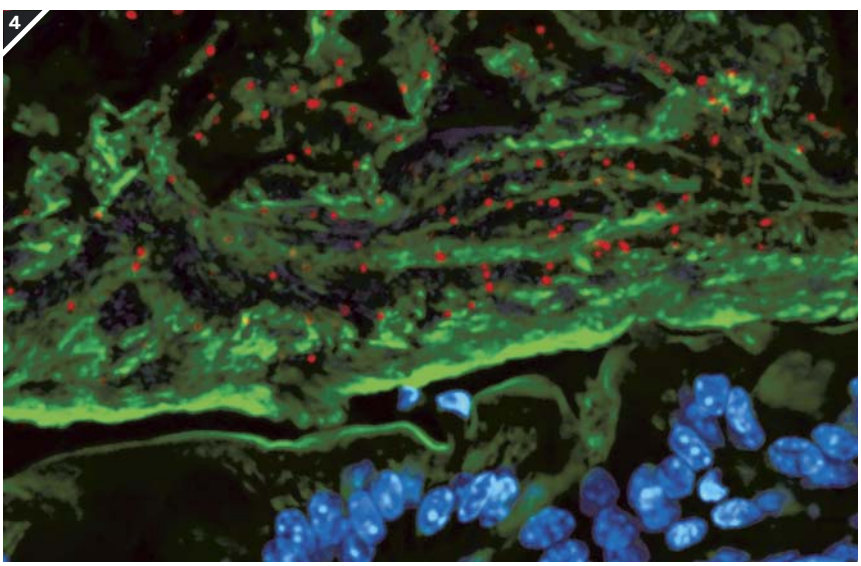
Understanding the association between *Streptococcus gallolyticus* and colorectal cancer

Streptococcus gallolyticus is a commensal bacterium of the human gastrointestinal flora. However, it is also responsible for an increasing number of septicemia and endocarditis cases in the elderly. Epidemiological studies have revealed a strong and unambiguous link between the presence of *S. gallolyticus* and the occurrence of colorectal cancer (CRC). CRC is the third most common cause of cancer mortality worldwide. Current medical recommendations advise to perform colonoscopy on patients with invasive *S. gallolyticus* infections to detect early asymptomatic colon neoplasia.

The team led by Shaynoor Dramsi in the Biology of Gram-positive Pathogens Unit (headed by Patrick Trieu-Cuot) aims at determining whether *S. gallolyticus* is the cause or the consequence of colorectal cancer.

In a recent study performed in collaboration with the teams of Philippe Sansonetti (Institut Pasteur) and Catherine Robbe-Masselot (CNRS-USTL), they uncovered a key role of Pil3, a surface appendage of *S. gallolyticus,* in the binding to colonic mucins. Pil3 was shown to be required for adhesion to human colonic HT29-MTX cells that secrete mucus but also for the colonization of mouse distal colon. *In vivo*, S. gallolyticus was found localized in the outer mucus layer.

This work paves the way for future studies aimed at evaluating the contribution of *S. gallolyticus* in the oncogenic process of the colon using cellular and murine models.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Two European ERC starting grants awarded for the study of bacterial cell shape and of the CRISPR immune system

Bacteria come in a wide variety of shapes and sizes controlled through the robust morphogenesis of their rigid cell wall. During the RCSB ERC project, the group of Sven van Teeffelen (G5 Microbial Morphogenesis and Growth) will use a combination of high-resolution microscopy and microfluidics to decipher how different proteins are involved in cell-wall remodeling processes and how these processes are coordinated.

The group of David Bikard (G5 Synthetic Biology) focuses on the study of CRISPR, an immune system allowing prokaryotes to defend against viruses. The goal of the CRISPAIR ERC project is to study the consequences of DNA breaks introduced by this system during immunity. The knowledge gained will then be used in the development of novel tools to study and fight pathogenic bacteria.

Changing to adapt: an environmental tale

Respiratory infectious diseases are the third cause of death worldwide. The nasopharynx is the portal of entry to *Neisseria meningitidis* and *Moraxella catarrhalis,* two bacteria that can cause severe systemic infections such as septicemia and meningitis. Frédéric Veyrier in the "Biology and genetics of the bacterial cell wall unit" (head Ivo G. Boneca) and the "invasive bacterial infections unit" (head Muhamed-Kheir Taha) discovered a major event that, during evolution, allowed these bacteria to become able to colonize the nasopharynx. Indeed, changes in cell morphology, from rod shape to cocci, were observed between an ancestral species and *N. meningitidis* and *M. catarrhalis* that correlated with the acquisition of the capacity to colonize this niche. A genome wide analysis led to the identification of two genetic events that were associated with this change of shape, the loss of the *yacF* gene first, followed by the loss of the cell wall elongation machinery. Moreover, the reconstruction of this genetic deletion in a bacterium harboring the ancestral version of the locus suggests that this gene is coordinating the transition from cell elongation to cell division. These changes seem to confer a selective advantage to these bacteria to survive in the new nasopharynx niche by enhancing binding to epithelial cells, favoring escape of the host immune system and improving nutrient acquisition.

Frédéric Veyrier is currently heading his own team at the INRS-Institut Armand-Frappier, Canada, which is an institute member of the Institut Pasteur International Network.

Mycology

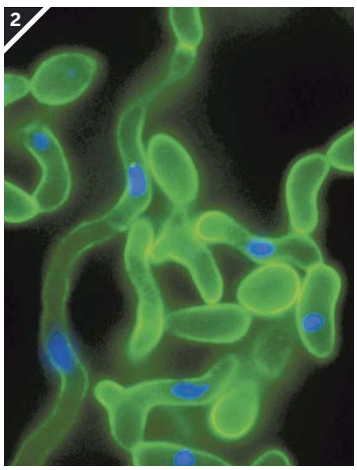
— Over the last thirty years, fungal infections have become a major public health concern. The Mycology Department is studying the biology of fungi that are pathogenic for humans and their virulence mechanisms, with the aim of developing new diagnostic, prevention and treatment strategies for fungal infections.

The Mycology Department is focusing its work on the three main fungi responsible for invasive fungal infections in humans: *Aspergillus fumigatus, Candida albicans* and *Cryptococcus neoformans*. The researchers are studying the genetic diversity of these species and the 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.

1. Cryptococcus neoformans. *Stain: India ink. This pathogenic yeast can cause cryptococcosis, a severe fungal infection in immunodeficient patients, especially AIDS sufferers.*

2. Photograph of Candida albicans *cells showing the nuclei (blue) and a surface protein (green), taken using fluorescence microscopy.*

3. Interaction between Aspergillus fumigatus *and* Pseudomonas aeruginosa *observed using scanning electron microscopy.*

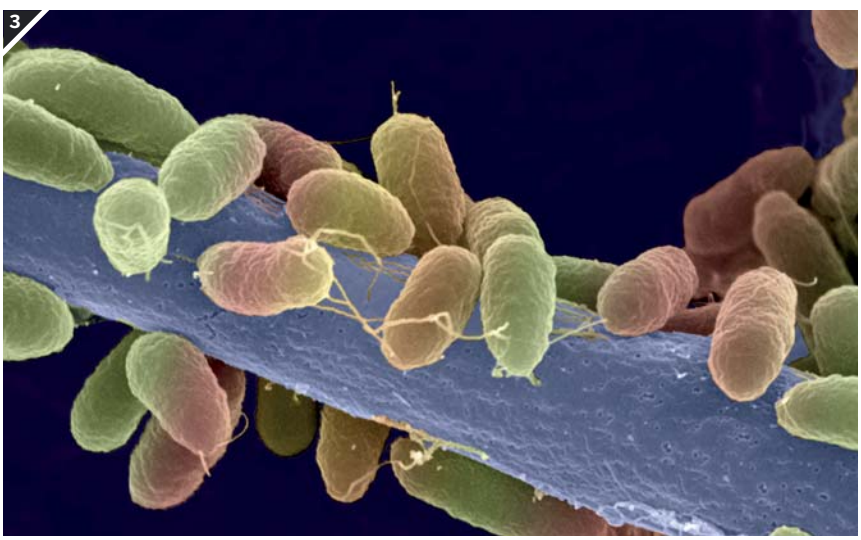


New genes involved in regulating genome plasticity in *Candida albicans* yeast

Candida albicans yeast is naturally diploid and has high genome plasticity. This plasticity results in a loss of heterozygosity – transition of genome regions from a heterozygous to a homozygous state – which helps increase resistance to antifungal drugs. In humans, loss of heterozygosity is one of the mechanisms in genome rearrangement that leads to tumor progression. Scientists from the Fungal Biology and Pathogenicity Unit developed an approach that uses reporter genes coding for fluorescent proteins to detect loss of heterozygosity events in single cells. This technique enables them to measure the frequency of these events during the growth of *C. albicans* and to pinpoint the environmental factors that trigger this phenomenon. The scientists used this method to identify several genes whose overexpression results in a significant increase in loss of heterozygosity. These genes serve as genome plasticity regulators, and some of them have human homologs that are involved in tumor progression. This innovative technique paves the way for the systematic identification of genes involved in regulating genome dynamics in *C. albicans,* and more generally in eukaryotic cells.

A new target for antifungal drug development?

A joint research project carried out by four Institut Pasteur units, two in the Mycology Department (Aspergillus, Chemistry and Biocatalysis, Fungal Biology and Pathogenicity, and Genetics of Macromolecular Interactions), the Normandy Drug Research Center (CERMN), and the University of Cincinnati led to the identification of an antifungal molecule, sr7575, with an unusual mechanism of action. This molecule, which is not toxic for mammal cells, shows broad-spectrum activity that blocks the growth of a wide range of fungi including *Aspergillus fumigatus, Candida albicans, Cryptococcus neoformans,* and *Saccharomyces cerevisiae.* The scientists used a chemogenomic approach to demonstrate that the antifungal activity of sr7575 is exacerbated when the ERAD pathway, for the degradation of misfolded proteins in the endoplasmic reticulum, is impaired. These findings, obtained using the *S. cerevisiae* yeast model and the *A. fumigatus* pathogenic fungus, indicate that the mechanism of action of sr7575 is conserved between yeast and filamentous fungi. They also show that the impact of sr7575 on protein quality control is compensated by the ERAD pathway, although it remains independent from the more general response to abnormally folded proteins in the endoplasmic reticulum. The discovery of sr7575 therefore reveals that protein quality control in the endoplasmic reticulum could serve as a new target for the development of antifungal molecules.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Creation of a new unit

Guilhem Janbon is the Director of the RNA Biology of Fungal Pathogens Unit. This newly created unit will focus on the structure and plasticity of the transcriptomes of human fungal pathogens. It aims to draw up a full list of all the coding and non-coding RNA molecules in the fungal cell and also to shed light on the mechanisms that regulate the dynamics of their expression depending on the environmental conditions. These essential questions will improve understanding of how the structure of fungal transcriptomes is regulated during infection and the consequences of these variations for the fungus and the infected host.

Cryptococcus neoformans adopts a dormant state during infection

Cryptococcus neoformans is a cosmopolitan yeast found in the environment, which, unusually, is able to survive phagocytosis in several organisms ranging from single-cell protozoa to specialized immune cells in mammals (macrophages, dendritic cells, and neutrophils). This yeast is capable of lying dormant in humans for several years before reactivating if immunodeficiency occurs. Scientists in the Molecular Mycology Unit used cryptococcosis mouse models and models of macrophage interaction to examine the metabolic state of yeast and its morphology during interaction with the host. They revealed the existence of a yeast population in the lungs with a reduced response to stress, altered capacity for growth, and impaired expression of the genes involved in adaptation to nutritional deficiency, entry into stationary phase, autophagy, and cell-wall and capsule synthesis. These findings suggest that *C. neoformans* enters a dormant state during interaction with the host. This research will shed new light on the biology of fungi for which dormancy plays an important role in the survival of individuals within a microbial population. It paves the way for the identification of molecules that target dormant forms of *C. neoformans* to prevent reactivation in immunodeficient patients at risk of cryptococcosis.

Neuroscience

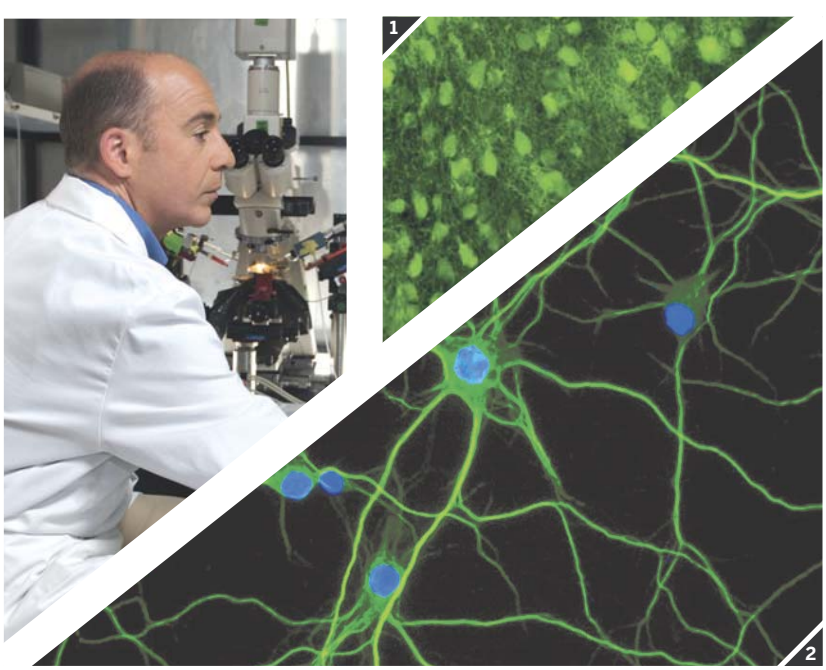
— The Department of Neuroscience attempts to understand how molecules, cells, synapses, and neural circuits work together to perform mental functions. This fundamental research led to many significant medical breakthroughs.

At the beginning of the 21st century, understanding the mechanisms underlying brain function represents a major challenge for fundamental research and its applications, particularly in the area of public health. The Department of Neuroscience is committed to improving knowledge in this area by using multiscale approaches that involve all hierarchical levels, from molecules to behavior. The department is looking to extend its activities over the next few years, especially by stepping up cooperation with partners to develop a systems approach, with the aim of building a strong foundation of knowledge and expertise. This will also facilitate the development on campus of innovative transversal research programs, which make use of data from a range of disciplines within the life sciences such as microbiology, structural biology, immunology, and development. The department's approach involves understanding the brain as an open system that interacts with other systems (endocrine, microbial, and immune), with the aim of opening up new avenues of research to shed light on how the brain works and propose new therapeutic applications.

1. Use of bi-photonic imaging to analyze human neurons transplanted into a mouse cortex.

2. Mouse hippocampal neurons in culture.

3. Microglia in the mouse olfactory bulb. Microglia are the only population of cells in the immune system that reside permanently in the brain. They are the main form of active immune defense for the protection and maintenance of the brain.



Diversity in synaptic behavior helps co-detect multiple sensory stimuli

The brain is a fantastically powerful computational machine that must process information about sensations arising from the external world, the state of our body (internal world), as well as both subconscious and conscious cognitive processes. To deal with the sheer magnitude of information, the cerebellum takes charge of processing subconscious-sensory-motor and sensory-cognitive tasks, thereby freeing up the rest of the brain for other important cognitive behaviors. To do this, the cerebellum utilizes the largest neuronal population (granule cells), which comprises 50% of the neurons in the brain. This extraordinary anatomical arrangement inspired computational neuroscientists to suggest that if the different information streams (modalities) could be processed (correlated) by a single granule cell, the cerebellar cortex could function as a universal computing machine (multi-layer perceptron, Marr-Albus theory). However, this anatomical feature had not been satisfactorily demonstrated for several decades. Nevertheless, multilayer perceptron learning models have provided a critical theoretical basis for neural networks and machine learning algorithms used in digital face and speech recognition.

The laboratory of David DiGregorio provided some of the first definitive evidence that multiple senses converge on single granule cells, the missing link supporting a biological basis of pattern separation using multilayer perceptron learning. They also found that synaptic inputs carrying the different senses behaved similarly for a given sensory modality, but very differently across modalities. This synaptic diversity supports a temporal basis for pattern separation, which further extends the computational power in cerebellum beyond what was originally thought.

Find out more: Chabrol et al., Nature Neuroscience. 18, 718-727, doi: 10.1038/nn.3974 (2015).

Hypervulnerability to sound-exposure: understanding an underlying mechanism opening up therapeutic perspectives

The laboratory of Christine Petit had previously found that mutations of PJVK, which encodes pejvakin, cause the DFNB59 recessive form of sensorineural hearing impairment. Pejvakin-deficient individuals and mice (Pjvk-/-) exhibit variable auditory phenotypes. This lab set out to understand the origin of the unusual phenotypic variability of this form of deafness. This called for the elucidation of the role of pejvakin, hitherto entirely unknown. Based on the correlation noted between the elevation of hearing thresholds and the number of pups per cage, the researchers hypothesized a possible harmful effect of pup vocalizations on the auditory system of Pjvk-/- mice, i.e., a hypervulnerability to sound exposure in the absence of pejvakin. They showed that the auditory sensory hair cells and auditory pathway neurons of Pjvk-/- mice and also of individuals defective for pejvakin are exceptionally vulnerable to sound. The auditory sensory organs of Pjvk-/- mice display features of marked oxidative stress and impaired anti-oxidant defenses. Pejvakin, they found, is associated with peroxisomes, organelles involved in redox homeostasis. These organelles in Pjvk-/- hair cells show structural abnormalities after the onset of hearing. Based on their finding that pejvakin is required for peroxisome oxidative stress-induced proliferation, they then questioned whether the response to noise exposure, known to trigger oxidative stress in all animals, could involve peroxisome proliferation in normal mice. This is the case: noise immediately induces an upregulation of PJVK transcription in wild-type mice and peroxisome proliferation in the auditory system.

These findings reveal that peroxisome proliferation protects the auditory system against noise-induced damage, by the anti-oxidant activity of this organelle. They indicate that patients with the affected gene coding for pejvakin should avoid noisy environments and the use of auditory prostheses unless associated with an effective anti-oxidant treatment. Because the researchers could prevent noise-induced hearing loss in Pjvk-/- mice by intracochlear transfer of Pjvk cDNA, this opens therapeutic avenues for hearing loss from overexposure to noise which, according to WHO, may affect one billion people worldwide, in 2050.

Find out more: Delmaghani et al., Cell. Nov. 5, 2015; 163(4):894-906. doi: 10.1016/j.cell.2015.10.023.

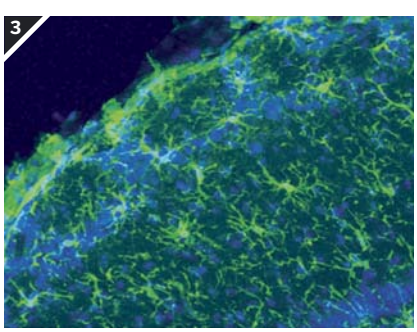
A new strategy for human neuron analysis

Many human psychiatric disorders have a genetic component and are linked to a brain development impairment. This is the case of autism spectrum disorder (ASD) and schizophrenia. A new strategy was developed to analyze the development of human neurons after transplantation in rodent brains.

The human neurons undergo their innate maturation program between 3 and 12 months. This technology provides unique access for detailed analysis of the development of human neurons and their functional properties, and for identifying the consequences of genome mutations and human polymorphisms related to mental illnesses. These approaches are used by the Integrative Neurobiology of Cholinergic Systems Unit to study human neurons derived from human induced pluripotent stem cells (iPSC), expressing polymorphisms in genes specifically coding for nicotine receptors.

Loss of adult neurogenesis leads to depression

Increasing clinical reports show that major depression is characterized by pronounced olfactory deficits, yet the underlying mechanisms remain unknown. We used an animal model of depression to study whether hypothalamic-pituitary-adrenal axis perturbation could be sufficient to provoke olfactory deficits. We found that chronic corticosterone not only induces marked deficits in olfactory acuity, fine discrimination and olfactory memory, but also significantly decreases adult brain neurogenesis. Importantly, the antidepressant fluoxetine (i.e., Prozac)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restores both adult neurogenesis and depressive states, and improves olfactory performances. Detailed analysis of adult-born neurons showed that their morphology was flourished by fluoxetine in the two parts of the brain where neurons continue to be produced all life long (i.e., the hippocampus and the olfactory bulb). Our data reveal that high levels of corticosterone during chronic stress lead to olfactory deficits while treatments with antidepressants could successfully restore olfaction. These findings highlight a novel therapeutic effect of fluoxetine. We are carrying on a preclinical study on olfactory dysfunction in major depressive disorders at Kremlin-Bicêtre Hospital using our novel olfactory tests to assess the severity of depression.

Find out more: Siopi et al., The Journal of Neuroscience, January 13, 2016, 36(2): 518-531.

Parasites and Insect Vectors

— The Parasites and Insect Vectors Department investigates the life cycle of parasites and their vectors. The research program undertaken addresses global public health concerns in terms of prevention, control, and antiparasitic treatment.

The department focuses its research on three key eukaryotic parasites responsible for severe diseases of major health and economic burden in most of the world's regions: *Plasmodium* species, which cause malaria; *Leishmania* species, the causative agents of leishmaniasis; and *Trypanosoma* species, responsible for sleeping sickness. The *Anopheles* mosquito (the vector of *Plasmodium* and numerous arboviruses) is also studied, as is the tsetse fly (the African trypanosomiasis vector). The department combines fundamental research on *in vitro* and *in vivo* models – including field work, particularly in Africa and Asia – with applied research, notably on resistance to antimalarial drugs, and the identification 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 the virulence factors, pathology, and survival strategies of these organisms.

6 research units

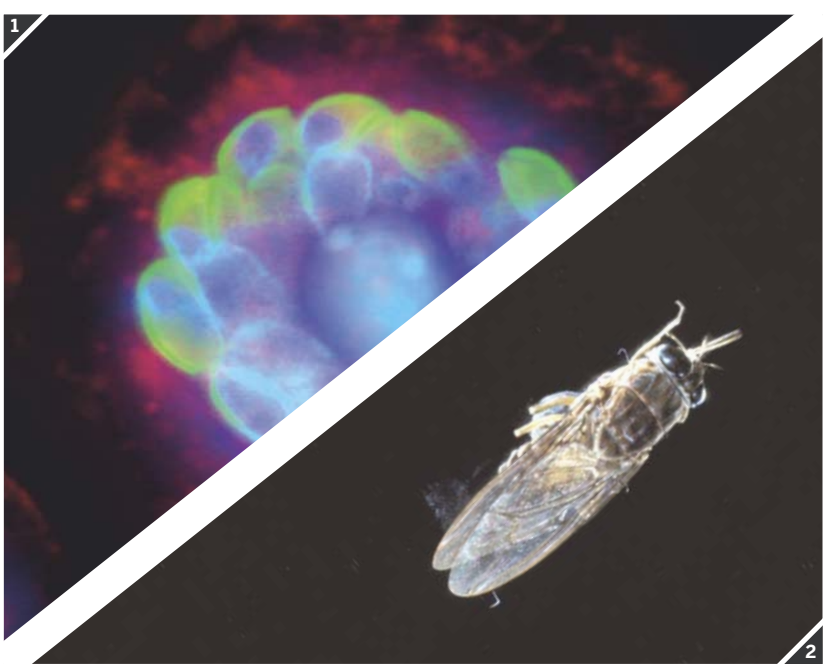
1 Center for the Production and Infection of Anopheles (Cepia)

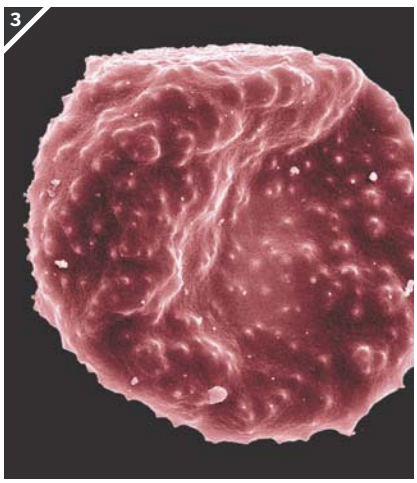
1. Peritoneal macrophage cell infected by the protozoan parasite Leishmania major *(red, actin; green, tubulin; blue, nuclear labeling).*

*2. Tsetse fly (*Glossina*). Vector of African trypanosomiasis, or sleeping sickness.*

3. Electron microscopy of a red blood cell infected by the Plasmodium falciparum *parasite.*

4. Trypanosoma vivax *– blood form. Responsible for animal trypanosomiasis or Nagana disease.*





Malaria: post-transcriptional gene regulation of invasion proteins

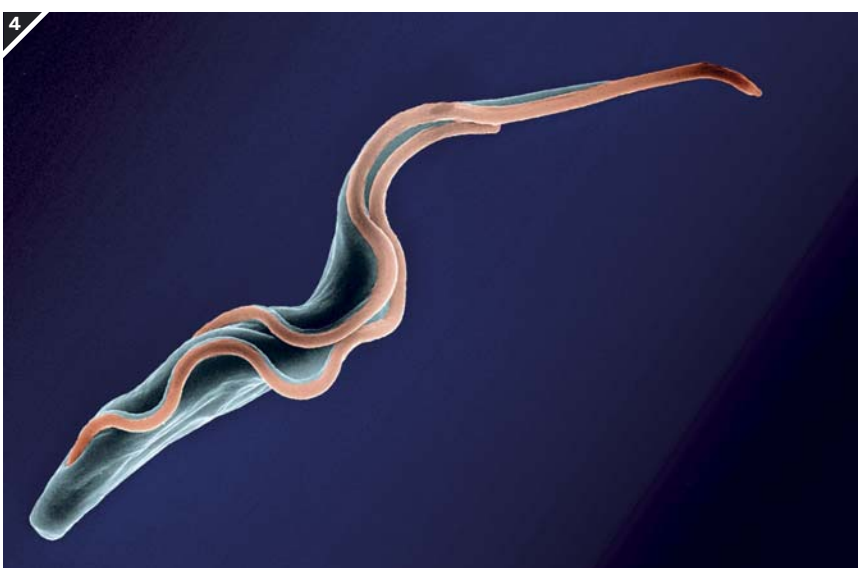
Plasmodium, the parasite responsible for malaria, infects red blood cells.

The aim of this research was to establish the key molecular role played by the RNA binding protein Alba1 in the post-transcriptional gene regulation of the blood stage of the *P. falciparum* parasite. The scientists began by using transcriptomic profiling to identify a number of messenger RNAs that bind to Alba1, some of which code for invasion proteins.

They then established that the binding of some of these messenger RNAs to Alba1 correlated with translational repression in trophozoites, whereas the release of these messenger RNAs from Alba1 in mature stages was associated with protein synthesis (Vembar et al., *Genome Biology,* 2015). An off-line application known as "Protospacer Workbench" was developed as an interface for rapid, flexible design of Cas9 guide RNA, for CRISPR/Cas9 genome editing. Designing an optimal guide RNA is vital in order to avoid the non-specific activities of the endonuclease Cas9. Given the drawbacks of existing programs, the use of Protospacer Workbench revolutionizes CRISPR/Cas9 genome editing for pathogenic parasites whose genomes have always been difficult to edit, such as *P. falciparum* and *Leishmania spp* (MacPherson and Scherf, *Nature Biotechnology,* 2015).

African trypanosomiasis: a new virulence factor regulating tsetse fly infection identified in the parasite's flagellum

The unicellular parasite *Trypanosoma brucei,* responsible for sleeping sickness, has to travel from the intestine to the salivary glands of the tsetse fly, its vector host, before it can be passed on by bites to vertebrates, including humans. Trypanosomes have organelles known as flagella, which are responsible for various cell functions. We purified the intact flagella of the parasite to determine their molecular composition. One of the new proteins belongs to the arginine kinase family, which has three members. The Trypanosome Cell Biology Unit demonstrated that only one gene codes for arginine kinase 3 (AK3), which is characterized by a short insertion of thirty amino acids required for flagellar membrane targeting. AK3 is expressed at all stages of parasite development, especially during infection in the tsetse fly. Deleting the gene which codes for the enzyme disrupts the energy regulation of parasitic mobility. This causes a sharp fall in the migration and development of trypanosomes deprived of AK3 within the insect, demonstrating the key role of this enzyme in the infectious power of parasites in tsetse flies (Ooi et al., *PLoS ONE,* 2015).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Profile

Dr. Rogerio Amino,
Head of the Malaria Infection & Immunity Unit

In October 2015, the Malaria Infection & Immunity Unit directed by Dr. Rogerio Amino was set up within the Department of Parasites and Insect Vectors. In recent years, Dr. Amino made a major contribution to the field of malaria research, especially with his discovery of a new cutaneous stage in malaria infection, demonstration of immune mechanisms for the elimination of infected hepatocytes, and identification of the escape and manipulation strategies used by parasites in host cells. His new unit will use functional approaches to study the behavior of the parasite *in vivo* and to screen protective antigens; it will focus on identifying the determinants needed for infection and immune protection in the host with the aim of developing a multigene malaria vaccine.

Vectors: the microbiome of mosquito vectors may influence the spread of malaria

Members of the *Anopheles gambiae* complex are the main mosquito vectors of the parasite responsible for human malaria in Africa. Other species of mosquitoes related to this complex transmit the parasite effectively despite exhibiting ecological differences, especially in the composition of the microbial flora found in larvae breeding grounds. We examined the hypothesis that differing levels of exposure to environmental pathogens influence the development of the mosquitoes' immune genes. The sequence of a panel of candidate immune genes was analyzed using wild *A. gambiae* populations from Burkina Faso in West Africa (Mitri et al., *PLoS Pathogens,* 2015). This analysis revealed signs of genetic differentiation among the mosquito population, enabling the identification of new immune factors in these mosquitoes. The gene inactivation of these new immune factors made the mosquitoes much more susceptible to infection by the parasite responsible for malaria. The scientists also demonstrated that some of these immune factors were capable of biochemical interaction to form immune protein complexes. This evolving genetic profile, identified in the natural mosquito population, provides scientists with a new set of tools to identify genes capable of blocking the development of the parasites responsible for malaria in mosquito vectors.

Virology

— Viruses that are pathogenic for humans are vast in number, causing chronic or occasional infections of varying degrees of severity that may even prove fatal. The Virology Department studies all aspects of viruses with the aim of improving our defenses against them.

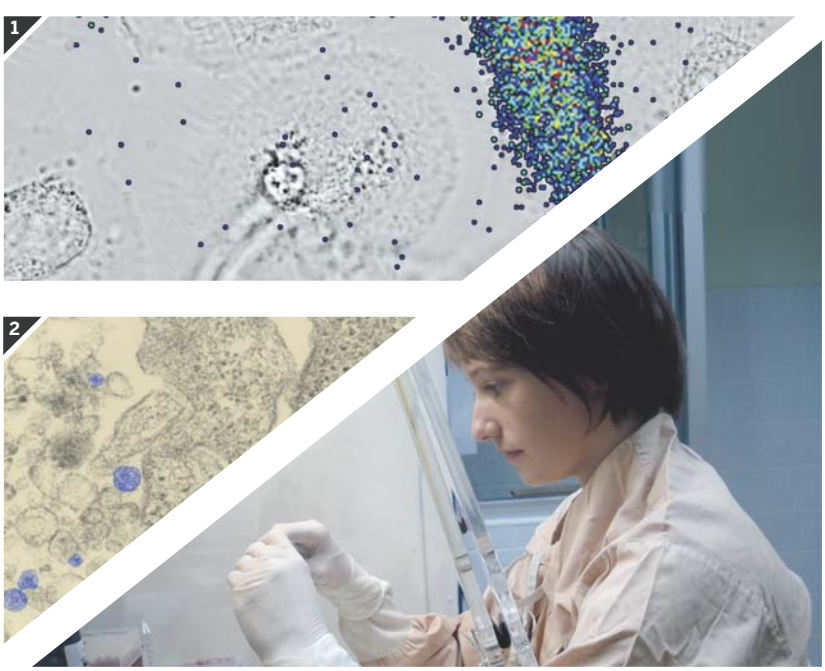
The department's 17 units seek to determine the structure of viral proteins or molecular organization, discover new determinants of viral pathogenicity and multiplication mechanisms, as well as understand their complex interactions with host defense mechanisms. The viruses under study include respiratory viruses such as influenza; viruses that cause cancer (papillomaviruses, HTLV, and the hepatitis B and C viruses); retroviruses such as HIV; insect-borne viruses that are responsible for severe diseases including dengue, chikungunya, yellow fever, and Rift Valley fever; and viruses causing hemorrhagic fever (such as the Lassa fever virus). The department's scientists work in close collaboration with others on the Paris campus and also with the Institut Pasteur International Network. The Virology Department also implements translational research projects for the design of vaccine candidates, screening of new therapeutic targets and development of diagnostic tools. It houses several National Reference Centers and WHO Collaborating Centers, thereby playing a major role in the epidemiological monitoring of viral infections.

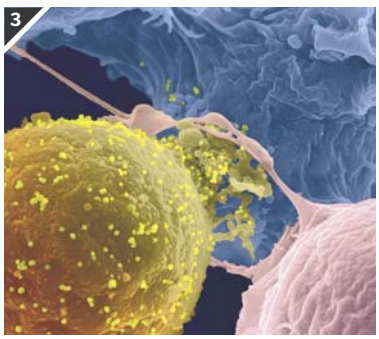
1. A primary human macrophage infected by an HIV pseudovirus carrying the luciferase gene.

2. One of the very first photos of the HIV-1 AIDS virus taken on February 4, 1983.

3. Cell-to-cell transmission of HIV-1. A lymphocyte infected by HIV-1 (yellow pseudocolor) in contact with non-infected lymphocytes (blue and pink).

4. Aedes albopictus *in an insectarium.*





Remission from HIV infection in a patient infected via mother-to-child transmission who was given antiretroviral therapy from birth

The HIV, Inflammation and Persistence Unit helped demonstrate a case of prolonged remission from HIV infection in a patient born with HIV who was given antiretroviral therapy from birth, although the treatment was stopped six years later. This case of a young adult infected with HIV since birth confirms the results already obtained by the same team and their partners in the ANRS EP47 VISCONTI cohort, consisting of patients infected during adulthood whose remission from HIV infection was due to a course of antiretroviral therapy initiated in the first few months after infection. The members of this cohort continue to show the ability to control their infection more than ten years after stopping treatment. This young adult does not share the genetic factors usually associated with those who are naturally able to control HIV infection; she was unable to control her viremia after birth in the absence of effective treatment. The early administration of antiretrovirals therefore seems to be what has enabled her still to be in remission twelve years after she last took them. These initial observations played a role in the recent therapeutic recommendation that all patients infected by HIV, especially babies born to HIV-positive mothers, should be given antiretroviral therapy as soon as possible after birth, once HIV infection is confirmed.

New strategies for the development of an effective vaccine for the four forms of dengue

Dengue is a viral disease transmitted by mosquitoes that is widespread in tropical regions. Most patients suffer mild flu-like symptoms, but dengue can sometimes develop into hemorrhagic fever, which often proves fatal. There are four serotypes of the dengue virus: DEN1, 2, 3, and 4. Although there is no cross-protection between these serotypes, infected patients produce antibodies capable of neutralizing all four, known as "universal antibodies". This discovery led scientists to believe that the four serotypes may have a structure that forms common antigenic determinants which are recognized by universal antibodies. This structure could serve as a target for the development of an effective vaccine for DEN1, 2, 3, and 4. The difficult task was to locate and identify this shared structure. The Structural Virology Unit rose to this challenge, using crystallography and 3D reconstruction methods to identify the site recognized by universal antibodies at the surface of the virus. The description of this antigenic structure shared by the four serotypes paves the way for the development of a dengue vaccine that would be effective for all four forms of the virus.


4

Ebola epidemic in West Africa: the Institut Pasteur's response

After the Ebola-Zaire strain was first confirmed in West Africa in March 2014, the Ebola epidemic, which spread across the whole of Guinea and also to Liberia and Sierra Leone, infected 28,600 people and claimed 11,300 lives, making it the most severe Ebola outbreak since the virus was first described in 1976. The Institut Pasteur and the Department of Virology were closely involved in the Ebola Task Force created in 2014, developing vaccine candidates and helping to set up a diagnostic laboratory at the Macenta treatment center in the forest region of south-eastern Guinea. The Department of Virology sent volunteers, scientists, engineers, and students to the affected areas to make sure the center ran smoothly. The first trials of the new diagnostic tests using RT-PCR, including the paper-based test – developed by the Ebola Task Force teams – were carried out at the Macenta center.

Profiles

Felix Rey receives the 2015 Pasteur-Weizmann/Servier Prize for his work in the field of emerging pathogenic viruses

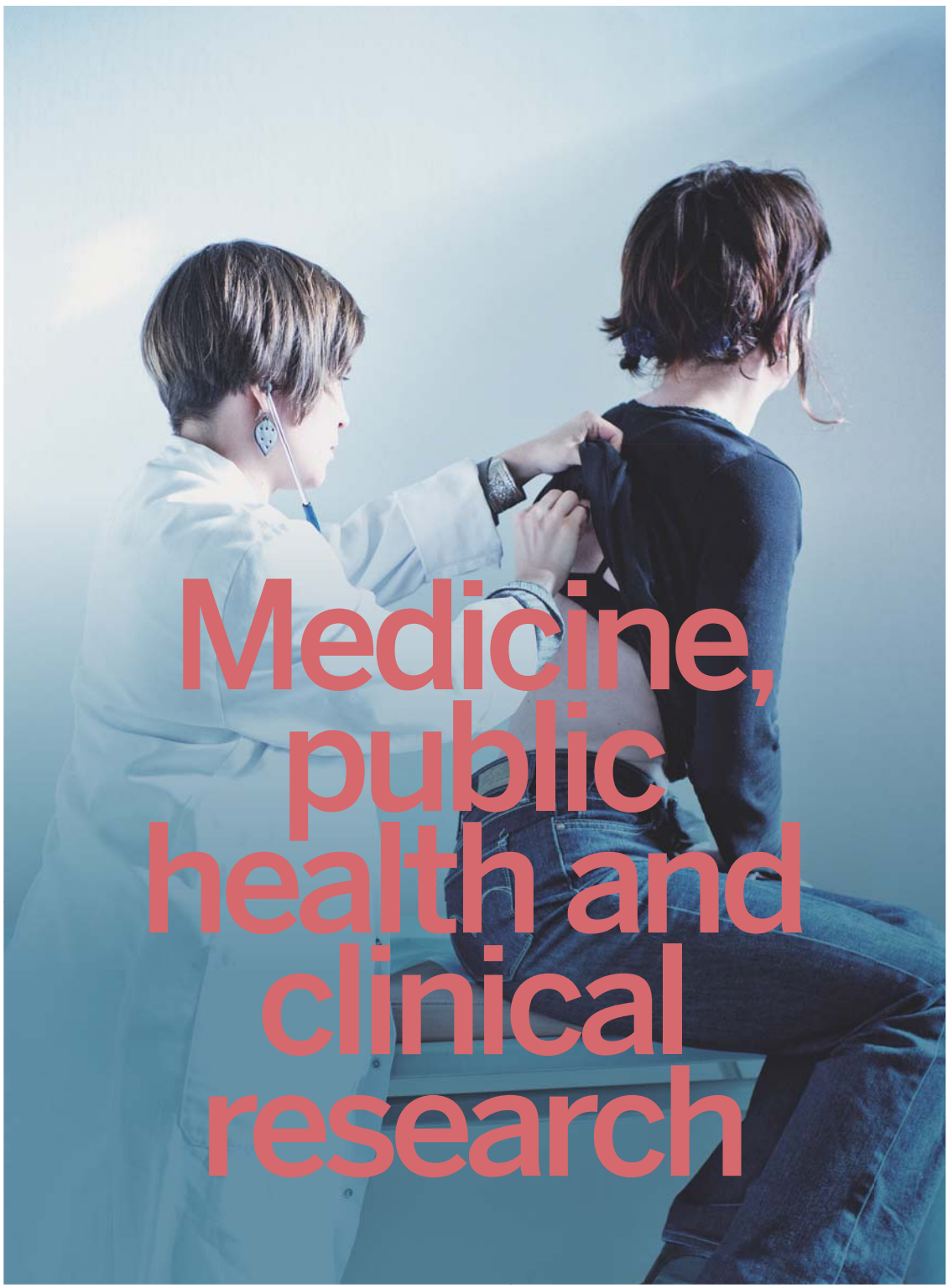
Felix Rey, Professor at the Institut Pasteur and Head of the Structural Virology Unit, conducts research into the viruses responsible for severe global epidemics such as dengue, chikungunya, hepatitis C, respiratory syncytial virus, and rotaviruses. The work carried out by Professor Rey and his teams focuses on the structure of pathogenic viruses and on improving understanding of the mechanisms they use to enter cells. This preliminary research is vital for the development of antiviral agents and vaccines.

Marco Vignuzzi, winner of the Sanofi-Institut Pasteur Award

Marco Vignuzzi, Head of the Viral Populations and Pathogenesis Unit, received the Sanofi-Institut Pasteur Award in the "Junior" category for his work on how to predict which mutations will confer a high epidemic potential on a given virus, and which mutations will attenuate it. His discoveries pave the way for improved monitoring of viral populations during epidemic outbreaks and also for the identification of mutations that can be introduced into a viral genome to create a live vaccine that has lost its virulence.

Noël Tordo heads up the Institut Pasteur in Guinea

Noël Tordo, Head of the Antiviral Strategies Unit in the Department of Virology, became Director of the new Institut Pasteur in Conakry, Guinea. This institute will become an independent department of Gamal Abdel Nasser University. The first two research units, for virology and entomology, will have first-rate diagnostic platforms. The aims of the Institut Pasteur in Guinea will be to provide training for students, technicians and laboratory managers and to diagnose diseases with epidemic potential, in particular those caused by the Ebola, Lassa fever, yellow fever, Rift Valley fever, and influenza viruses.



Medicine, public health and clinical research

The consolidated approach of the CRT

— Medicine and public health are never far from the headlines, and are at the very heart of the Institut Pasteur's priorities, guiding our strategic choices. Due to its cross-sectoral approach, the Center for Translational Science (CRT) is instrumental in coordinating the actions of the various players involved in these fields, with the aim of developing applications via preclinical or clinical phases.

The CRT's aim is to provide concrete support to scientists, by offering them everyday guidelines for formalizing their scientific questions, helping them find essential clinical partners, draft their projects and carry out ethical and regulatory procedures. This support is based on a number of CRT strengths, including in-depth structuring of these complex activities, a broad range of skills (clinical, technological, bioinformatics and biostatistics), and strong external partnerships with clinicians.

The Center for Translational Science is founded on the excellence of its research teams, and is available to help scientists set up ambitious projects calling upon cutting-edge technologies (technical core of the CRT), or improve the feasibility of their projects. From this perspective the various sections of the CRT or the Medical Affairs and Public Health Department are consulted not only in connection with access to samples and the constitution of cohorts and biobanks (ICAReB, National Reference Centers, the "Milieu Intérieur" project, etc.) but also in connection with the management of ethical and regulatory aspects affecting projects (ethics unit, clinical core of the CRT). The consolidated view provided by this comprehensive approach to translational science strengthens the validity of the discipline as a whole.

The fact that, with the exception of the Medical Center, the campus has no hospital to provide clinicians with direct access to patients is a challenge that has led to a "re-medicalization" policy, which in turn is leading to closer institutional relationships with hospitals. This initiative has resulted in the following new developments:

1. temporary posts for interns and chief residents;
2. contracts with "affiliated hospitals", the first of which was signed with Sainte-Anne Hospital on November 27, 2015; there are other projects planned with hospitals in the Paris Public Hospital Network (AH-HP), which involve leading institutions such as Necker-Enfants Malades and Cochin hospitals;
3. "partnership contracts" set up in 2015 by four doctors who have been partially released from their hospital duties to work directly in the research units with which they collaborate;
4. "joint units", which combine a clinical department and a research unit, and which enhance this initiative by providing a link between clinical departments and Institut Pasteur research units;

This "re-medicalization" initiative now encompasses individuals (partnership contracts), research units (joint units) and institutions (affiliated hospitals).

The various partnerships that have been forged transcend the notion of project-based science, and constitute the building blocks for core actions over the long term that will provide a solid base for translational science in the years to come. The full range of these actions, including concrete support to scientists and detailed structuring of activities, can be seen throughout the entire Institut Pasteur International Network. The far-reaching and international vision of clinical research is fundamental to the studies carried out by the CRT in association with other departments such as the Department of International Affairs or the Center for Global Health.

Center for Translational Science (CRT)

— The aim of the Center for Translational Science (CRT) at the Institut Pasteur is to further the transfer of knowledge from basic research to applied clinical research and vice versa, in order to enhance patient care and provide a better understanding of diseases.

The Center comprises a number of different departments and additional activities:

• A clinical department that instigates and coordinates clinical research activities, oversees the ethical and regulatory authorization process, and monitors project advancement;
• A technological structure that provides access to selected, state-of-the-art technologies in translational science, in association with the Citech;
• Expertise in bioinformatics and biostatistics, which is instrumental in data analysis in association with the C3BI;
• Sampling procedures, including gathering informed consent and sample collection from healthy volunteers (ICAReB, "Milieu intérieur") and patients;
• Patient care (the Institut Pasteur Medical Center, medical teams and other care structures including affiliated hospitals or hospitals with partnership contracts and joint units);
• Scientific and communication initiatives, operating both within the Institut Pasteur and externally.

The CRT's comprehensive approach provides a unique type of access to these sub-units, so that scientists interested in translational research receive integrated support throughout the development and execution of their projects.

Stanislas Pol – the new Director

Professor Stanislas Pol was appointed Director of the Center for Translational Science in January 2015. Stanislas Pol is a clinician, who manages the Hepatology Department at Cochin Hospital, is a professor at Paris-Descartes University and heads up a research team in Unit 1223 of the Immunology Department. His clinical and translational research focuses on viral hepatitis and hepatic fibrogenesis.

The technological platform of the CRT

The technological platform of the CRT unites the former human immunology center and the Cytometry platform. Three new laboratories – the cell sorting laboratory, the flow cytometry and protein analysis laboratory and the molecular laboratory – were opened in 2015. The molecular laboratory has been designed to accommodate all stages of the study of nucleic acids, from the preparation of RNA to the post PCR stages, with dedicated areas for each stage. A major focus of the platform is user training on a monthly basis, to ensure full autonomy in the use of the available technologies. In 2015, in collaboration with the Teaching Center, the Center for Translational Science organized the first practical session for 2nd year Master's students in Advanced Immunology. This practical work focused on studying the immune systems of healthy volunteers using the platform's cutting-edge technologies.

Scientific events

The **Pasteur-Medicine Quarter Hour** aims to unite the community and enable scientists to examine clinical issues. Clinicians are invited to give short presentations on the diseases they are treating. In general they begin their presentation by outlining clinical cases, and conclude by looking at unanswered questions relating to the specific pathology that could potentially give rise to collaborative initiatives. Nineteen Pasteur-Medicine Quarter Hour presentations were given in 2015, on a range of topics including Crohn's disease, Parkinson's disease, autism, scleroderma, pulmonary fibrosis, multi-resistant tuberculosis, HIV, allergies and immune deficiencies.

In the same vein, the CRT organizes **Pasteur-Science Quarter Hour** presentations, where scientists are invited to present their research findings to hospital departments, thereby forging new links with hospitals.

Every two months, participants in clinical research are invited to give presentations on current topics at CRT Workshops

Forging links with the medical community

The Center for Translational Science is strengthening the Institut Pasteur's links with the medical community on several levels: via the funding of individuals (second-year Master's students, temporary posts, partnership contracts), the creation of Institut Pasteur and AP-HP joint units, the creation of an "affiliated hospital" status, with the first such agreement having been signed with Sainte-Anne hospital.

In 2015 the CRT funded three medical students in their second Master's year. One of these students is working in the team headed up by Christine Petit, investigating gene therapy models for a rare hearing disorder, another is studying the relationship between depression and muscular homeostasis, in the team headed up by Fabrice Chrétien, and the third is working on gastric cancer and infections, in the team led by Philippe Sansonetti.

Eight young doctors were appointed to temporary posts, enabling them to continue their research with the Institut Pasteur.

Four partnership contracts were also funded, enabling doctors who are more advanced in their careers to develop research projects. Various fields are concerned: infectiology, neuropsychiatry and rheumatology.

Joint units were created between the unit led by Lars Rogge and the Department of Rheumatology at Cochin hospital, as well as with the Department of Hematology at Saint-Louis hospital. Similarly, a joint unit was created between the unit led by Philippe Sansonetti and the Department of Gastroenterology at Henri Mondor Hospital.

Examples of projects funded

The fight against the formation of bacterial biofilms

The formation of bacterial biofilms on medical devices is the cause of infections acquired during hospital stays (nosocomial infections). Since biofilms are not highly susceptible to antibiotics, conventional treatments are inefficient, and often the only therapeutic course of action is to withdraw the device that has been contaminated by biofilms. The fight against biofilms is a serious public health issue. The team led by Jean-Marc Ghigo has discovered new anti-biofilm strategies that have proved effective *in vitro* and *in vivo,* and these must now be assessed in clinical trials. The Center for Translational Science is funding pre-clinical trials in connection with this work.

Hidradenitis suppurativa

About 700 patients suffering from *hidradenitis suppurativa* – a chronic and debilitating skin disease – are currently being treated by Dr. Aude Nassif at the Institut Pasteur Medical Center. A collaborative initiative has been launched with the Department of Immunology, aiming to shed light upon the immune responses in skin biopsies from these patients, and to screen the molecules present in the sebum.

Neutralizing antibodies against hepatitis B

The project led by Hugo Mouquet is aiming at more effective characterization of neutralizing antibodies against hepatitis B in patients with chronic hepatitis B infection who undergo HBs/anti-HBs seroconversion, and comparison of these antibodies to those found in vaccinated subjects.

Pasteur-Medicine Quarter Hour presentations unite the community and enable scientists to examine clinical issues.

PASTEUR-SCIENCE QUARTER HOUR PRESENTATIONS, FOR SCIENTISTS TO PRESENT THEIR RESEARCH TO HOSPITAL DEPARTMENTS SO AS TO FORGE NEW LINKS

CNRs and WHOCCs

— The Institut Pasteur houses 15 National Research Centers (Paris and Lyon) as well as four associated CNR laboratories (French Guiana), which are able to draw upon the scientific expertise of the research units and support structures such as the Laboratory for Urgent Response to Biological Threats (CIBU). Seven of these CNRs are also WHO Collaborating Centers (WHOCCs), and one CNR/WHOCC has been designated as a reference laboratory for the World Organization for Animal Health. Another WHOCC has expertise in enteroviruses (in particular the poliovirus).

Designated as such for five years by the Minister for Social Affairs and Health, these expert laboratories are observatories for monitoring communicable diseases on French soil. They support health authorities in diagnostic, epidemiological surveillance and research activities, thus playing an important part in the Institut Pasteur's public health mission.

The PIBnet project: a comprehensive, united and innovative approach to public health monitoring. For the last few years, developments in communicable disease epidemiology have highlighted the need for national response structures that are able to respond swiftly, developing and implementing effective tools for diagnosis and microbiological characterization of cases as part of epidemiological investigations. These technological developments form the core expertise of the CNRs, based on their experience of syndromes, diseases and pathogens, their affiliation with research units and their links with parallel institutions in other countries.

The Institut Pasteur's role in this mechanism is carried out at national and international level. At the start of 2015, the launch of the PIBnet initiative within the Institut Pasteur (which also stands to benefit the entire Institut Pasteur International Network) created a dual-purpose national structure that includes a technological facility available to all CNRs, which also offers cutting-edge expertise within each CNR individually. It comprises:

- a shared facility for microbial characterization (P2M) which will enable the development of tools for analyzing entire genomes, as well as diagnostic tools; these tools will offer a combination of not only the latest technological equipment (high-throughput sequencing, mass spectrometry, etc.), but also the associated skills, particularly in bioinformatics and bioanalysis;

- the CIBU – a structure dedicated to emergencies (24/7), in particular relating to unknown pathogens; this structure is geared towards interaction with specific CNRs. It is also able to intervene in the field to support local teams handling epidemics;

- CNRs, which are at the very heart of this mechanism, and benefit from the technological support provided by the platform, access to the CIBU and their strongly rooted origins in the research units.

This structure provides a basis for planning cross-disciplinary projects and even syndromic approaches to be conducted within the Institut Pasteur, between CNRs and with partner hospitals. Specific skills (MOT, animal experimentation, L3 environment) also facilitate the management of regulatory constraints. Lastly, it complements the role of the CNRs in training health professionals working in the community, in particular via technology transfer, training courses and the hosting of trainees.

In 2015 the Listeria CNR received, characterized and typed 1,903 samples from human and non-human

species. The number of human cases of listeriosis observed in Europe is rising (404, +8%). Of the 16 investigations carried out on clusters of cases, in association with the relevant authorities, five were able to identify the contaminated food concerned.

The Listeria CNR is part of a platform for exchanging information from the European Center for Disease Prevention and Control (ECDC) during European health alerts, and participates in European molecular microbiology monitoring. The WHOCC for Listeria has taken part in the investigation of four European epidemics and contributes to the work of INFOSAN (International Food Safety Authorities Network) managed by FAO and WHO.

The CNR has refined its analytical process and now uses the MALDI-TOF platform and genome sequencing of strains. A method of core-genome allele analysis has been developed for *Listeria monocytogenes* typing. This method was endorsed in collaboration with American, Danish, Canadian and British National Reference Centers, as well as the French National Institute for Health Monitoring. In association with another team, the National Reference Center has already developed and patented a method for rapidly determining the major clonal complexes of *Listeria monocytogenes* by multiplex PCR. Lastly, the National Reference Center has conducted a study highlighting the existence of hypervirulent clones, and identified the genes associated with serious forms of listeriosis.

Work continued throughout 2015 on the prospective case-control study Monalisa, to analyze the clinical, radiological, biological, and genetic characteristics of this infection.

During the 2014-2015 season the high intensity influenza epidemic was characterized by the predominant circulation of the A(H3N2) influenza subtype, with co-circulation of the A(H1N1)pdm09 subtype and type B. The CNR Coordination Center for influenza viruses detected 1,373 viruses from 1,482 samples sent to them by outpatient services (Sentinelles network and GROG Géronto) and 633 samples sent by hospitals (RENAL – the French National Laboratory Network). Of the 842 influenza viruses detected by outpatient services, 75% were type A influenza viruses – including 18% A(H1N1) pdm09, 56% A(H3N2), 0.2% type A without subtype – and 25% were type B influenza viruses, 91% of which were of the B-Yamagata lineage. Antigenic characterization showed that the subtype A(H3N2) influenza viruses in circulation included a discernible proportion of variant viruses, which were antigenically distinct from the vaccine strain. The A(H1N1) pm09 influenza viruses antigenically characterized were all similar to the A/California/09/2009 vaccine strain, and the type B influenza viruses of the B-Yamagata lineage were mostly similar to the B/Massachusetts/2/2012 strain included in the 2014-2015 vaccine. The epidemic was particularly severe in the elderly, and was notable for the large number of deaths from all causes, mainly in patients aged 65 or more.

The **National Reference Center for Hantaviruses** reported the following in 2015: 1/ A level of human cases of hantavirus infection in mainland France that was well above the average number of cases detected annually over the period 2003-2014. 2/ The detection of a virologically confirmed case of Seoul hantavirus in central Paris. It is unusual for cases to be detected in Europe, and the only virologically confirmed cases have occurred in France. 3/ The detection of a virologically confirmed case of Tula hantavirus 60km east of Paris. Detection of this European virus is a very rare event. There was a great deal of discussion about the pathogenic potential of this virus in humans. It had previously been detected in a single, immunocompromised person in the Czech Republic. This case, detected by the National Reference Center, is the first case seen in an immunocompetent person. The patient presented with pain, fever and impaired liver function. Infection probably took place during the handling of infected voles brought into the patient's home by his cat.

Medical Center

— The Institut Pasteur Medical Center (CMIP) is the Paris-based entity in direct contact with patients (vaccination centers, consultations for travel medicine, infectious and tropical diseases, allergies and anti-rabies measures).

In 2015

45,000

people vaccinated at the Institut Pasteur's International Vaccination Center

70,000

doses of vaccine administered

CMIP activity. The Institut Pasteur International Vaccination Center (CVI) is the reference center for those who travel 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 wishing to be vaccinated, but also those seeking specific information relating to their planned trip abroad. In 2015 more than 45,000 people passed through the center, and received over 70,000 vaccinations. There are two categories of patient: those who attend the center privately (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 CMIP within the framework of health monitoring contracts drawn up with the Institut Pasteur. These travelers are seen before departure, and very often also when they return to France. This activity falls within the context of travel medicine consultations, for which the expertise of the Medical Center is internationally renowned. As a result of this expertise, the Center is often in the news, and is consulted in the case of emerging infectious diseases. During the Ebola crisis in 2015, doctors working at the Center were regularly called upon to provide expert advice to people returning from affected countries or who feared that they might have been in contact with the infection. The calm professionalism of the Center's staff has also played a significant part in allaying public fears.

In all these areas, the CMIP website gives invaluable support to the general public in matters such as health recommendations for travelers, vaccination schedules or for advice on particular pathologies on an individual basis. The health page on the Institut Pasteur website is one of the site's most visited pages. In addition to vaccinations and advice to adult and child travelers – particularly for fragile patients (i.e. those with HIV, organ transplants or other immune deficiencies), and humanitarian travelers (including, in 2015, those leaving for the Ebola epidemic region) – a major part of the Medical Center's activities is dedicated to the treatment of imported diseases in returning travelers, HIV infection, and widespread infectious diseases such as Lyme disease. Some of these pathologies are monitored in collaboration with Necker-Enfants Malades University Hospital, via the Necker-Pasteur Infectiology Center (CINP). Within this framework, there are ten CINP doctors, from both the infectious and tropical disease department at Necker Hospital and the CMIP, in addition to the CMIP doctors for monitoring the significant caseload of HIV+ patients. These consultations generate a high level of clinical research and give rise to collaborative initiatives, particularly with the French National Agency for AIDS Research (ARS).

There are also consultations in dermatology, particularly to treat hidradenitis suppurativa, which have led to remission in a significant number of patients via an innovative therapeutic strategy that specifically targets this orphan disease. The CMIP 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 post exposure to rabies. Although there has been no case of infection reported in France for many years, there are still occasional deaths in people who have been infected abroad. Two types of risk have been discerned: 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 (a bite, scratch, the licking of a wound or mu-

cous membrane). Treatment consists of several vaccine injections, usually in combination with serotherapy. Current vaccines are highly effective and well tolerated.

The multidisciplinary team providing consultations for allergies is able to treat allergies of all types.

Clinical research at the CMIP. The CMIP also undertakes clinical research, which is directly relevant to its specialist medical areas: cohorts in the field of HIV infection, the pathophysiology of hidradenitis suppurativa (microbiology and genetics, in collaboration with Necker Hospital and the ICAReB platform), vaccinology (interaction of the yellow fever and measles vaccines in children).

2015 saw the publication of microbiological and therapeutic results obtained for hidradenitis suppurativa. These results provided a better understanding of the microbial composition of this disease, by demonstrating the presence of a characteristic bacterial flora in the lesions, which also varies depending on the severity of the cutaneous lesions themselves. These results also offer an initial explanation of the efficacy of the new therapeutic strategy currently being offered at the Medical Center, which is based on prolonged antibiotherapy specifically targeting the level of severity. The positive results observed to date with these strategies should be confirmed by a therapeutic trial to be conducted within the next few years.

The new insights offered by these projects fully justify the CMIP's place in the Center for Translational Science, and demonstrate the support that can be provided for questions raised by clinicians.

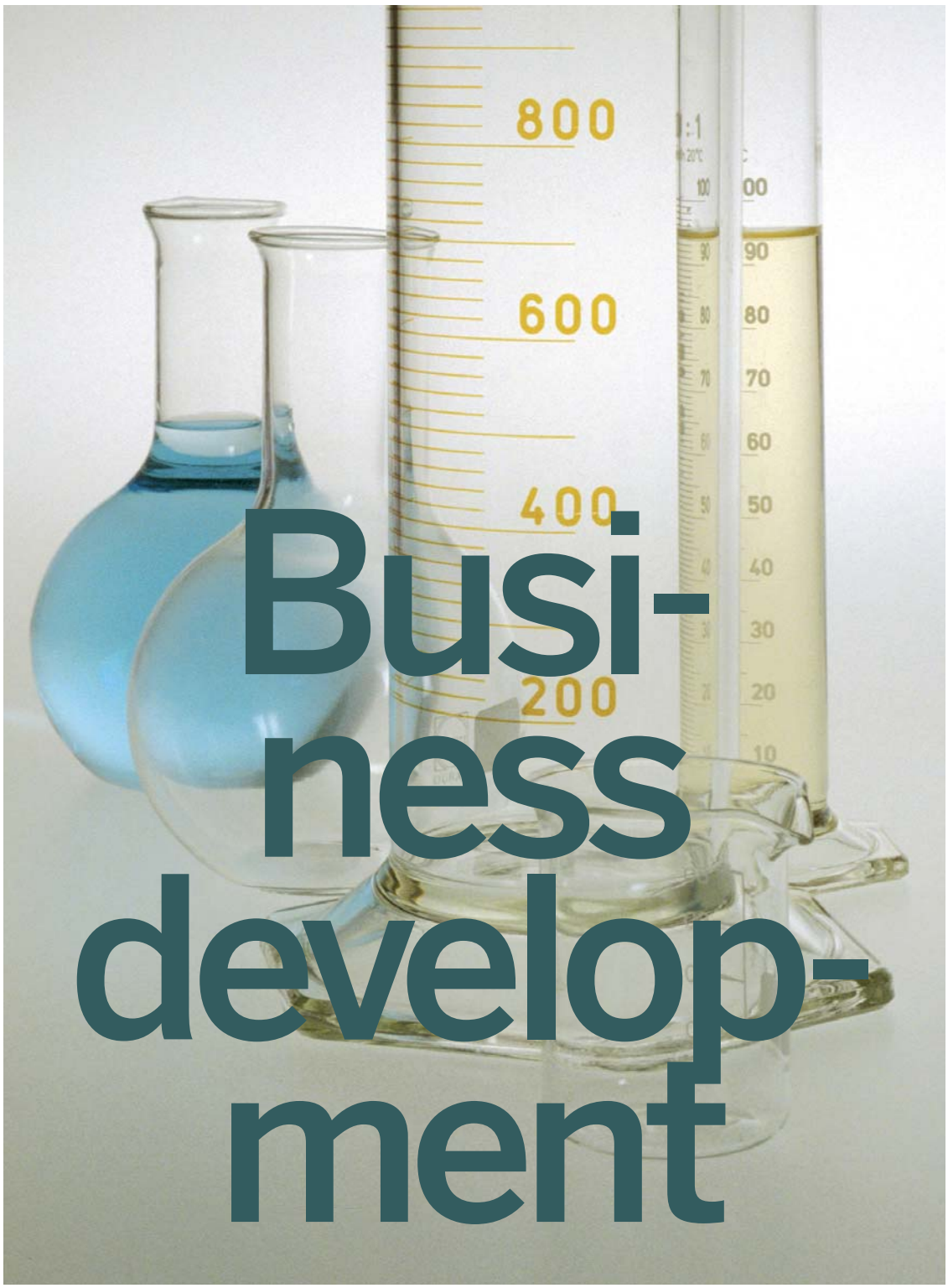
The calm professionalism of the Center's staff plays a significant role in allaying public fears.

In 2015

12,286
consultations in infectious and tropical diseases, travel medicine and dermatology

2,419
consultations for rabies

3,588
consultations for allergies



Busi-ness develop-ment

Developing and sustaining research

— A year after it was set up, the Department of Development is now fully operational and is working to support researchers. It promotes scientific activity by helping to build projects, and fosters the development of topics that meet the challenges of biomedical research and the strategic plan. It also boosts cooperation, particularly between Paris and the International Network.

Significant progress in mapping Institut Pasteur and International Network scientific activities. Work was undertaken to map the scientific activities of the Parisian campus and International Network for the purpose of describing, analyzing and promoting researcher projects, in partnership with other support departments. In 2015, Department of Development scientists provided a comprehensive view of over 30% of the Institut Pasteur's activities, and a target of 100% has been set for June 2016. A customized tool was introduced to organize and handle the content generated. In-depth analysis based on this work led to the publication of a full report on our research for diagnostic purposes. This resulted in a project portfolio being put together which is now used to support business development.

A record year in terms of successful European calls for proposals. In 2014, a systematic campaign was launched to raise awareness of European calls for proposals among researchers in a bid to gain external funding. It is led by the Representation and Information on Europe Group, which also represents the Institut Pasteur on issues relating to research policies introduced by European institutions. Today, the success rate of European Research Council (ERC) grants among our researchers means the Institut Pasteur ranks top of recipient European research organizations.

4 ERC Starting Grants, **2** ERC Consolidator Grants, **2** ERC Advanced Grants, **6** Marie Sklodowska-Curie individual grants – the Institut Pasteur leads in France for this type of funding

30% of Institut Pasteur scientific activities mapped, close to **100** meetings linked to Parisian invention disclosures

€5 M pledged through incentive programs

Over **550** projects submitted in response to national, European and international calls for proposals

Major investment in innovative and multidisciplinary curiosity-driven incentive programs. Close to €5 M were pledged through a combination of specific calls for proposals and strategic research incentive initiatives. Fifty-six new incentive programs were backed in 2015, calling on 65 units, the Citech and involving 17 International Network institutes. In particular, the Major Federating Program "Microbes & Brain" (7 projects) really took off, and the first international symposium was also held on the campus in July 2015. Concerted Incentive Actions (AIC) in synthetic biology, in particular, led to the launch of the iGEM PlastiCure project (led by the Department of Education) and the industrial application of Institut Pasteur biological resources (for example with the Cyanobacteria AIC).

Development of African-focused partnerships. In 2015, the Department of Development undertook several initiatives with the Bill and Melinda Gates Foundation Global Health Program, and together they are working to form a community of leading African biomedical research scientists, and foster innovations to meet UN objectives in terms of health and sustainable development.

Research applications

— The mission of the Research Applications and Industrial Relations Department (DARRI) is to detect, promote, support, protect, and transfer inventions arising from research efforts by Institut Pasteur scientists to industry partners in France and abroad. The aim is 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.

61 invention disclosures registered, i.e. a 13% increase in relation to the average of the previous three years

30 new priority patents and 13 provisional applications

Industrial application is one of the Institut Pasteur's historical callings. It is also a key strategic issue, as it generates essential resources for the Institut Pasteur and boosts funding for new projects. Academic and industrial partnerships enable patients to benefit from innovations developed on campus and help to fund effective research that meets global public health challenges.

Proactive intellectual property management. With 61 invention disclosures registered in 2015, i.e. a 13% increase in relation to the average of the previous three years, resulting in 30 new priority patents being filed and 13 provisional applications (software, expertise and biological material), the campus maintained its high level of innovation by national and international standards. In particular, patents were filed on applications in microbiology and infectious diseases with CRISPR-CAS9 technology, on sensitive and rapid diagnostic tests for serious fungal infections, and on the activation of dormant stem cells *in vivo* or *ex vivo*, paving the way for cell therapy and tissue repair.

The *Nature Biotechnology* journal ranked the Institut Pasteur among the top ten best institutions worldwide thanks to its 185 US and European patents granted for the 2010-2014 period. This highlights the quality of patent applications and their content both in technical and scientific terms.

Partnerships at all stages of negotiation. In 2015, the Institut Pasteur reached an agreement with the US company BlueBirdBio to develop Lentivirus DNA-Flap technology. The aim is to foster sub-license agreements to distribute the Lentivirus technology as widely as possible and enable clinical developments with many industrial stakeholders in the field of gene therapy, particularly for cancer with CAR-T cells, or even with reprogrammed stem cells to correct genes involved in many genetic diseases.

The Institut Pasteur also successfully concluded discussions with Qiagen for diagnostic tests for high-risk types of HPV infections.

A worldwide exclusive intellectual property license agreement was signed with the Swiss company Stragen in May 2015. It focuses on new compound derivatives, called STR-324 or endogenous dual ENKephalinase inhibitors (DENKIs), for pain management. It entered phase I clinical trials in the third quarter of 2015.

Collaborative research partnerships with industrial stakeholders remain a major challenge for transferring Institut Pasteur research innovations to new products for society, and for responding to global public health issues. This is why a new strategic partnership was signed between the Institut Pasteur and the Institut Mérieux in 2015. In the same vein, a framework agreement and initial specific research agreement were concluded with the US company Moderna Therapeutics to investigate chemically modified mRNAs for vaccine applications. Finally,

a partnership agreement was signed with Integragen in March 2015 for high-throughput sequencing activities in National Reference Centers (CNRs) and the Institut Pasteur microbiology collections.

The Research Applications and Industrial Relations Department generated €38.4 M in royalties in 2015 – an 8% increase compared with the average of the previous three years – and €3.3 M from collaborative research agreements with industrial partners, resulting in a gross revenue of €41.7 M.

This strong year is particularly important given difficulties linked to the gradual expiry of historical patents, and the complicated legal context in the US following the Supreme Court's "Myriad" ruling.

In line with measures undertaken and new HIV patents granted in 2012 and 2013, initiatives were launched in 2015 that will be pursued in 2016 to conclude a major new agreement in this field.

The Institut Pasteur in the top 10* best institutions worldwide.

**Research Biotech Patenting 2014, Brady Huggett & Kathryn Paisner, Nature Biotechnology, July 2015.*

Educa-tion

Relaying knowledge

— Teaching and training are at the heart of the Institut Pasteur's activities and they form an essential part of the legacy of its founder, Louis Pasteur. For over 125 years, and since the first microbiology course given by Émile Roux in 1889, the Institut Pasteur has had a key role in science teaching.

Each year, over 900 students, PhD students and healthcare professionals from over 60 countries take one of the 48 courses taught at the Institut Pasteur in Paris or at one of the 33 institutes of the Institut Pasteur International Network. Over 600 young scientists are also welcomed by the Parisian campus laboratories to be trained as researchers and complete their undergraduate, Master's and PhD research projects.

An overhaul in teaching. In 2015, the Institut Pasteur President Christian Bréchot continued and stepped up the profound overhaul of teaching and training, according to the principles set out in the 2014-2018 strategic plan. Many stakeholders were involved in this overhaul and several people joined the Institut Pasteur's Education Department – Monica Sala as Executive Director; Roberto Bruzzone, Head of the Institut Pasteur International Teaching Program; Susanna Celli, Dean of the Institut Pasteur-Paris University (PPU) International Doctoral Program and Thierry Lang, who joined the department more recently as Teaching and Training Project Coordinator. Dominique Franco also played an active part in the overhaul by developing MOOCs (Massive Open Online Courses), the MD-PhD training program and entrepreneurship courses. And finally, Simon Legendre significantly contributed to the development of teaching at the Institut Pasteur through his mediating role between senior management and the Education Department.

The Institut Pasteur – a unique setting for training. Research excellence at the Institut Pasteur provides a unique setting for training in research for young French and foreign scientists, who, hosted in the various research structures, can complete their undergraduate to doctoral level training courses. In addition to this initial training in research through research, the Institut Pasteur offers students high-level Master's and doctoral courses, as well as vocational science courses leading to recognized university diplomas. Courses in Paris are taught in the Teaching Center and prepared by campus researchers, with valuable support from lecturers from other partner institutions, such as the Paris Descartes, Pierre & Marie Curie, Paris Diderot and Paris-Sud universities, the CNRS and INSERM, both in France and abroad.

The fact that Institut Pasteur scientists and partner higher education and research institutions are involved in Institut Pasteur courses on a daily basis is pivotal to the success of our teaching, as students have permanent access to the latest developments in research. The focus on laboratory testing and practical work is one of the key features of teaching at the Institut Pasteur and is part of its strength and uniqueness. From the outset, teaching has also been profoundly influenced by the development of the Institut Pasteur International Network, both in terms of the scientific subjects taught and the countries of origin of Institut Pasteur students. To remain

Outstanding facilities for theoretical and lab sessions in a wide range of biology disciplines.

550 students each year

250 PhD students on the Institut Pasteur campus

at the forefront, the Institut Pasteur is planning to extend its teaching activities, by increasing the emphasis on online teaching, opening up courses to younger students, supporting multidisciplinarity and links with medicine, and promoting entrepreneurship and business development.

A dedicated environment and varied course selection. The Teaching Center, situated in the center of the Parisian campus and fully refurbished in 2007, offers outstanding facilities for theoretical and lab sessions in a wide range of biology disciplines, thanks to several teaching labs, laboratories, and technical suites that enable high-quality research in small groups. The teaching labs work closely with the research teams and also have use of all the Institut Pasteur's technological platforms, particularly the Imagopole but also the Center for Human Immunology, state-of-the-art microscopy and new-generation sequencing.

The Teaching Center has dedicated staff who are strongly committed to teaching, including engineers, technicians, laboratory technicians, technical assistants and administrative managers. These specialized staff members work closely with the Institut Pasteur Registrar's Office, which, in particular, handles enrollment and relations with partner universities. These professionals provide course directors with valuable help in setting up the practical and theory courses taught at the center.

Lasting from one to twelve weeks, the Institut Pasteur courses focus on a broad range of disciplines – infectiology, virology, microbiology, immunology, vaccinology, mycology, neuroscience, genomics, cell biology, bioinfomatics, biostatistics and epidemiology. They are taught in French or English and are open to students from French or foreign universities and Master's and PhD students from university teaching hospitals, as well as working professionals (scientists, doctors, pharmacists, veterinarians, engineers) wishing to top up their training.

Many of the courses can be counted as part of a Master's degree program, either as second-year teaching units for the Master's offered at Paris Descartes, Pierre & Marie Curie, Paris Diderot and Paris-Sud universities, or as part of the specialized Master's in Public Health run by the Pasteur-CNAM School of Public Health. Outside these university programs, they can lead to the award of a university diploma (DU). For several years, 12 courses have led to the award of a university diploma (DU) from Paris Diderot University. Since 2015, a new course (Business Development and Biomedical Innovation) has led to a DU from Pierre & Marie Curie University. Most courses can also be taken by PhD students as part of their doctoral studies.

New courses are regularly introduced to keep up with the most recent advances in science. The *Insectes vecteurs & transmission d'agents pathogènes* (Insect Vectors and Transmission of Pathogenic Agents), *Valorisation de la recherche et de l'innovation biomédicale* (Business Development and Biomedical Innovation), Infectious Disease Outbreak Investigation, and Principles and Applications of Fluorescence Microscopy courses were added in 2015. These new courses demonstrate a desire to open to new training topics whilst meeting the Institut Pasteur's strong commitment to training in public health and moving towards interdisciplinary knowledge as an essential source of learning. In a similar vein and to increase its international visibility, the Teaching Center has, since 2015, been involved in organizing several workshops in partnership with European funding bodies (Antigone FP7 EU, ITN Clospore) or with French or international research organizations (INSERM, EHESP, CARD). These workshops are geared towards research and health professionals who come and meet at the Institut Pasteur to discuss and learn more about topics such as public health vaccination and global health.

Teaching students from around the world. The Teaching Center welcomes students, scientists, doctors, pharmacists, engineers, and veterinarians from all over the world. Over 200 students representing 60 different nationalities therefore take

PhD students rewarded
The third PhD graduation ceremony was held at the Institut Pasteur on December 11, 2015 for campus doctoral students who defended their thesis during the 2014-2015 academic year. This formal yet friendly event welcomed guest speaker Françoise Barré-Sinoussi (Nobel Prize in Medicine 2008), who gave a talk on scientific practice and the research discovery process. For the first time, four recipients from the Institut Pasteur International Network were also honored at this ceremony alongside PhD graduates from the Institut Pasteur in Paris – Nimol Khim (Institut Pasteur in Cambodia), Mingyuan Li (Hong Kong University – Pasteur Research Pole), Mihaela Oprea (Cantacuzino Institute) and Sun Rui (Institut Pasteur of Shanghai). This ceremony brought together Parisian campus staff, the new graduates' guests, representatives from partner organizations, and figures from political, diplomatic and business circles with links to the Institut Pasteur. Launched in 2013, this ceremony has become a major event in the Institut Pasteur's calendar, a showcase for the professional excellence produced by its research and training. The next ceremony will be held on December 16, 2016 with guest of honor Alim Louis Benabid, a renowned French neurosurgeon and member of the French Academy of Sciences.

courses on the campus. To meet this growing international demand, an increasing number of courses are taught in English (14 courses to date).

With the support of senior management and in a move towards innovative teaching strategies, the Teaching Center has more recently invested in the development of MOOCs based on onsite courses. In 2015, a vaccinology MOOC was offered in English on the online platform FUN and was followed by over three thousand people, 75% of whom were non-French residents from 116 different countries. At the same time, the Institut Pasteur is developing e-learning courses, lecture streaming and video conferences to offer access to as many people as possible (particularly those at institutes in the International Network). The Institut Pasteur also offers the specialized Master's in Public Health in partnership with the CNAM, a program which draws on the complementary expertise of both institutions. The course, which leads to the award of a Master's, combines eight months of full-time lectures with a

With its 130 research units, the Institut Pasteur is truly a higher-education hotspot for many young scientists. Some 250 doctoral students conduct research projects in Institut Pasteur laboratories.

six-month internship, most often carried out in the Institut Pasteur International Network (http://ecole-pasteur.cnam.fr). The specialized Master's run by the Pasteur-CNAM School of Public Health offers students many job opportunities in various different sectors, including research institutes, health agencies, NGOs and international organizations, healthcare institutions and major hospital groups, the food, pharmaceutical and cosmetic industries, public and para-public sectors, health insurance funds and even journalism.

Institut Pasteur predoctoral programs. The Institut Pasteur would like to strengthen its presence in the earlier stages of student training. Several predoctoral programs have therefore been developed at the undergraduate and Master's level for students from around the world. The Amgen Scholars Program, for example, enables around 20 students from European universities and *grandes écoles* to come and work on a research topic for eight weeks in one of the Institut Pasteur's laboratories. This international program is prepared and conducted entirely in English and ends with a conference in Cambridge where the students present their research findings.

The Institut Pasteur also welcomes interns of the Erasmus+ Program, thanks to partnerships with many European universities (Sapienza University of Rome, Semmelweis University in Budapest, University of Coimbra, etc.). As part of a program run by the Pasteur Foundation, five or six undergraduate interns from the US also complete training courses through research. To vary its predoctoral courses and be 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 across the world have competed to offer an innovative and effective synthetic biology project. The team from the Institut Pasteur brought together around 20 undergraduate and Master's students from different disciplines (biology, chemistry, mathematics, journalism and political science). In 2015, the Institut Pasteur team won the bronze medal at the competition. This program will continue in 2016 by broadening the interdisciplinarity of the team through new partnerships with the ESPCI (Industrial Physics and Chemistry Higher Education Institute), the ENSCI (Industrial Creation Higher Education Institute), and the Jean-Monnet Faculty of Law.

Training through research – PhDs at the Institut Pasteur. With its 130 research units, the Institut Pasteur is truly a higher-education hotspot for many young scientists. Each laboratory is affiliated to a Doctoral school accredited by a Parisian university and is involved in supervision and training for doctoral students. Some 250 doctoral students conduct research projects in Institut Pasteur laboratories. Different types of funding are available, through either the university, the laboratories' own resources from regional, national or European themed programs, non-governmental organizations or the Institut Pasteur's international doctoral program (see below). In addition, the Institut Pasteur provides scientific monitoring of the doctoral program with thesis committees, and also personal support through a specific tutoring program.

Specific doctoral programs. The Institut Pasteur offers specific doctoral programs, like the Pasteur-Paris University (PPU) international doctoral program. This program is open to students with a Master's degree (or equivalent) from a foreign university wishing to carry out their PhD research in an Institut Pasteur laboratory. Launched in 2008 in partnership with Paris Descartes, Pierre & Marie Curie and Paris Diderot universities, this excellence program was extended in 2015 to include a new partner – Paris-Sud University – and its Paris-Saclay SDSV (Structure and Dynamic of Living Systems) doctoral school.

Led by Susanna Celli since November 2015, this program consists of a three-year course leading to a PhD from a French university. The "Metchnikoff" 2015 year group had 14 students from Europe (Portugal, Italy, Russia and Ukraine), the Americas (Canada, Argentina, Brazil, Mexico, Uruguay) and Asia (China, India, Taiwan). Each year group includes students from very different disciplines, who are brought together during joint activities led by the PPU organization committee, for example bibliography seminars or the international doctoral program annual retreat. In 2015, this retreat was held in Nantes in April and doctoral students from all year groups came together during a conference to discuss their research progress. The atmosphere was both focused and relaxed and the aim was to provide constructive suggestions to boost projects.

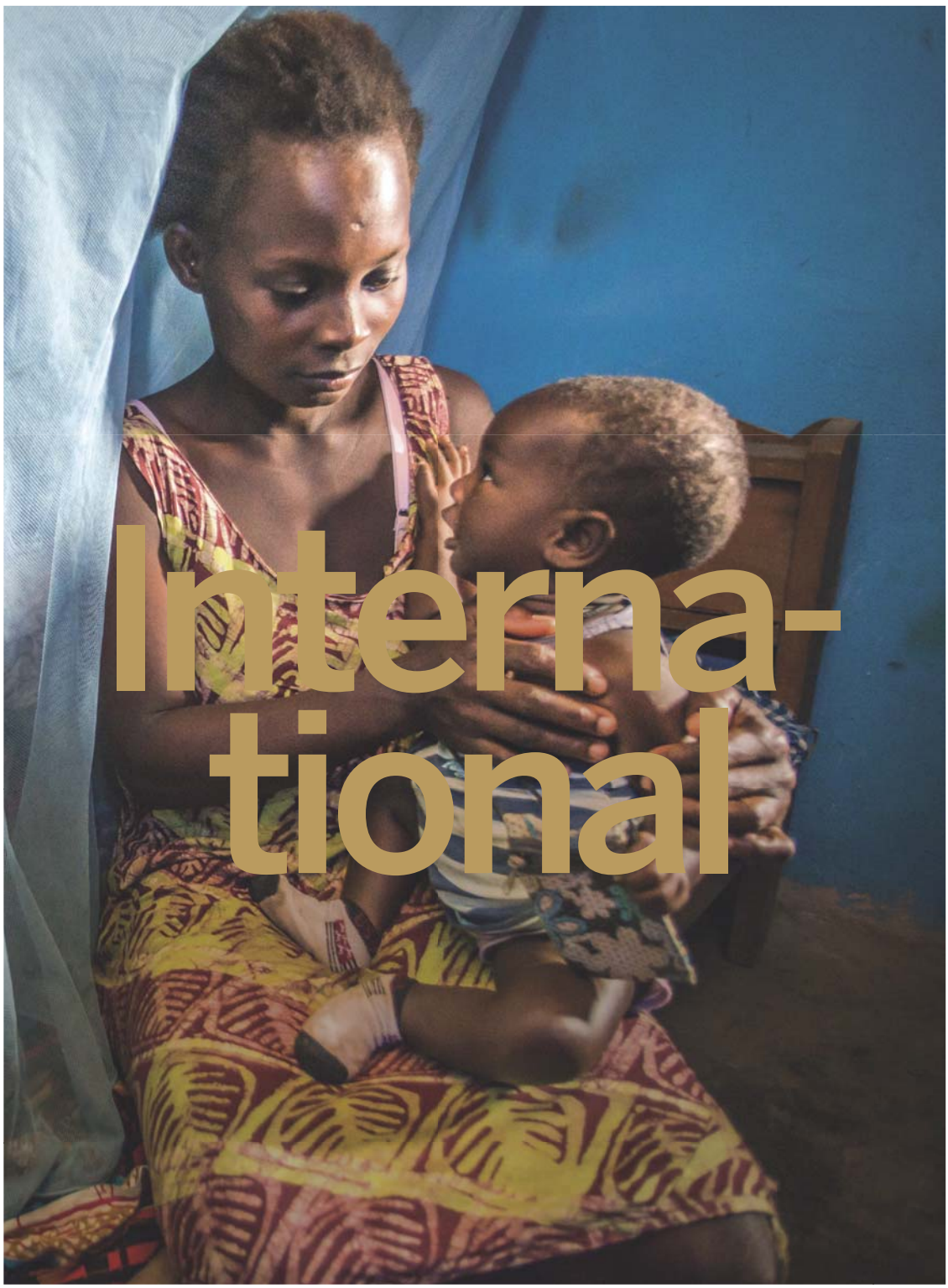
Each year, the Institut Pasteur Department of International Affairs also awards doctoral grants for the completion of PhDs in an International Network institute (outside mainland France). The research topic can be related to any theme developed at International Network institutes, such as infectious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

To keep up with wide-ranging changes in medical practice and biomedical research, linked to scientific breakthroughs and recent technological advances, the Institut Pasteur, the Institut Curie and the École Normale Supérieure set up an advanced Medical Scientist Program in 2015 offering joint medical and scientific training. This program includes an early introduction to research to enable a core group of professionals to gain both scientific and medical expertise. Students are recruited through a competitive examination at the end of their second year of medical or pharmacy school and the course provides interdisciplinary and integrated training, and varied and high-quality teaching, lectures and internships. It also offers guaranteed funding for students for the first 3 years, close scientific and medical tutoring, a prestigious ENS qualification and a PhD in Science. It paves the way for top-level jobs in both academia and the healthcare industries in France and abroad.

New courses in business development and entrepreneurship for science. Out of conviction and in keeping with its calling, the Institut Pasteur has made a deliberate effort to develop business based on its research, and this is reflected in its teaching. Several initiatives have been set up with this in mind, in particular informal monthly meetings between a leading figure – a successful entrepreneur in the field of biotechnology – and Institut Pasteur researchers interested in business development ("Creating your own company" event), and participation in dedicated courses.

To conclude, the Institut Pasteur has a highly organized local, national and international teaching structure that is further boosted by top-level stakeholders. The courses and initial and continuing training on offer at the Institut Pasteur enjoy major international renown, and thus attract promising young scientists from across the world, helping to build an international network of researchers.

The Institut Pasteur has a highly organized local, national and international teaching structure that is further boosted by top-level stakeholders.



International

Stakeholder for global public health

— Inspired by the "Global Health/One Health" concepts and in keeping with its strategic plan, the Institut Pasteur stepped up its international cooperation efforts in 2015. At the same time, the Institut Pasteur International Network demonstrated its fast response to health crises, its involvement in epidemiological monitoring and the quality of its research programs throughout the year.

Developing strategic partnerships. Given the ever more frequent outbreaks of disease, particularly vector-borne diseases, in tropical regions, the Institut Pasteur has chosen to consolidate its international cooperation in Latin American and the Caribbean. On June 8, 2015, the Institut Pasteur, its long-standing partner Fiocruz and the University of São Paulo signed a tripartite cooperation agreement in Rio de Janeiro, laying down scientific guidelines for the partnership between the three research and global public health stakeholders. From late 2015, this agreement served as a basis for joint cooperation in the fight against the Zika virus outbreak.

In Cuba, partnerships were renewed with the Center for Genetic Engineering and Biotechnology (CIGB) and the Pedro Kouri Tropical Medicine Institute, a potential partner for a regional monitoring and control network for *Aedes aegypti* – the vector for dengue and chikungunya – which may be set up in the Caribbean, involving the Institut Pasteur in French Guiana and Guadeloupe, and Brazilian partners. A memorandum of understanding was signed with the Finlay Institute in May 2015 with the aim of developing translational research projects in the field of vaccines. The Institut Pasteur is also expanding its partnerships in the Asia-Pacific region. In November 2015, an agreement was signed with Monash University (Melbourne) to supervise and consolidate scientific collaboration, particularly through young researcher mobility. Discussions are underway with other Australian institutions to boost cooperation and promote our shared expertise throughout South-East Asia. Two Pasteur joint international research units were selected for set up in Japan following the 2015 call for proposals. The first, with Kyoto University, will study links between genetic factors and response to vaccination. The second, with the University of Tokyo, will focus on research in vaccinology and mucosal immunity.

Promoting science within the network. The creation of five-year Institut Pasteur joint international research units is also one of the innovative tools used to develop synergies among members of the Institut Pasteur International Network (RIIP). In 2015, three new joint units were therefore chosen that link a laboratory in the Institut Pasteur in Paris to the following laboratories:

Researcher mobility is a key factor for boosting exchanges between network members.

Since 2014, newly recruited researchers at the Institut Pasteur must spend at least three months in a network institute during the first two years of their career.

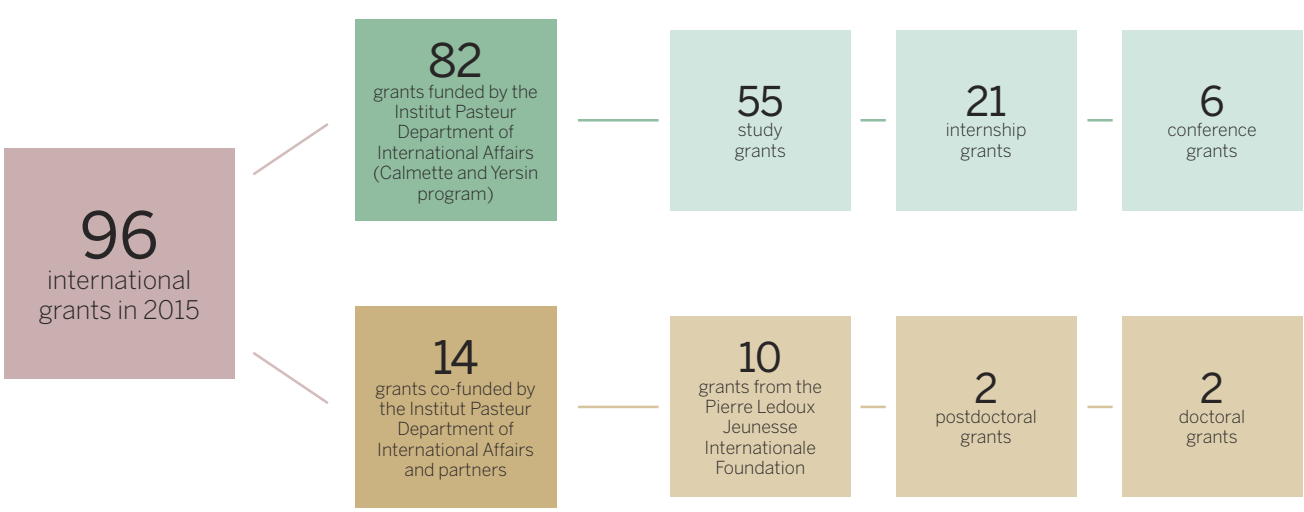
- The Institut Pasteur in Montevideo for research into *Leptospira* survival and persistence mechanisms in the host and the environment;
- The Institut Pasteur in Cambodia for research into the evolution and adaptation of plasmodia (malaria);
- The Institut Pasteur of Shanghai for research into host-pathogen interactions to identify new therapeutic targets and develop new treatments.

Four-year groups serve to promote young scientific talent within the network. Two researchers therefore received support for their projects in 2015. Cheikh Loucoubar set up his group dedicated to bioinformatics and biostatistics applied to infectious diseases at the Institut Pasteur in Dakar, and Tineke Cantaert is focusing on immunology of dengue at the Institut Pasteur in Cambodia.

Researcher mobility is a key factor for boosting exchanges among network members. In 2015, 96 grants were awarded, particularly as part of the Calmette and Yersin program funded by the Institut Pasteur Department of International Affairs. Since 2014, newly recruited researchers at the Institut Pasteur must spend at least three months in a network institute during the first two years of their career. In 2015, among the 7 researchers recruited, 3 spent time at the Institut Pasteur in Montevideo and 2 at the Institut Pasteur – Cenci Bolognetti Foundation in Italy (the other two will head to Madagascar and Korea in 2016).

In October 2015, the Institut Pasteur launched the first call for proposals for the "Enhancing Mobility in Health and Environment between Latin-America and Europe (EMHE)" program, the aim of which is to foster mobility between Latin America and Europe at the doctoral and postdoctoral level on the "Health and Environment" theme.

Finally, 710 participants from 50 countries gathered in Paris for the 2015 Scientific Symposium of the Institut Pasteur International Network. This annual event contributes to the international renown of Institut Pasteur research.



The network on the frontline of Zika

The first cases of infection by the Zika virus were confirmed in Brazil in May 2015. The virus then quickly spread in the tropical regions of the Americas and the Caribbean. As early as November 2015, the Institut Pasteur in French Guiana confirmed the first cases of infection in Suriname, and then identified the first case in French Guiana on December 18, 2015. The same team published the complete genome sequence of the Zika virus, responsible for this outbreak, in *The Lancet* medical journal. Their findings demonstrate almost complete homology with the strains that caused the epidemic in the Pacific in 2013 and 2014. Many International Network institutes are involved in the fight against this epidemic through their expertise in monitoring, and their experience in setting up joint research programs, particularly in epidemiology and entomology.

01 September 2015

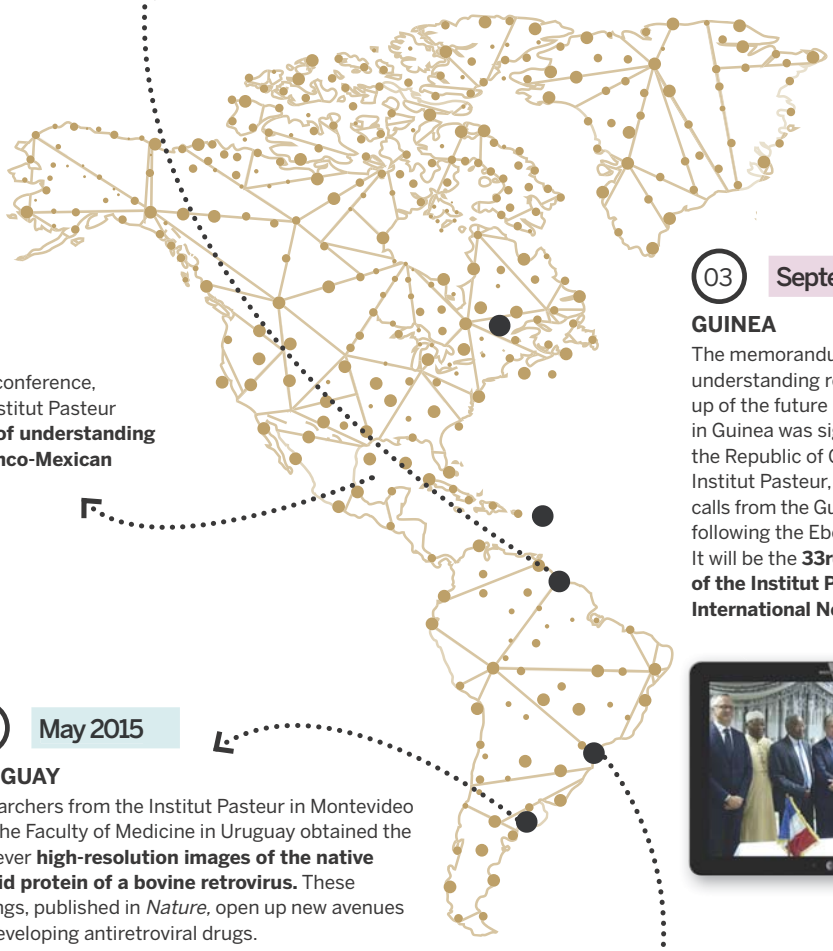
FRENCH GUIANA

Researchers from the Institut Pasteur in French Guiana described **a new mutation that reverses resistance to chloroquine,** which is used to treat malaria. This discovery will help optimize the use and design of antimalarial drugs.

02 July 2015

MEXICO

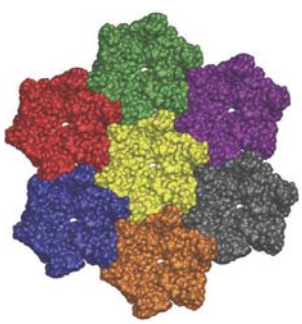
During the Franco-Mexican health conference, the Mexican Health Minister and Institut Pasteur President signed **a memorandum of understanding to supervise and consolidate Franco-Mexican scientific cooperation.**



03 September 2015

GUINEA

The memorandum of understanding relating to the set up of the future Institut Pasteur in Guinea was signed between the Republic of Guinea and the Institut Pasteur, in response to calls from the Guinean authorities following the Ebola crisis.
It will be the **33rd member of the Institut Pasteur International Network**



04 May 2015

URUGUAY

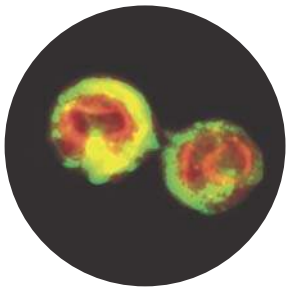
Researchers from the Institut Pasteur in Montevideo and the Faculty of Medicine in Uruguay obtained the first ever **high-resolution images of the native capsid protein of a bovine retrovirus.** These findings, published in *Nature,* open up new avenues for developing antiretroviral drugs.

International
Highlights of 2015

05 June 2015

BRAZIL

Signing of an agreement between the Institut Pasteur, Fiocruz and the University of São Paulo. This tripartite agreement lays down the broad scientific guidelines for the partnership, **and paves the way for a future Institut Pasteur in Brazil.**



11 September 2015

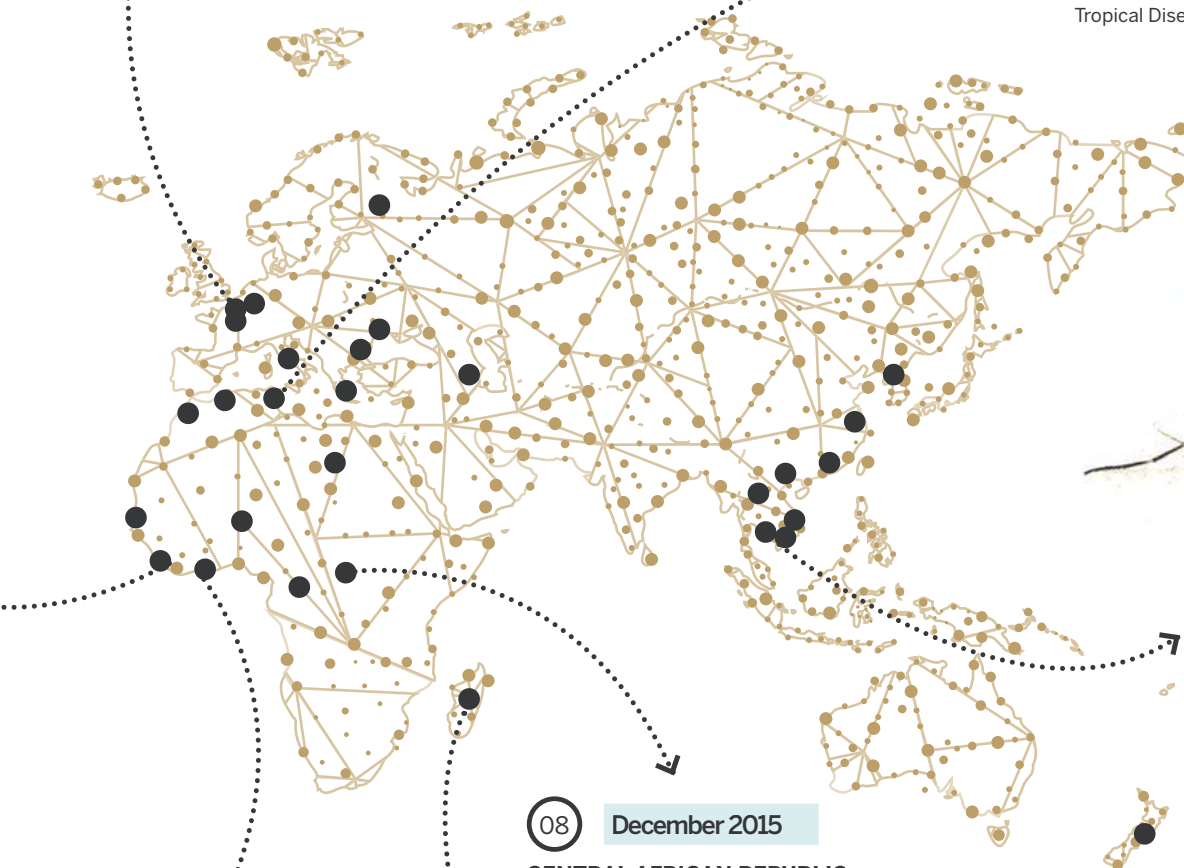
FRANCE

The Institut Pasteur and the **World Organization for Animal Health signed an agreement to strengthen cooperation in the field of public and animal health protection.** The resulting policies aim to prevent and control pathogens at the human-animal-environment interface.

10 April 2015

TUNISIA

The Institut Pasteur in Tunis became a **Regional Training Center for the Eastern Mediterranean region** as part of the WHO Special Program for Research and Training in Tropical Diseases.



09 November 2015

CAMBODIA

Researchers from the Institut Pasteur in Cambodia, the Institut Pasteur in Paris and the CNRS revealed **the role asymptomatic people infected with dengue play in transmitting the virus to mosquitoes.**

08 December 2015

CENTRAL AFRICAN REPUBLIC

The Institut Pasteur in Bangui confirmed an outbreak of monkeypox virus, 800 km from the capital of the Central African Republic, in the border area with the Democratic Republic of the Congo. In humans, this virus can cause a disease with symptoms similar to smallpox.

06 December 2015

CÔTE D'IVOIRE

First stone laid for the High-Risk Pathogen Research Center at the Institut Pasteur in Côte d'Ivoire. It will host BSL-3 and BSL-4 laboratories for better foresight in response to endemic threats.

07 August 2015

MADAGASCAR

The Institut Pasteur in Madagascar responded quickly to **the rise in cases of pneumonic plague.** It was also on the front line throughout the year to confirm **cases of acute flaccid paralysis,** caused by the emergence of the poliovirus.

Research doesn't necessarily mean peering into a microscope. From behind their computer screens our engineers in bioinformatics, biostatistics and integrative biology work in close cooperation with our scientists. Their work paves the way for the creation of efficient new tools for analyzing the big data produced at the institut and for the development of new techniques to model biological data.

Institut Pasteur

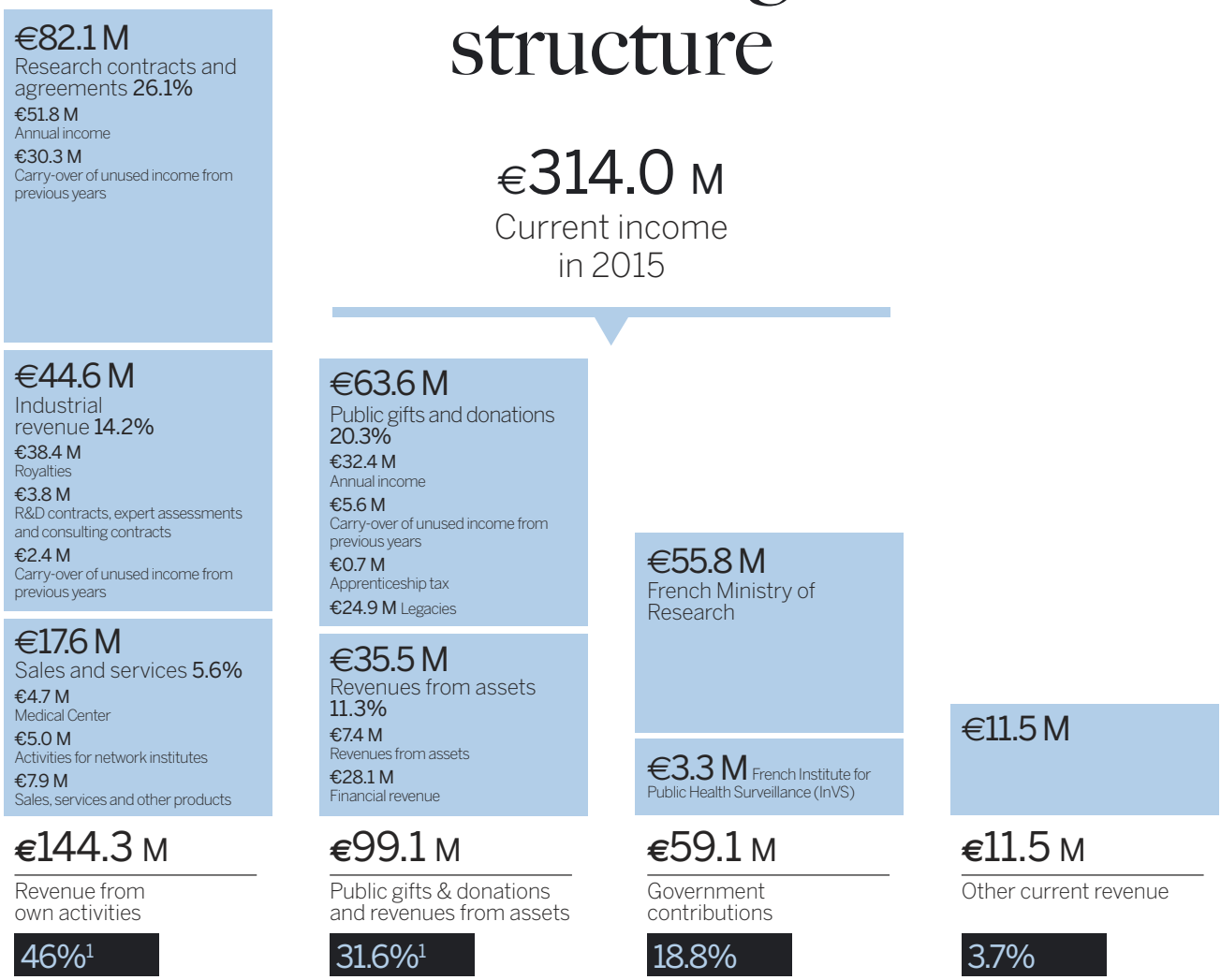
OUR RESOURCES

A unique model

— Thanks to its unique business model and financial equilibrium, the Institut Pasteur is able to maintain its independence and freedom of research, and to provide a fast response when called upon in an emergency. Its future development relies on the talent and skills of its staff, with their varied cultural backgrounds and complementary fields of expertise. Fully aware of its environmental and social responsibilities, the Institut Pasteur has also made its commitment to sustainable development a special priority.

Financing structure

€314.0 M
Current income in 2015



REVENUE FROM OWN ACTIVITIES

Research contracts and agreements

Overall, research contracts and agreements (accounting for €82.1 M and 26.1% of income) rose by €2.9 M in relation to 2014 due to research contracts and agreements with the public sector, particularly funding from the French Development Agency (AFD), the French Ministry of Foreign Affairs, France expertise and the Red Cross (+ €2.4 M) for the Ebola outbreak, as well as European contracts thanks to ERC contracts awarded in 2015.

Industrial revenue

Industrial royalties (€38.4 M) down €1.2 M compared with 2014 yielded marked variations according to license family:

- Diagnostics (€17.8 M / - €5.5 M) recorded a loss of €5.4 M due to the resolution of a litigation with an industrialist in 2014.
- Therapeutics (€3.7 M / + €2.6 M) recorded a significant rise due to an expanding license agreement.
- Vaccines: on the rise (€4.4 M / + €0.7 M). Revenue from brand license agreements was stable at €10.8 M.

Contracts signed with industrialists (€6.2 M), related to research & development or expert assessments by scientists, were down €3.0 M in relation to 2014. This fall resulted from a decline of roughly €1 M in each of the Institut Pasteur's main three R&D sectors (food, diagnostics and therapeutics R&D).

Sales and services

Sales and services (€17.6 M, accounting for 5.6% 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 (€63.6 M accounting for 20.3% 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 €11.8 M in relation to 2014 (+ €7.6 M for legacies and + €4.8 M for donations, whereas apprenticeship tax is down €0.6 M).

Revenues from assets (€35.5 M accounting for 11.3% 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 is stable, whereas financial revenue rose by €0.6 M.

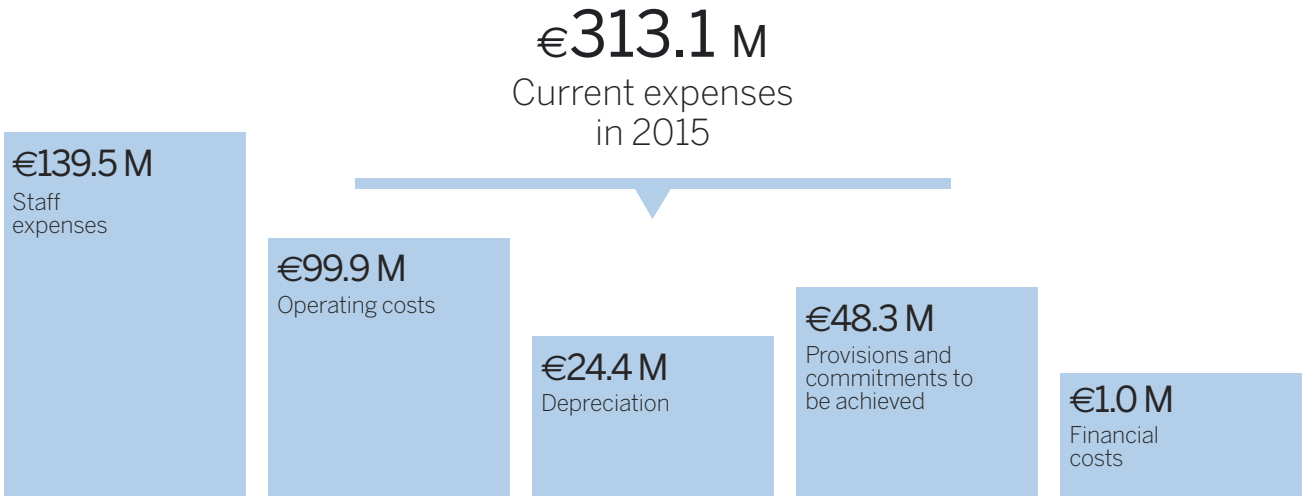
GOVERNMENT CONTRIBUTIONS

These are made up of the grants from the Ministry of Research and InVS, which cover some of the cost (less than 40%) of National Reference Center activities. The Institut Pasteur benefited from the part release of the Ministry of Research grant over the financial year.

OTHER INCOME

This item includes recovery of provisions and transfer of charges.

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



Financial statements

— In 2015, the operating deficit grew by €1.7 M compared with 2014, reaching -€27.1 M. The financial result (€27.1 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 €43.5 M.

Current operations. Current revenue increased by 6.0% compared with 2014.

The highest rises were recorded on research contracts and support from our donors. Government contributions, which remain key to balancing the Institut Pasteur's current result, are on the rise, notably due to the part release of the Ministry of Research grant. On the other hand, industrial income was down.

Current expenditure was up by 6% from 2014 owing to the implementation of the 2015-2018 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. 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 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 2015, the donations and legacies recorded as exceptional income amounted to €29.3 M, up by €9.8 M compared with 2014. The financial component showed a positive balance of €12.7 M, up by €12.0 M from 2014 due to the good performance of financial investments over the year.

In addition to these two recurring items, exceptional income for 2015 also includes €3.9 M of various expenses and capital gains resulting from the sale of assets.

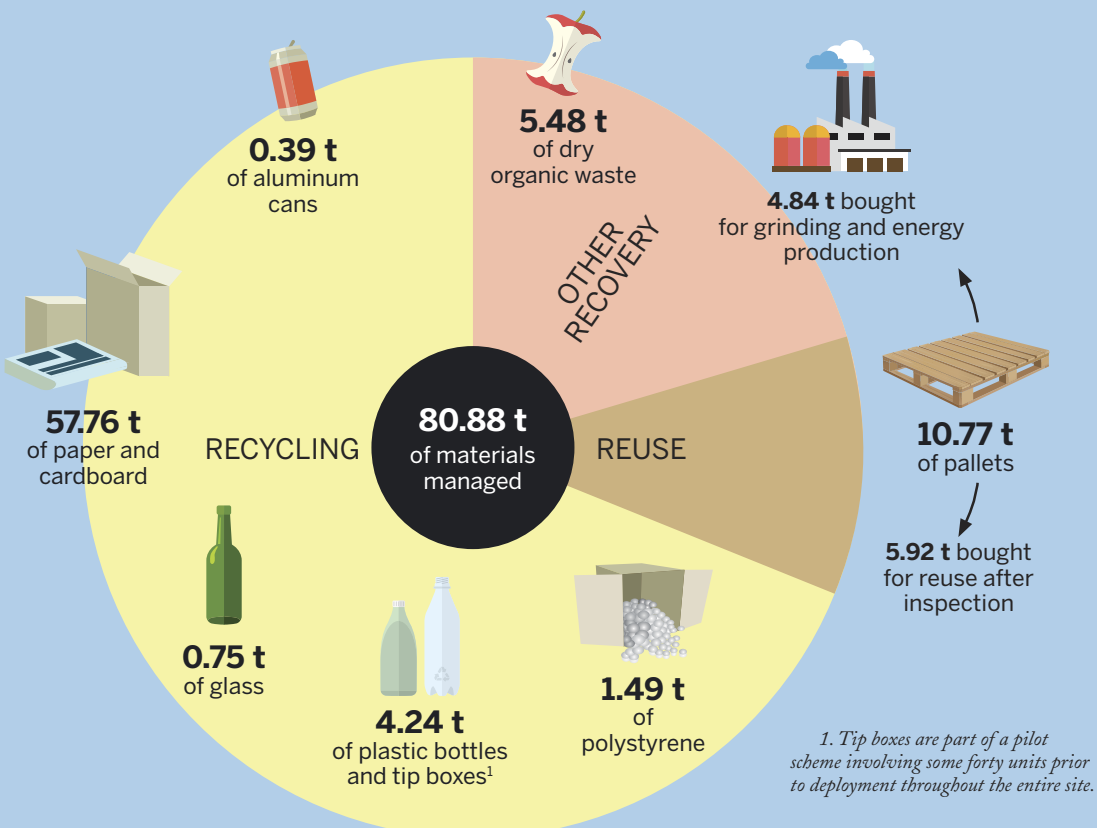
Net result. The Institut Pasteur's net result at year-end 2015 was €43.5 M.

SUSTAINABLE DEVELOPMENT

Preserving the environment

— The Institut Pasteur has been a member of the United Nations Global Compact since 2010, thus confirming its commitment to preserving the environment.

Optimized waste management



1. Tip boxes are part of a pilot scheme involving some forty units prior to deployment throughout the entire site.

More spaces for "clean" transport

6 parking spaces for electric cars

100% of drivers eco-trained

120 parking spaces for bicycles

i.e. a **4**-fold increase

Logistics reviewed

87%

reduction in trips required for recyclable waste collection

HUMAN RESOURCES

Putting individuals back at the heart of Institut Pasteur strategy

— In line with the strategic plan, the Human Resources Department pursued and consolidated Institut Pasteur restructuring initiatives and support for talent in 2015.

Fostering recruitment, integration and reception. In 2015, the Institut Pasteur recruited 462 new employees, including 60 on permanent contracts and 402 on fixed-term contracts. The recruitment of six heads of new units, including four G5 heads and a head of research, together with the recruitment of 12 talented bioinformaticians falls within the scope of the strategic plan. The scheme for welcoming newcomers to the Institut Pasteur was also boosted in 2015. To build on its image as a leading employer in the field of research and to lay the foundations for its employer brand, the Institut Pasteur raised its profile on the Linkedln social network, by creating an alumni community that brings together past and present Institut Pasteur staff from all over the world.

Supporting careers and developing skills. Boosting the employment potential of Pasteurians is a key objective for supporting the strategic restructuring. 2015 saw the consolidation of a Jobs and Skills Guide for all Institut Pasteur professions. This project, which paves the way for the gradual introduction of a careers management policy at the Institut Pasteur, will be rolled out from 2016. A pilot Careers Committee was also set up in 2015 to offer individual and customized support (for career plans). To maximize the employment potential of young scientists, a customized professional development program offers various initiatives – CV workshops, lunch meetings, careers events (Beyond the PhD, etc.). A Science and HR task force, bringing together Human Resources professionals and scientists, also fosters internal mobility and career development. Finally, all Institut Pasteur staff members called on to lead a team now receive management training.

Simplifying and modernizing. In 2015, the Human Resources Department pursued its restructuring efforts, particularly by digitizing its processes and services. An IT tool (Talentsoft) was chosen to meet campus requirements and follow on from the HR portal, rolled out in 2014. It will include several modules – training, recruitment, annual appraisals and career development reviews, onboarding, career management, and pay. In addition, 2015 was marked by the use of electronic voting for the employee representative body elections. Finally, the pay structure changed in May 2015 when the six-monthly bonus was incorporated into the basic salary, thus simplifying its payment (over 12 months instead of 14).

Recognizing the involvement of Institut Pasteur staff. The year also saw the introduction of a profit-sharing scheme to boost employee involvement in achieving the strategic plan. Furthermore, Chairs of Excellence were created and pay rises were agreed for post-doctoral fellows. Finally, 81 employees were given the Group Leader job title.

KEY FIGURES FOR 2015

Workforce

2,593 staff members on campus

2,078 Institut Pasteur employees (including 69% with permanent contracts)

446 employees from external research organizations

69 interns and students*

Of the **2,524** people working on campus (excluding interns and students)

52% scientific managers

31% non-managerial staff

17% executive administrative and technical staff

Average age: **43** years

59.9% women

66 nationalities on campus

Recruitment

462 people hired in 2015

275 women and **187** men

42% scientists

16% of employees under 25 years recruited

Training

1,727 people trained for **28,158** hours of training

€2.8 M invested overall in professional training

(as of December 31, 2015)*

DONATIONS, SPONSORSHIP AND LEGACIES

Thank you

— In 2015, nearly a third of the Institut Pasteur's resources came directly from individual and corporate donations and legacies. This source of funding for our research activities is constantly growing.

The funds raised through the generosity of individuals and companies will enable the Institut Pasteur's scientists to continue their vital work and explore new avenues for research.

In 2015, we received €32.4 million in donations and legacies, an increase of 25% over 2014.

The Institut Pasteur is currently supported by almost 200,000 individuals, a number that is steadily growing. 23,500 of our supporters chose to set up a direct debit, which enables them to spread their donations over the entire year.

Our regular email campaigns and our major annual fundraising campaign, Pasteurdon, which ran from October 8 to 11, 2015, attracted 50,000 new givers this year. Pasteurdon is now a firm fixture on the Institut Pasteur calendar. In 2015 we proudly presented the ninth edition of the campaign, which was followed by a record number of people. The success of this event is due in no small part to the efforts of our partners, which include 20 French DTTV channels, 13 radio stations, and several companies: AG2R La Mondiale with its "Roulons solidaires" ("Riding in solidarity") campaign, which really took off this year thanks to the *Vivons vélo* application, and Assu 2000 with the second edition of its "Défi Run Assu 2000". For each person who entered this original obstacle course race, Assu 2000 pledged to give one euro to the Institut Pasteur to support research into cardiovascular disease. The Le Roch-Les Mousquetaires Foundation, a long-standing Pasteurdon partner, showed its support in two ways: it made a sizable donation which was allocated to a research program on food safety, and it introduced a range of charity-linked products in two stores in the Les Mousquetaires group, Intermarché and Bricomarché.

In 2015, donations from companies and foundations raised a total of €10.5 million, an increase of €1.5 million over 2014, as new companies joined the Institut Pasteur cause, including the Michelin Corporate Foundation and the Daniel and Nina Carasso Foundation. The latter decided to support one of the Institut Pasteur's three interdisciplinary Major Federating Programs by setting up the "Daniel and Nina Carasso – Microbes & Brain Fund".

MSD France also joined the ranks of our sponsors in 2015 when it launched MSDAvenir, a major research support fund for life sciences, and chose the Institut Pasteur as one of its first beneficiaries. MSDAvenir plays a key role in funding cutting-edge equipment that can be used to analyze the biological collections within the Institut Pasteur International Network as part of the Pibnet project, which aims to develop an extensive biobank.

Our new sponsors also include Mutuelle Air France, Intériale, and the Professional Products Division of the L'Oréal Group, which chose the Institut Pasteur as a key partner for its "Hairdressers Against AIDS" program.

Their contributions are our most valuable asset as we strive to advance knowledge and make significant progress in biomedical research.

Long-standing partner Sanofi renewed its support for the Institut Pasteur in 2015. For the fourth year in a row, the Sanofi-Institut Pasteur Awards for biomedical research recognized the work of four world-class scientists in two fields that are vital for world health: tropical and neglected diseases, and immunology.

The Total Foundation, another loyal supporter for many years, again demonstrated its commitment at the beginning of 2015 with a major new partnership agreement to combat childhood diseases in Africa and Asia.

Odyssey Reinsurance Company is helping consolidate the Institut Pasteur's technological capabilities by contributing to funding for the Titan project, which will result in the world's most powerful microscope being set up on our campus by the end of 2016. It is also continuing its support for our cancer research.

The AXA Research Fund was set up to encourage scientific research in the area of risk prevention. In 2015 it awarded a sizable grant to one of our scientists for the development of an epidemic modeling program.

Finally, our efforts to strengthen our international visibility paid off this year, with a total of €5.2 million being raised in Europe and the United States.

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. The number of new legacies and gifts received in 2015 was 128, an increase of 28% over 2014. The legacies bequeathed to the Institut Pasteur are increasingly shared with other institutions, which reduces the amounts received by the Institut Pasteur. A total of €35.3 million was received in 2015, compared with €36.6 million in 2014 – a fall of 3.5%.
Life insurance policies continued to represent a leading source of recurring income, amounting to €7 million in 2015, up by 25% over the previous year. These policies, like legacies and gifts, offer favorable tax arrangements in that they are exempt from transfer duties.

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 2015.

Communications activities. A promotional campaign for legacies and gifts was launched in 2015 on radio stations and TV channels and in the mainstream and legal press to raise awareness of these funding methods that 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 gifts, as well as more innovative schemes such as the temporary transfer of usufruct rights and posthumous gifts. Since 2012, the office has employed a dedicated staff member in charge of legator relations; those interested in giving to the Institut Pasteur can contact her for advice and guidance or speak to one of the office's legal experts. To answer some of the more frequent questions, the office has decided to publish a six-monthly "Legacies and Gifts Newsletter", with each issue covering a specific aspect of gifts, legacies, and life insurance policies.

The fourth Conference on Philanthropic Trusts, organized by the Institut Pasteur and the newspaper Le Monde, was once again a great success. Some 550 philanthropy and assets management professionals gathered in March 2015 at the Institut Pasteur Conference Center in Paris to learn more

about the development of a sector that is constantly changing. The plenary session, round tables and workshops helped participants discover the new faces of philanthropy. Some highlights of this day:

• emblematic figures from the "philanthropreneur" generation shared their thoughts on new trends in philanthropy in France and abroad. The idea is increasingly to replace gifts by socially-oriented investments;

• a closer look at two promising tools used by our European neighbors which blur the boundaries between gifts and investments: first, the little-known "shareholder foundation" model (a preview of the first European study on this scheme was presented at the conference), and second, the innovative but controversial "social impact bonds".

The think tank Fiducie philanthropique (philanthropic trust), 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.

Major sponsors

Sponsors

AG2R LA MONDIALE
BALSAN
BANQUE PRIVÉE EUROPÉENNE
CHRONOPOST
CONNY-MAEVA
CHARITABLE FOUNDATION
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“Supporting the Institut Pasteur was a logical step for me, maintaining the links that my father had created. The Institut Pasteur is a unique place, where intelligence and creativity are combined with curiosity and an outward-looking approach. Supporting its scientists and their projects is a fascinating human adventure that benefits society as a whole.”

Marina Nahmias,
President of the Daniel and Nina Carasso Foundation

“Since I don’t have any children, I wanted my assets to go to a good cause where they can really make a difference. I have supported the Institut Pasteur for several years. I believe that health is the most precious thing in the world, and that is why in my will I have decided to leave all my assets to help your scientists. Since I made this decision it’s as though a weight has been lifted from my mind – I know that this money will be used to help advance science.”

MM

“Keep going. Well done for who you are, well done for what you’re doing. I will continue to contribute, as I do every year, in my own small way, to funding your needs. Kind regards.”

FD

“I would like to thank your foundation for its devotion to the human cause.”

LD

“I’ve been supporting the Institut Pasteur’s scientists every month for many years now. I have every confidence in the work they do and I very much admire what goes on at the Institut Pasteur.”

CD

“I would like to thank you for the letter of thanks I received recently for my latest donation. I really didn’t expect that the small contribution I had made to help these scientists would merit such a kind letter. Please pass on my best wishes to them and let them know how much I appreciate their efforts to combat terrible diseases such as leprosy and Buruli ulcer.”

AC

Since 1887, thousands of men and women have devoted themselves to learning, sharing, listening, giving, and researching, to carry forward the mission started by Louis Pasteur and serve the needs of public health.

Institut Pasteur

BY ERIK ORSENNA

Ambassador of a country called “Institut Pasteur”!

What is an ambassador?
The representative of a country abroad.
What is an Institut Pasteur ambassador?
The representative of a country called “Institut Pasteur”, in France and across the globe.

But how could I possibly claim to be in a position to “represent” 23,000 employees?
I mainly see myself as a reporter, attempting to understand their research, to explain it and to share it with as many people as possible.
That has led me, in my capacity as “ambassador” (a title which makes me so proud!), on a trip to Cayenne, to one of the 33 institutes that make up this remarkable network of Pasteurians.

French Guiana is a wonderful place – and it was a challenging mission for me as a new ambassador, on the front line of the battle against the Zika virus.

I learned first hand all about larvae breeding grounds and how to identify them.

I visited a wonderful Vectopole, where experts are beginning to learn a great deal about the astonishing 135 mosquito species that have been identified in the region. Which species harbor parasites – and which parasites? Which species are resistant to insecticides – and which insecticides?
I greeted around 50 pensioners living in a large cage – these were squirrel monkeys, being fondly cared for by two devoted veterinarians in grateful appreciation of their services back when the center was working on vaccines.

I met a team working on other vectors, mainly bats. The director explained that French Guiana is unique in that the forest is very close, almost extending into the town. So humans and wild animals are in frequent – and not always harmonious – contact. French Guiana can be seen as a sort of laboratory for relations between humans and nature.

I admired the work being carried out by the group tasked with assessing and mapping the spread of the Zika epidemic.

I saw that the Institut Pasteur in Cayenne, through its analysis and diagnostics laboratory, was upholding one of the missions entrusted to it by Louis Pasteur, namely to provide valuable support for public health in French Guiana.

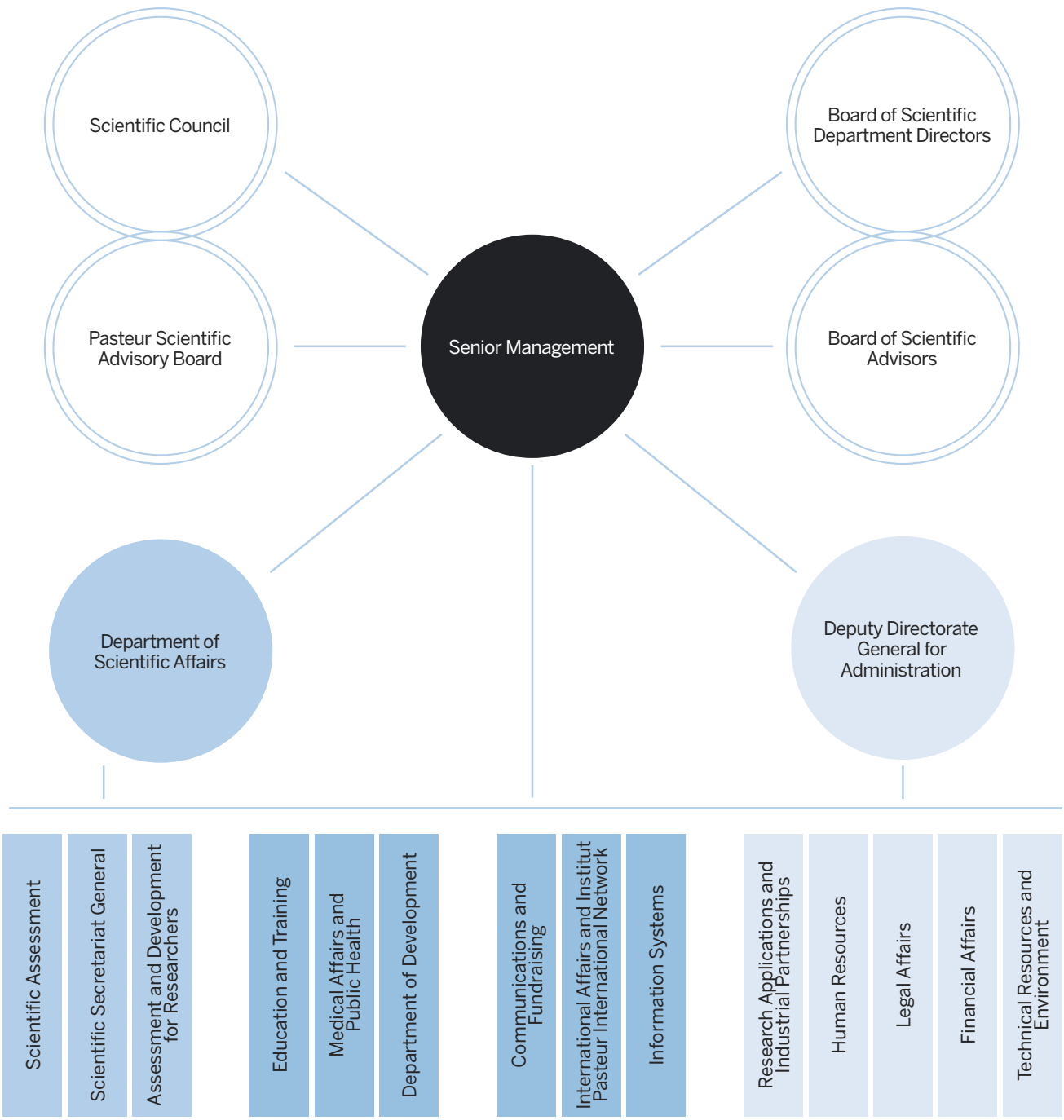
As you can see, the new ambassador is learning the ropes.

The next stage in my apprenticeship will come in Cambodia, on the trail of “resistant strains”.

And then of course there’s the work going on in Paris. I’ll soon be telling you all about the first images produced by the giant microscope, Titan.

APRIL 2016

Departments and governing bodies



Board of Directors

APRIL 2016

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

Board of Directors Bureau

Chair

→ **ROSE-MARIE VAN LERBERGHE**
Corporate Board Member

Vice-Chairman

→ **BERNARD GUIRKINGER**
Regional Delegate for Eastern France at Groupe SOS, Member of the French Economic, Social and Environmental Council

Vice-Chairman

→ **LAURENT DEGOS**
Professor of Hematology, Saint-Louis Hospital
Treasurer

Secretary

→ **ALAIN JACQUIER**
Head of the Macromolecular Interaction Genetics Unit, Institut Pasteur

Treasurer

→ **SOPHIE MANTEL**
Head of Department in the Budget Division, French Budget Ministry
Secretary

→ **MICHÈLE FROMENT-VEDRINE**
Chief Advisor to the French Government's Accounting Office
Chairman of the Finance and Audit Committee

Other members

→ **STEWART COLE**
Director of the Infectiology Research Institute, École polytechnique fédérale de Lausanne (EPFL)

→ **JEAN-FRANÇOIS DELFRAISSY**
Director of the French National Agency for Research on AIDS and Viral Hepatitis (ANRS)

→ **DOMINIQUE DEVILLE DE PERRIERE**
Directorate-General of Research and Innovation, French Ministry of Higher Education and Research

→ **ALAIN FUCHS**
President of the CNRS (French National Center for Scientific Research)

→ **CLAUDE LECLERC**
Head of the Immune Regulation and Vaccinology Unit, Institut Pasteur

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→ **YVES LÉVY**
Chairman and Chief Executive Officer of Inserm (French National Institute for Health and Medical Research)

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Director of Research in the Molecular Microbial Pathogenesis Unit, Institut Pasteur

→ **THIERRY PLANCHENAULT**
Molecular Microbial Pathogenesis Unit, Bacteria-Cell Interactions Unit, Institut Pasteur

→ **ODILE PUIJALON**
Guest Researcher, Institut Pasteur

→ **KORY SORENSON**
Corporate Board Member

→ **FRANÇOIS TADDEI**
Director of the Center for Research and Interdisciplinarity (CRI)
Head of Research Team 2 in laboratory U1001 (Inserm)

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

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Vice-President
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→ **ISABELLE BUCKLE**
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Vice-President
Technical Resources and Environment

→ **CORINNE FORTIN**
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Financial Affairs

→ **ODILE GELPI**
Vice-President
Medical Affairs and Public Health

→ **OLIVIER GRAMAIL**
Vice-President
Human Resources

APRIL 2016

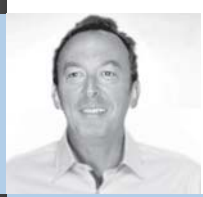
Management of the Institut Pasteur

— 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.

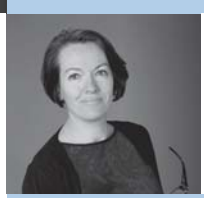
→ **ALAIN ISRAËL**
Vice-President Scientific Assessment

→ **MARC JOUAN**
Vice-President
International Affairs and International Network

→ **PIERRE LEGRAIN**
Vice-President
Development



→ **JEAN-CHRISTOPHE OLIVO-MARIN**
Chief Technology Officer



→ **NATHALIE DE PARSEVAL**
Scientific Secretary General

→ **MICHAËL PRESSIGOUT**
Vice-President Information Systems

→ **LLUIS QUINTANA MURCI**
Scientific Director

→ **MONICA SALA**
Executive Director for Education

→ **PATRICK TRIEU-CUOT**
Vice-President
Scientific Careers

Scientific Council

APRIL 2016

— 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 & Physiology of Hearing Unit

→ **JEAN-PAUL LATGÉ**
President
Head of the *Aspergillus* Unit

→ **FRÉDÉRIC TANGY**
Head of the Viral Genomics and Vaccination Unit

Appointed Pasteurian Members

→ **CARMEN BUCHRIESER**
Vice-President
Head of the Biology of Intracellular Bacteria Unit

→ **FABRICE CHRETIEN**
Head of the Human Histopathology and Animal Models Unit

→ **PASCALE COSSART**
Head of the Bacteria-Cell Interactions Unit

→ **ARTUR SCHERF**
Head of the Biology of Host-Parasite 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

→ **RICHARD MOXON**
Professor Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK

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

→ **DAVID SIBLEY**
Professor Washington University School of Medicine, Department of Molecular Microbiology, St. Louis, USA

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

SYMBOL

The scientist's lab coat

As they enter middle school, children start science lessons and put on a lab coat for the first time. Dressed for the part, they can now take their place in the scientific family, in the pantheon of illustrious scientists who have devoted their lives to advancing knowledge. They dream of what it must have been like to be Louis Pasteur discovering the rabies vaccine, or Albert Calmette or Camille Guérin creating the BCG.

And the story goes on. The white lab coat is universal, worn by scientists in all disciplines and all countries. White symbolizes cleanliness and hygiene. The coat covers the arms, protects the body, and prevents the spread of microbes outside the confines of the laboratory. It is a universal symbol.

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

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The Institut Pasteur, founded in 1887, is a private foundation for biomedical research with officially recognized charitable status. Its research has been honored by ten Nobel Prizes. Our campus and our 33 institutes worldwide are home to almost 23,000 staff members. Every day, we work to tackle viruses, infections, epidemics, and diseases – AIDS, Ebola, influenza, cancer, brain disease, autism, heart disease, and many more.

In the pursuit of our mission to fight against diseases in France and throughout the world, we operate in four main areas: scientific and medical research, public health, education, and business development and technology transfer.

Join us

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Institut Pasteur