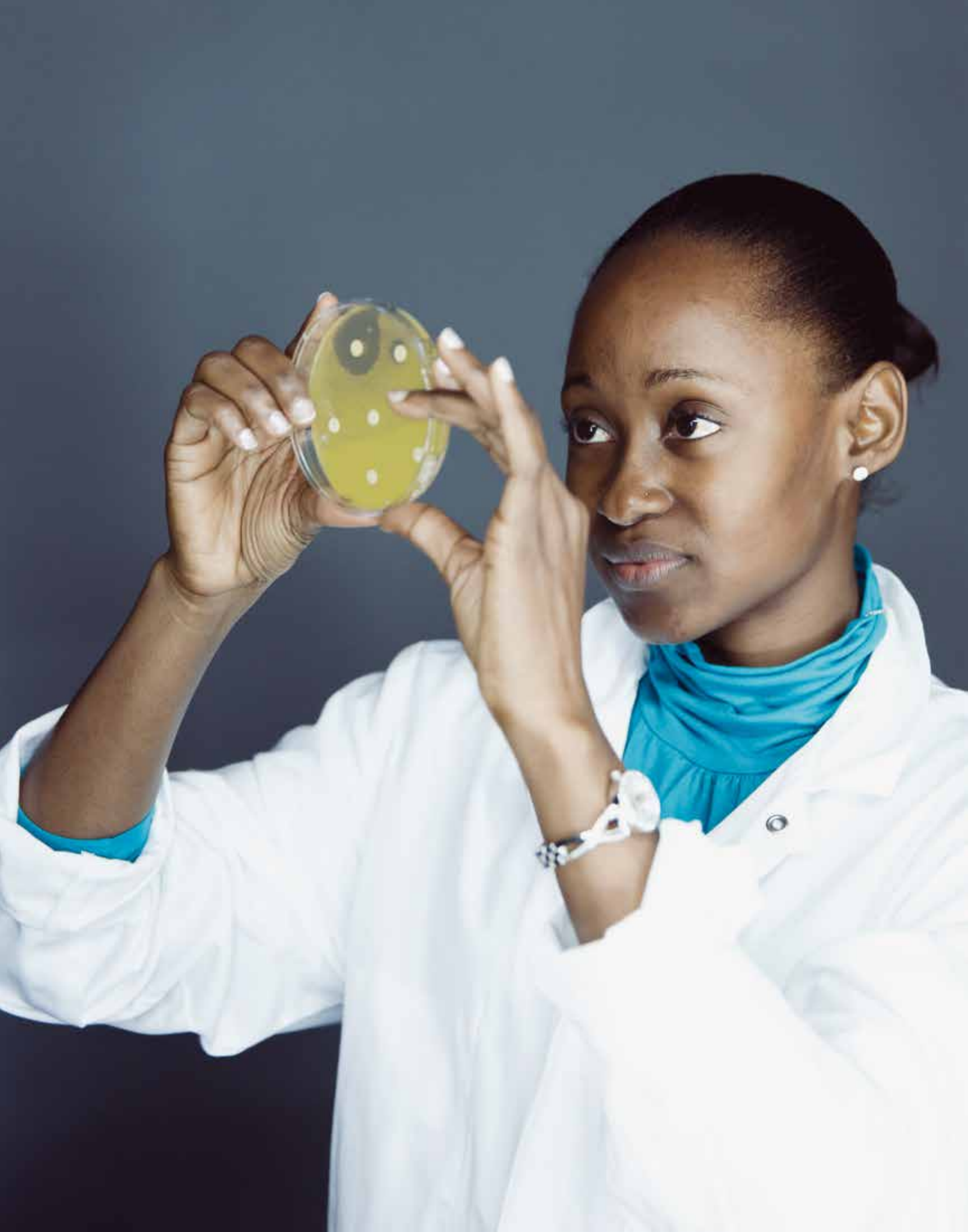
Annual Report 2013

Incurably curious

Institut Pasteur

“Science is an inexhaustible field.
The more we dig into it
the greater the treasures we find.”

Louis Pasteur

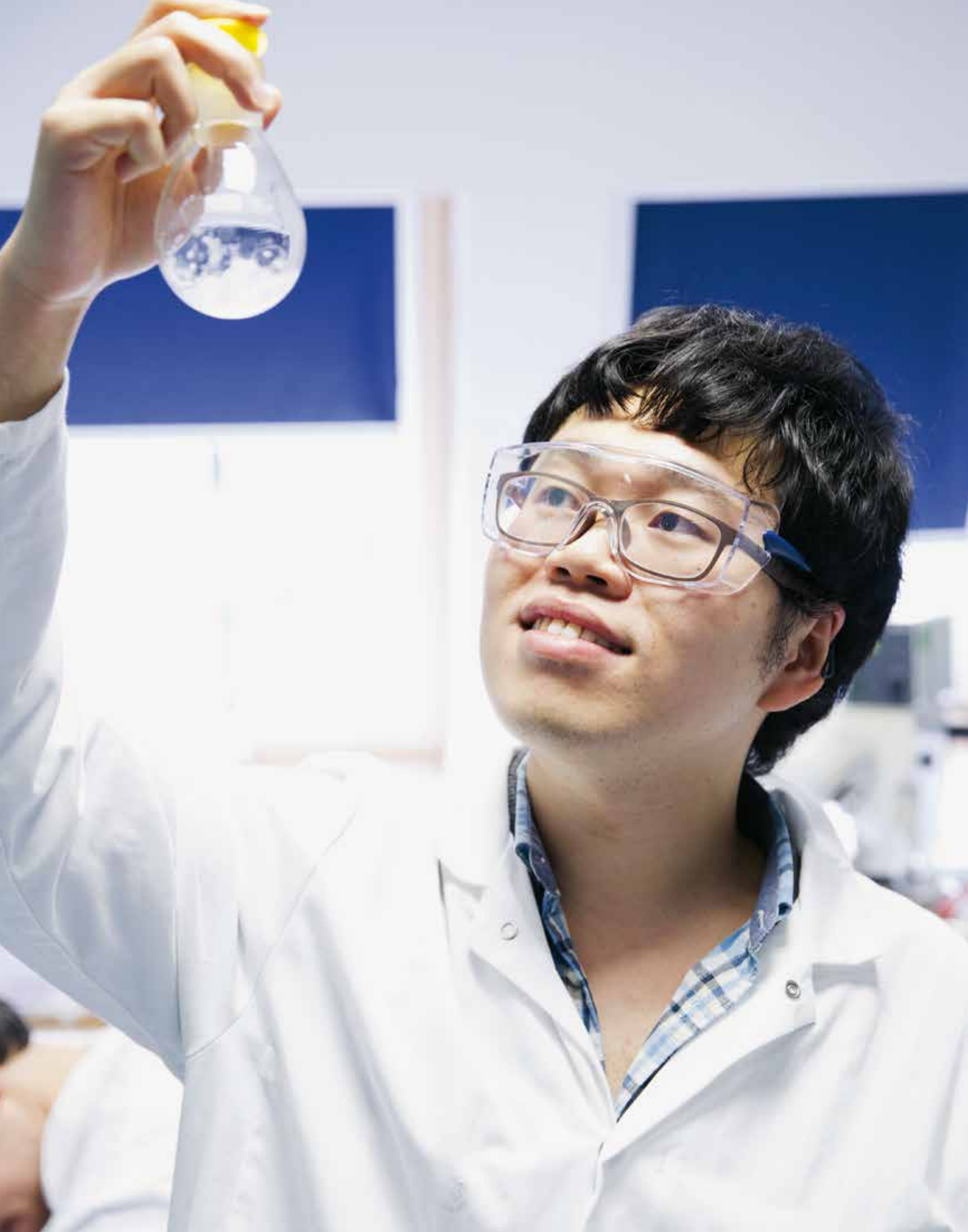


Foundation

The Institut Pasteur is a private, state-approved foundation for biomedical research, and was established by Louis Pasteur in 1887. On its Paris campus, over 2,400 employees wage a constant battle against the diseases that threaten human health. This work improves our knowledge of living organisms and helps develop new prevention methods and therapeutic strategies.

Missions

Since the very beginning, the Institut Pasteur's mission has been built upon three cornerstones.
Research. Its 130 units work at the very forefront of research into infectious diseases, and are also dedicated to neuroscience, developmental biology and genomics. Since its foundation, 10 of its scientists have been awarded the Nobel Prize for Medicine.
Teaching. Each year, about 500 students attend the 27 courses offered by the Institut Pasteur teaching center. The Institut Pasteur is also a training center for some 300 young scientists who choose to carry out their Masters or PhD research in its laboratories.
Health. Through its medical center and teams dedicated to disease surveillance, the Institut Pasteur provides a public health service in close association with the health authorities.
Just as Louis Pasteur wished, these missions are being developed on a global scale via the Institut Pasteur International Network, with a constant focus placed on technology transfer and business development based on discoveries made by the Institute's laboratories.

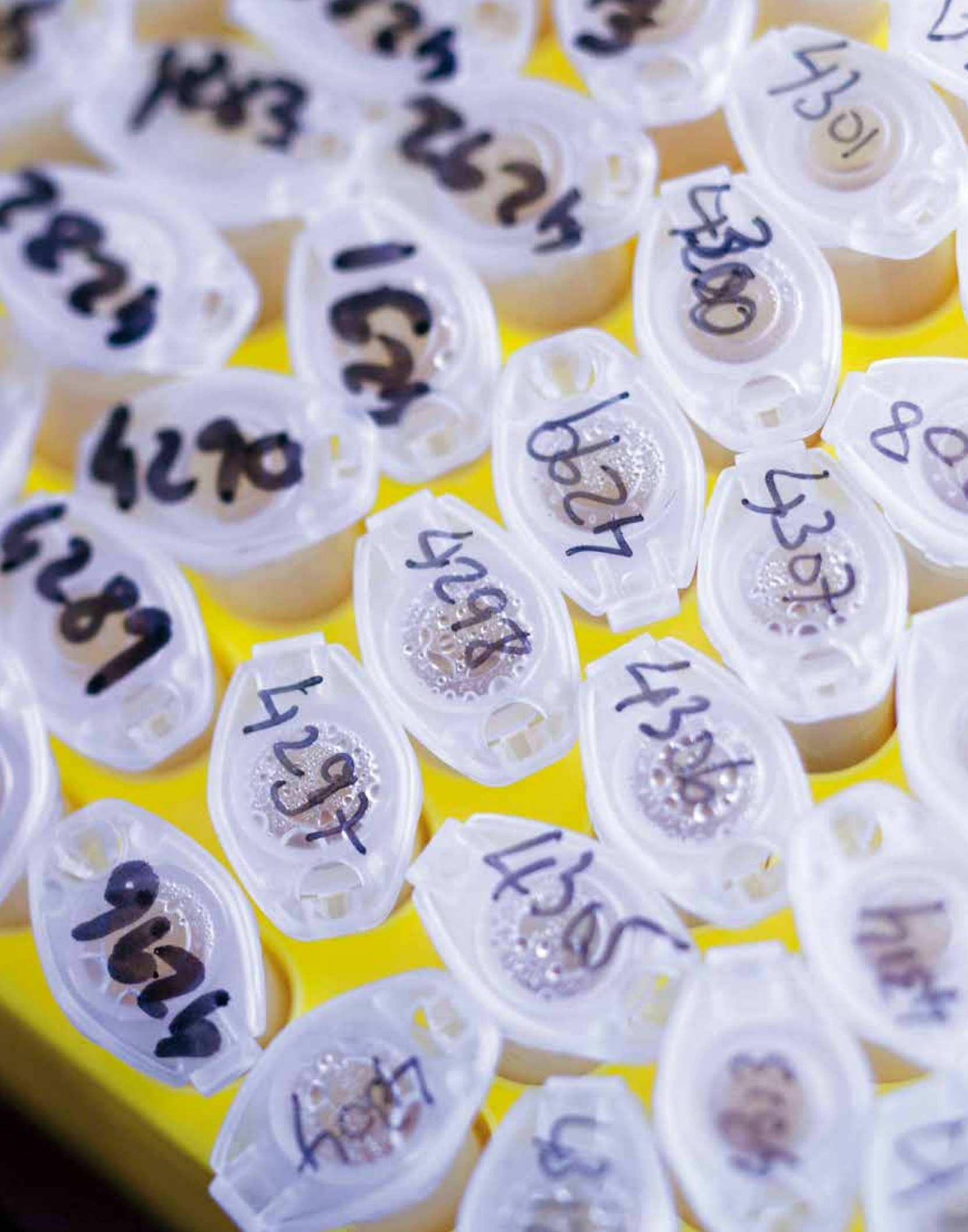


Global network

The Institut Pasteur is at the hub of a unique international network of 32 institutes, stretching across all five continents. These structures are affiliated in partnerships that focus on scientific research, training and public health services. In parallel, the Institut Pasteur collaborates with the most prominent international stakeholders in order to advance our knowledge of the life sciences.

Funding

The Institut Pasteur's budget is based on four funding sources: public generosity and revenues from assets, government contributions, development of business based on Institut Pasteur research, and research contracts and agreements. This original economic model guarantees the independence of the Institute's research policy. In 2013 its budget was €282.4 million.



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Interview

Rose-Marie Van Lerberghe
Chairman of the Institut Pasteur Board of Directors

The key event of 2013 was the departure of Alice Dautry and the arrival of Christian Bréchot as Institut Pasteur President. Can you describe the selection process and subsequent appointment?

The Board of Directors implemented a selection process using a search committee, and I was part of this committee. The process was overseen by Daniel Louvard, who is Vice-Chairman of the Board of Directors. There were a good many high quality applications, including a number of international candidates. This was a very positive indicator for us, since it is testament to the appeal of the Institut Pasteur as an employer. Ahead of the candidate sourcing procedure, the search committee drew up a job description and a list of criteria and necessary skills. Following initial screening, thirteen candidates were invited for interview, where they talked about their plans for the Institut Pasteur, their skills and their career to date. Three candidates were then shortlisted and presented to the Board of Directors by the search committee. The Board of Directors conducted final interviews and made its decision in conjunction with the Scientific Council. Following this process Christian Bréchot was appointed on March 8, 2013 to replace Alice Dautry and head up the Institut Pasteur starting October 1, 2013.

"Many foreign scientists commented on the freedom they enjoy at the Institut Pasteur, which puts them under less pressure to achieve results, and gives them the time and the resources to develop their research in their own way and take certain risks."

What is your impression of these first three months, in terms of the relationship between the Board of Directors and Christian Bréchot?

Since his arrival here Christian Bréchot has shown application, enthusiasm and talent. The Board of Directors asked him to present a ten to fifteen-year scientific forecast and a five-year strategic plan. We wanted this thinking process to be widely collaborative, since strategies are always drawn up collectively within the board. And I was pleased to see that Christian Bréchot's work has been the result of extensive consultation and significant collective input. Far from being a collection of good intentions, the strategic plan that was put before the Board of Directors was a serious plan that set out priorities with the corresponding figures. This is an important process since it is crucial for the board to have a clear understanding of the President's scientific and strategic vision, so that it can release the necessary resources to put the strategy into practice.

“Struck by the scientists’ enthusiasm and dedication”

Other than the appointment of Christian Bréchot, what were the key items on the Board of Directors’ agenda in 2013?

The appointment of the President required a good deal of time and work on the part of the Board of Directors. Another issue also dominated 2013. In accordance with its mandate, the general inspectorate of social affairs conducted an investigation of the use of funds collected by the Institut Pasteur through public generosity. By treating as a single item the notions of legacy and donation, the resulting report suggested that the Institut Pasteur was misleading its donors. This was a difficult and painful episode for the campus and the Board of Directors. The Ministers of Health and of Research lent their support to us throughout this period.

“A crucial issue is the ability not only to attract talent from outside, but also to develop internal skills.”

Tell us about your first few months as Chairman of the Institut Pasteur’s Board of Directors.

I devoted a lot of time to meeting the scientists and each scientific department. I feel that this is an essential part of carrying out my responsibilities in the best possible way. I was always made very welcome, and was struck by the scientists’ enthusiasm and dedication. This also reassured me that the Institut Pasteur is seen as an attractive employer by foreigners. I realized that, compared to other French organizations, the Institut Pasteur boasts a high standard of resources and equipment and good quality administrative support. The Institut Pasteur also attracts employees on account of its multidisciplinary approach and the quality of the relationship between the various teams and disciplines. Compared to other countries where salaries for scientists are perhaps higher, many foreign scientists commented on the freedom they enjoy at the Institut Pasteur, which puts them under less pressure to achieve results, and gives them the time and the resources to develop their research in their own way and take certain risks.

What are your thoughts on the International Network?

I was impressed with the reputation and weight of the Institut Pasteur in the countries in which it operates, both in the field of public health and in terms of training local scientific elites. I also noticed a certain difference in status between the various institutes and consequently in their relations with the Institut Pasteur in Paris. It is disappointing that the Institut Pasteur in Paris provides so little support and financial aid to these institutes. Locally, the teams suffer greatly from an image of being little more than suppliers of samples. However, there are plans for the development of major research projects between several of the network’s institutes. And the potential sources of biological resources to be explored and exploited are considerable.

How do you view the Institut Pasteur’s current financial situation?

The financial situation is currently relatively favorable, particularly as a result of the very careful expense management exercised by my predecessors. We must bear in mind that the Institut Pasteur receives funding from a number of different sources: government funding, research contracts, donations, legacies, revenue from assets, as well as industrial applications. This context allows us to be ambitious and to invest in the future, as long as we remain rigorous and mindful of risks.

What is on the horizon for the Institut Pasteur in 2014?

The strategic plan drawn up by the President is to be a key aspect of 2014: it will result in a schedule of actions to be implemented. I shall pay particular attention to all aspects of human resources. A crucial issue is the ability not only to attract talent from outside, but also to develop internal skills. I feel that addressing this issue is fundamental if we are to remain at the forefront in the coming years, and to remain faithful to our original mission.

Interview

Christian Bréchot
President of the Institut Pasteur

Talk us through your first few months with the Institut Pasteur.

Since my arrival in October 2013, my time with the Institut Pasteur has been extremely insightful and stimulating. I was already very well acquainted with the Institut Pasteur but I have been impressed by the enthusiasm, the warmth and the team spirit that exist here. More specifically, these first few months have provided opportunities firstly to meet the people within the Institut Pasteur and secondly to measure the role of the Institut Pasteur in the field of scientific research in France, as well as the importance of relations with the Ministries of Health and of Research and the health agencies that depend on them. This meant that, in conjunction with the Board of Directors, I have been able to put in place a four-year strategic plan. I have managed to meet the teams of each research department, technological platform and administrative department, and this was a very important step for me. With the input of the Scientific Council, I have been able to work on defining the Institute's priorities. I have valued my meetings with the Works Committee, the Committee for Health, Safety and Working Conditions (CHSCT) and trade union members at the Institut Pasteur. In addition, I would like to thank Alice Dautry and her predecessors for everything that has been put in place to date. They have ensured that the Institut Pasteur is ready to face important changes and meet the major challenges that lie ahead.

What is your assessment of 2013?

2013 was a prolific year with a number of very positive achievements. We saw the recruitment of several high-caliber scientists. On a scientific level, there were some major discoveries, some of which are detailed in this annual report. In addition, 2013 saw the launch of a clinical trial for a therapy for Sanfilippo syndrome. Last year also marked the 30th anniversary of the discovery of HIV. The inauguration of the François Jacob building was another important event in the life of the Institut Pasteur. Fundraising saw a significant increase against the previous year, despite the difficult economic climate. This is a strong indication of donor commitment, which to my mind should be seen as a measure of success.

"The International Network is one of the Institut Pasteur's great strengths, and should be seen as a fully integrated scientific partner."

In what sense is the Institut Pasteur in a critical period? What are the current challenges?

We are currently in a period of rapid development in terms of scientific concepts. Great leaps in conceptual and technological areas have allowed us to explore hitherto unknown scientific fields. It is the Institut Pasteur's duty to continue to make great discoveries, on a scale that really alters the way we look at science. It is also important to integrate these advances into a holistic approach, which takes account of physiology and of the individual patient, so that we can make real progress for our fellow citizens worldwide. In the context of these new

“The Institut Pasteur is an international institute rooted firmly in France.”

challenges, the Institut Pasteur has to adapt to international competition, particularly in terms of recruiting scientists, not only by strengthening its appeal as an employer, but also by redefining the balance between external recruitment and internal career development. A key factor in this strategy will be the Institut Pasteur International Network. The Institut Pasteur’s financial resources should also be commensurate with its ambitions, and for this it must strengthen its academic and industrial partnerships, both nationally and internationally.

“I am absolutely certain that the way forward for the Institut Pasteur is to define an overall approach that is original and new and consistent with its recruitment and career management policy, while taking into account global competition between research institutes and universities – but which also remains faithful to the original spirit of the Institut Pasteur.”

What are your key ambitions for the Institut Pasteur?

Firstly, the emphasis should be placed on the monitoring and management of career paths and recruitment methods. During the last few years, with the implementation of five-year groups managed by young scientists, the Institut Pasteur has organized a very interesting and attractive program for junior employees. We have already developed this strategy, and will obviously continue to do so. However, in parallel, we plan to put more attractive packages in place for senior candidates and those in mid career. This external recruitment strategy is to be combined with an overall thought process on the management of careers internally, which will take into account the notions of working together and the fundamental Institut Pasteur vision. Lastly, I shall attach great importance to strengthening teaching and training.

What scientific vision do you intend to develop?

This is a key point on my agenda for the next four years. We must define a scientific vision for the Institut Pasteur that combines curiosity-driven research based on recruitment excellence and a cross-disciplinary strategy, with the strengthening of incentive schemes that offer the opportunity to pool our strengths in important scientific fields. With this in mind, a project was instigated involving Senior Management and the Scientific Council, the Board of Scientific Advisors, certain think tanks and departmental heads. The result of our work will be published in July 2014. The first areas for discussion and action focus on bioinformatics, integrative biology, epigenetics and antibiotic resistance, which are areas in which we aim to enhance our expertise. There is also a major future role for the Institut Pasteur in understanding the relationship between microbiology, whether it concerns infectious pathogenic agents or normally present bacterial flora – microbiota – and non-communicable chronic diseases, such as cancer, metabolic disorders such as obesity and diabetes, ageing and neurodegenerative diseases. This leads me on to our development plans for the technological platforms, which are another essential part of our strategic plan. We aim to improve coordination between the service activities on these platforms and technological research activities.

What is on the agenda for the International Network?

The Institut Pasteur is an international institute rooted firmly in France. This fundamental notion forms the basis for our strategy in the coming years. The International Network is one of the Institut Pasteur’s great strengths. This stems not only from the quality of the scientific work developed within the network, but also from a fruitful alliance between fundamental research and public health problems. The network should be seen as a fully integrated scientific partner. It should be firmly included in the Institut Pasteur’s strategy for the coming years. The network is also a source of funding, both in terms of fundraising and – an aspect to be further developed – through contracts with academic partners, major international organizations and industry partners. This is why I feel that it is now important to give it a higher profile and greater ambitions, and to strengthen its links with the Paris campus. Decisive actions are to be taken in terms of scientist mobility. As an example, all scientists recruited in Paris will now be required to spend at least three months in one of the Institut Pasteur International Network institutes during the first two years of their career. In addition, the Transversal Research Programs are to set up partnerships with at least one Institut Pasteur from the network.

These projects clearly represent financial investments.

Yes, we have very high ambitions. We must build on the significant increases in fundraising that we have seen over the last few years. We must also define a more ambitious international policy, targeting North America, China and Switzerland in particular. Targeting major donors is also a significant and crucial initiative to be developed.

What message would you like to send out to the Institut Pasteur as a whole?

The Institut Pasteur is an extraordinary organization with an excellent reputation, thanks to its high-caliber scientific community. We are currently at a very important period in our development, and we must be aware of our strengths – but also of our weaknesses, so that we can meet our challenges. How many institutes are there today operating in fundamental research that are also key players in medicine and public health, major centers of teaching and business development and that also have a network of 32 institutes in 25 countries? The Institut Pasteur is unique, and is synonymous with excellence the whole world over. We must continue in this vein. I am absolutely certain that the way forward for the Institut Pasteur is to define an overall approach that is original and new and consistent with its recruitment and career management policy, while taking into account global competition between research institutes and universities – but which also remains faithful to the original spirit of the Institut Pasteur.

Research

"Unpredictability is an intrinsic part of any scientific undertaking. If what we're going to find is really new, by definition it's something that we can't predict in advance."

François Jacob (1920-2013)
Researcher at the Institut Pasteur and pioneer in molecular biology
Nobel Prize in Medicine, 1965

Pablo Navarro-Gil

Head of the Epigenetics of Stem Cells five-year group

“I became a ‘Pasteurian’, as they say…”

During my studies I spent almost nine years at the Institut Pasteur – two Master’s internships, a PhD thesis and a first post-doc. Nine years of training during which time I became a “Pasteurian”, as they say. After four years of post-doc training in Edinburgh and a lengthy selection process, I was able to come back to the Institut Pasteur to direct a five-year group, a long-time personal ambition and one of my dreams as a student. This is the start of a new chapter of my career in a top scientific environment.

10 – CELL BIOLOGY AND INFECTION

12 – DEVELOPMENTAL AND STEM CELL BIOLOGY

28 – VIROLOGY

14 – STRUCTURAL BIOLOGY AND CHEMISTRY

A multidisciplinary, cross-cutting approach that harnesses collective intelligence.

26 – PARASITOLOGY AND MYCOLOGY

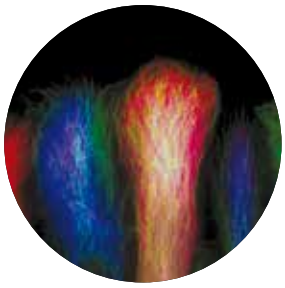
16 – GENOMES AND GENETICS

24 – NEUROSCIENCE

18 – IMMUNOLOGY

22 – MICROBIOLOGY

20 – INFECTION AND EPIDEMIOLOGY



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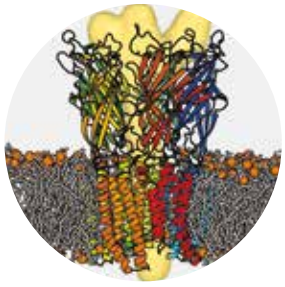

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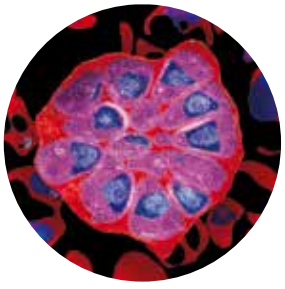
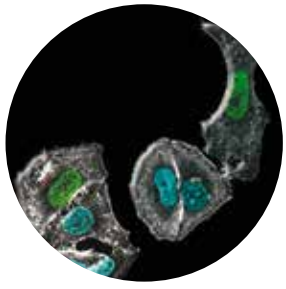
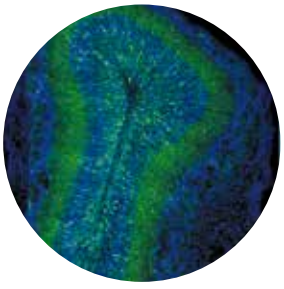


26 – PARASITOLOGY AND MYCOLOGY

10 research departments



16 – GENOMES AND GENETICS



24 – NEUROSCIENCE

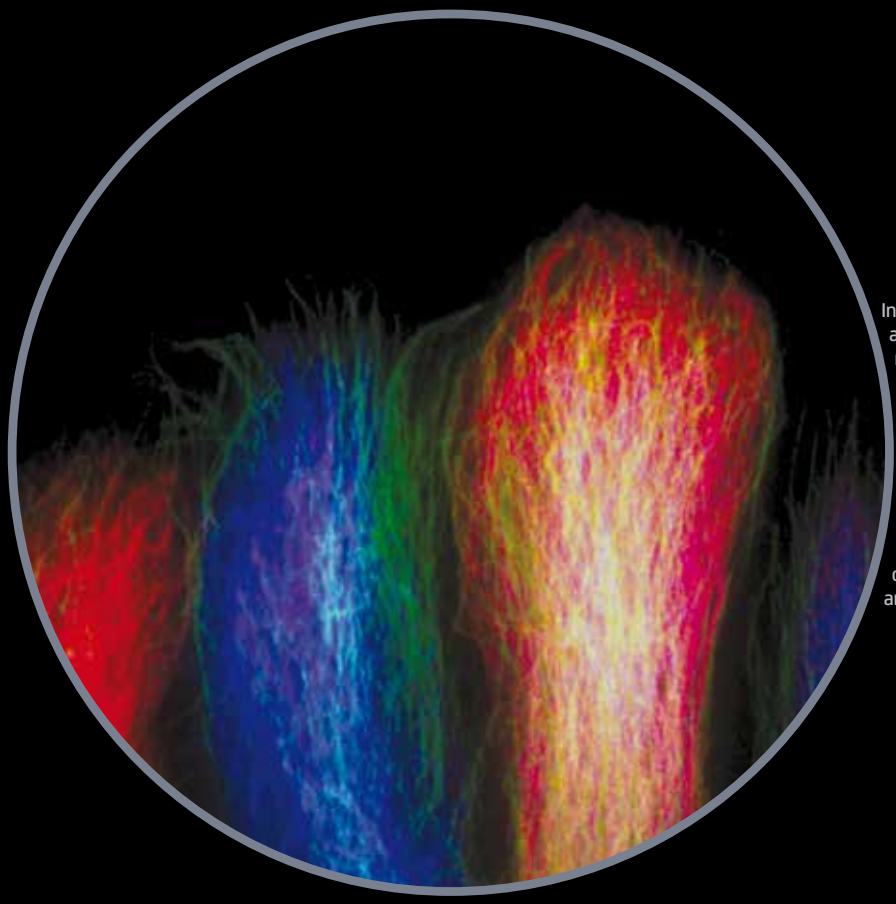
18 – IMMUNOLOGY

22 – MICROBIOLOGY

20 – INFECTION AND EPIDEMIOLOGY

Cell Biology and Infection

This department studies the mechanisms regulating normal or pathological cell function and the interactions between different types of infectious agents and their targets. It deploys imaging and genomics techniques to shed light on the intricate workings of microbes and cells.



In migrating astrocytes, microtubules (in green) and two intermediate filament components: GFAP (in red) and nestin (in blue). Immunofluorescence imaging. See opposite, “Cellular architecture”.

12 research units
2 technological platforms

The work of the Cell Biology and Infection Department is based on fundamental cell biology research, with a particular focus on infections and diseases in humans. This work is vital to help us understand how cells, tissues and organisms work in physiological conditions. It also sheds light on the ways in which these mechanisms are hijacked and deregulated in some human diseases and by microbes during infection. Processes such as cell polarization, endocytosis and signaling pathways, for example, are not only triggered when microbes invade, spread and colonize a host compartment; they also play a role in neuropathy, cancer, genetic diseases, and tissue regeneration. The department develops and uses sophisticated imaging, data analysis, mass spectrometry, next-generation sequencing and bioinformatics techniques to further its research.

CELLULAR ARCHITECTURE

Our cells have an internal skeleton, known as a cytoskeleton, which is vital for cell division and migration in the body. Cytoskeleton disorganization is thought to play a crucial part in the proliferation and spread of cancer cells. The cytoskeleton is the main focus of the research carried out by Sandrine Étienne-Manneville's team in the Cell Polarity, Migration and Cancer Unit. The team is studying the least known of the three cytoskeletal components, known as intermediate filaments. Together with the other components – microfilaments and microtubules – they create a highly complex network, but relatively little is known about how this network is formed and regulated. In 2013, the scientists demonstrated that the APC protein, a well-known tumor suppressor, interacts directly with intermediate filaments and links them with microtubules. Even more interesting is the fact that loss of APC, which often occurs in cancer cells, leads to the disorganization of the intermediate filament network, which affects cells' ability to migrate. This research highlights APC's essential regulatory function in organizing intermediate filaments, confirming the major role it plays in cytoskeletal regulation and shedding new light on its involvement in the spread of cancer cells.

TOWARDS NOVEL ANTI-INFLAMMATORY DRUGS

ATP is a molecule that is present inside every cell and is essential to many biological functions. It has been known for some years that ATP can convey a message of danger to the body and trigger a protective inflammatory process when it is found outside cells, for example following wounding. However, it was unknown whether microbes could induce such a response upon infection. Using the bacteria *Shigella, Salmonella* and pathogenic *Escherichia coli* as models, the scientists of the Molecular Microbial Pathogenesis unit led by Philippe Sansonetti have shown the key role of extracellular ATP during intestinal infections. In fact, the presence of these pathogens in the gut causes the opening of channels found in the membrane of cells, which allow the release of ATP. After binding to extracellular receptors, ATP triggers a quick cascade of reactions that set off the inflammatory response meant to eliminate the pathogens. The scientists have also shown that *Shigella* is capable of evading this immune response by stopping the opening of these channels. These findings could therefore lead to the development of novel anti-inflammatory drugs based on blocking the release of ATP. Indeed, ATP release likely contributes to several diseases such as chronic inflammatory disorders of the intestine, cancer, obesity and diabetes.

LIKE A PRION

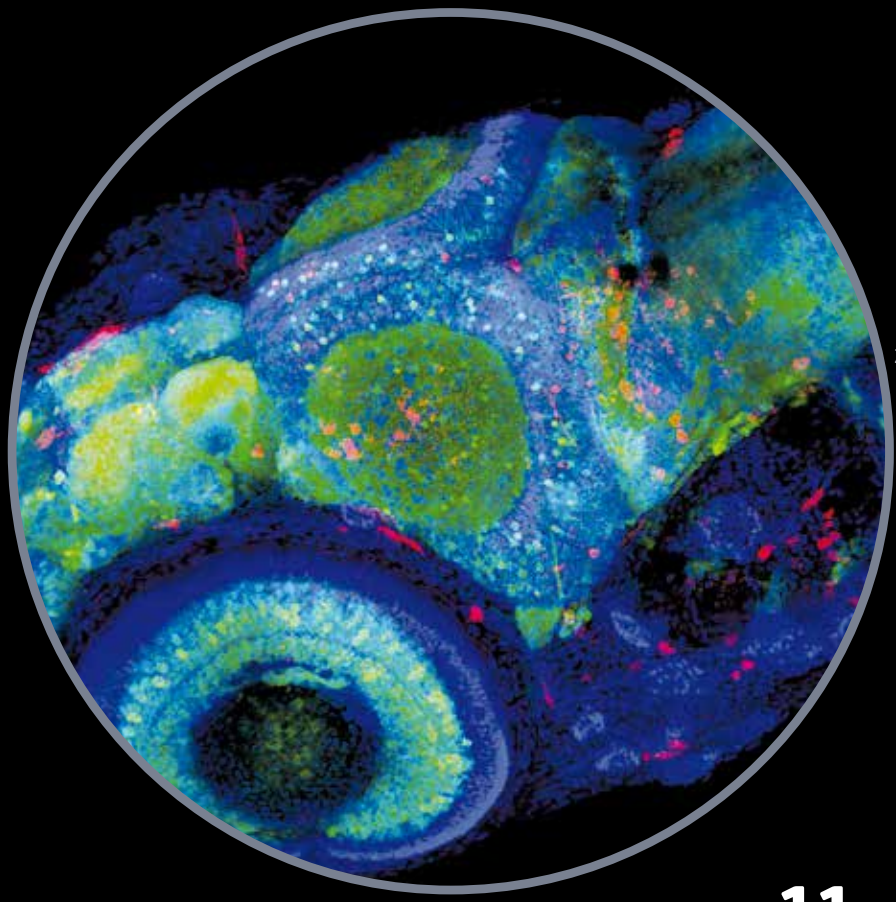
Chiara Zurzolo's team in the Membrane Traffic and Pathogenesis Unit focuses on cellular proteins involved in neurodegenerative diseases such as Parkinson's, Huntington's, and Alzheimer's. It is now known that the abnormal folding of a protein's structure can lead to several neurodegenerative diseases. In 2009, the team demonstrated that prions – proteins that become pathogenic because of an altered 3D structure – spread from cell to cell through long, narrow tunnels known as nanotubes, which are formed by neurons to connect to other neurons. The prions spread in the same way as an infection caused by bacteria or viruses, gradually invading the entire brain and resulting in widespread neurodegeneration. In 2013, the scientists identified similar behavior in the huntingtin protein, which is involved in Huntington's disease. Their research in neuronal cell culture showed that the mutated huntingtin forms aggregates that spread through nanotubes, much in the same way as prions. Moreover, the stress generated by the formation of these aggregates stimulates nanotube formation, thus facilitating the spread of the pathogenic protein. The scientists believe that these tubular structures, which have also been observed in some cancers, act as an effective mechanism for the spread of pathogenic proteins. It may therefore be possible to slow neurodegeneration by blocking the spread of these proteins via nanotubes.

PASCALE COSSART, WINNER OF THE BALZAN PRIZE

In 2013, Pascale Cossart, Head of the Bacteria-Cell Interactions Unit, was awarded the prestigious Balzan Prize. Each year, this prize is awarded to four people throughout the world who have made an outstanding contribution to culture, science and humanitarian work. Pascale Cossart was chosen for her seminal work on the biology of infections. Pascale and her team focus on infection by *Listeria monocytogenes*, the pathogen responsible for listeriosis, a serious food-borne infection that can result in gastroenteritis, meningitis, and miscarriage. She has revealed a series of mechanisms that shed light on the virulence of *Listeria monocytogenes*. Thanks to her research, *Listeria* is now one of the best known bacteria and is used as a model in infectiology and cell biology.

Developmental and Stem Cell Biology

The Department of Developmental and 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.



Zebrafish can be used as a model for infection with the chikungunya virus. The neurons are shown in green, and the infected cells in red. The cell nuclei are shown in blue.

11 research units
1 Mouse Genetics Engineering Center

The department explores the mechanisms that enable a multicellular organism such as a human being to develop from a single cell, the fertilized egg. Research is carried out along four principal themes:

- identifying cell movements in the embryo, cell polarity and shape changes for tissue and organ formation, and the information exchanges mobilized during this process;
- determining how the identity of each cell is established and maintained through specific programming mechanisms during prenatal development and in the adult;
- investigating stem cells, which play a predominant role not only in embryogenesis, but also in the regulation and maintenance of adult tissues;
- clarifying the respective roles of innate and non-genetic factors that impact on the phenotype of the individual, and genetic contributions to host resistance to infectious diseases and/or congenital and metabolic diseases.

In 2013, a junior research group directed by the young scientist Pablo Navarro was added to the Department. Other recruitments are also planned in connection with the LabEx (Laboratories of Excellence Program) project "REVIVE", installed as a result of the French government's "Investment in the Future" program. This ten-year funding will be used to build and coordinate a network of stem cell experts from the Institut Pasteur and the Paris region with the aim of developing a globally recognized hub for regenerative medicine.

THE EMBRYO AND ITS PARADOXES

Ribosomes are responsible for a vital function in the cell known as "translation", in which the genetic code carried by RNA is converted into protein. But scientists are also looking into the more specific role that ribosomes might play in normal processes (such as embryo development or cell differentiation) or pathological processes (response to infectious stress, tumor progression, etc.). In 2013, Michel Cohen-Tannoudji's team in the Mouse Functional Genetics Unit led by Jean-Jacques Panthier made a significant breakthrough in its research into the function of the Notchless gene in mammals. Notchless is essential for ribosome production and assembly (ribogenesis). Using a mouse model and sophisticated analytical tools, the team examined the relationship between ribogenesis and tissue regeneration in mammals. Their research revealed some surprises. The research team confirmed that the Notchless protein is vital for cell survival in adults, particularly for hematopoietic stem cells that produce blood cells. But absence of the protein has no impact on the more specialized cells derived from hematopoietic stem cells. The results therefore suggest that production of ribosomes may vary from cell to cell in a single individual. These findings can help us understand why ribosomal mutations in humans only affect the function of some tissues.

CONTROLLED BY NOTCH

Notch is a protein found on the membrane of multicellular organisms, and it regulates the transcription of a variety of genes. If Notch is deregulated, it can lead to severe defects in organogenesis and cancer. Notch is involved in maintaining muscle stem cells, but it first needs to be activated: it is cleaved to release a fragment within the cell, known as NICD, which then interacts with other proteins such as RBPJ to trigger the transcription of specific genes. Working with Henk Stunnenberg's team from the Netherlands, Shahragim Tajbakhsh's Stem Cells and Development Unit conducted a genome-wide study to identify how these genes are activated. Their research raises doubts on previously accepted models for Notch activity. It was generally thought that RBPJ remained permanently on the DNA sequence of regulated genes, but we now know that for most genes RBPJ is not always present – it is the NICD fragment that recruits this protein to DNA. This research sheds new light on the way in which Notch controls the regulation of some genes, particularly those in the extracellular matrix that surround and support muscle stem cells.

FISH USED TO STUDY CHIKUNGUNYA

Zebrafish can be infected by the chikungunya virus, and they represent a very useful model for studying the disease. That was one of the main findings of research conducted in 2013 by Nuno Palha and Jean-Pierre Levraud from Philippe Herbomel's Macrophages and Development of Immunity Unit, in collaboration with the Virus and Immunity Unit led by Olivier Schwartz. This fish has become a valuable model for Philippe Herbomel's team in studying the mechanisms of immunity. By injecting the transparent zebrafish larvae with a fluorescent chikungunya virus, the scientists were able to follow the infection and the resulting immune defense response from cell to cell in real time throughout the entire organism. The cells affected by the virus in different organs became fluorescent as the infection spread. While the virus kills some cells, others – such as cells in the brain – survive and serve as hosts for the virus ("reservoir" cells). When the immune system of the fish is attacked by the virus, it acts in the same way as in mammals, unleashing a defense mechanism based on the production of a key molecule known as interferon. This stage is critical if the fish is to survive and combat the disease. The scientists made the unexpected discovery that interferon is produced on a large scale by cells known as neutrophils. This surprising finding shows the usefulness of the zebrafish in studying how viruses spread in humans and how the immune system reacts.

2013 CNRS GOLD MEDAL

Margaret Buckingham, Professor Emeritus at the Institut Pasteur and Director of Research Emeritus at the CNRS, was awarded the 2013 CNRS Gold Medal, France's most prestigious scientific prize. Her main research subject is tissue formation from multipotent stem cells during embryo development. With her team, she identified a population of myogenic stem cells controlled by a genetic network that prompts them to become muscle cells. She also demonstrated the role of "satellite cells" in adult muscle regeneration. Her discovery of a second source of myocardial cells has had a major impact on the generally accepted view of heart formation, with significant repercussions for our understanding of human cardiac malformations.

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 and properties 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 strategies.

The structure of a bacterial analog of the nicotinic receptor (one color per subunit) inserted into the cell membrane (gray and orange). A representation of the volume accessible to ions is shown in yellow.

10 research units
5 technological platforms

The Structural Biology and Chemistry Department studies the three-dimensional structure of molecules (proteins, RNA, and DNA) to improve understanding of their biological functions and potential role in the development of infectious diseases (tuberculosis, Chagas disease, malaria, etc.), 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 for potential targets;
- nuclear magnetic resonance (NMR), which explores the structures of smaller molecules and provides information about their movements and molecular interactions;
- ultrastructural microscopy, which provides highly detailed images of the structures of large biological complexes;
- molecular modeling, which is vital for determining and manipulating structures.

A THERAPEUTIC CANCER VACCINE

Scientists working on a flagship Institut Pasteur vaccine project that has received vital support from donors took a major step forward in 2013 with the production of a clinical batch of the MAG-Tn3 cancer vaccine candidate. MAG-Tn3, the result of more than 15 years of collaborative research between Sylvie Bay's team in the Chemistry of Biomolecules Unit led by Laurence Mulard and the team directed by Claude Leclerc and Richard Lo-Man in the Immune Regulation and Vaccinology Unit, targets adenocarcinomas in the breasts, lungs, colon, and ovaries. Unlike preventive vaccines, MAG-Tn3 is a therapeutic vaccine that is designed to stimulate an immune response in patients already suffering from the disease. Producing a clinical batch means manufacturing a given quantity of the vaccine, in full compliance with applicable regulatory standards, for administration to patients for the first time in a clinical trial. Since MAG-Tn3 is a completely synthetic molecule, the preparation procedure had to be fully reviewed and optimized to ensure the feasibility of industrial-scale production. The scientists worked closely with the Clinical Research Department for the production of this clinical batch, a complex procedure that was crucial for the continuation of the project. A phase I clinical trial sponsored by the Institut Pasteur will shortly be carried out in France on around 30 breast cancer patients to assess tolerance to the MAG-Tn3 vaccine candidate.

3D TECHNIQUES TO UNDERSTAND HOW ALCOHOL AFFECTS THE BRAIN

Marc Delarue's Structural Dynamics of Macromolecules Unit uses X-ray crystallography to analyze and elucidate the 3D structures of biological molecules. For several years the scientists have been working in collaboration with Pierre-Jean Corringer's Channel Receptors Unit in the Neuroscience Department on a bacterial homolog for the nicotinic receptor, a protein found on the surface of inhibitory neurons in the brain. Messenger molecules of the nervous system can bind to it, as can nicotine, anesthetics, and alcohol. In 2013, the scientists revealed the effects of ethanol found in alcoholic drinks on this receptor for the first time and on an atomic scale. When ethanol binds to the receptor, it keeps the protein channel in an open position, meaning that activation messages are constantly sent to the inhibitory neurons and brain function is severely affected. Understanding the effect of alcohol on nicotinic receptors at atomic level paves the way for the synthesis of ethanol antagonist compounds that are able to keep the channels closed. Such molecules could be used to limit the effects of alcohol consumption on the brain and reduce withdrawal effects in cases of addiction.

THE SUPPORT OF THE CROWD

As a general rule, scientists study proteins in purified solutions, where they have all the space they need to spread out. But in the body, where thousands of biomolecules coexist side by side, conditions are completely different. Alexandre Chenal and his colleagues in Daniel Ladant's Biochemistry of Macromolecular Interactions Unit are researching how molecular crowding affects proteins. The scientists took as their model a protein derived from the CyaA toxin produced by *Bordetella pertussis,* the bacteria responsible for whooping cough. Calcium causes this protein to fold and adopt a compact 3D structure. The team used spectroscopic methods to show that crowding can have diametrically opposite effects depending on whether calcium is present or not, but that these effects are always in keeping with the life and functions of the toxin. In the absence of calcium, as inside the bacteria, the toxin remains unfolded, an ideal extended configuration that allows it to travel easily along the narrow membrane channels in the bacteria. But in the pulmonary tract, the strong concentration of calcium causes the secreted toxin to fold. In this instance, crowding helps the protein to fold and stabilize its 3D structure, which is vital for it to unleash the full force of its virulence against our cells. Remarkably, the protein relies on the support of the crowd in both cases.

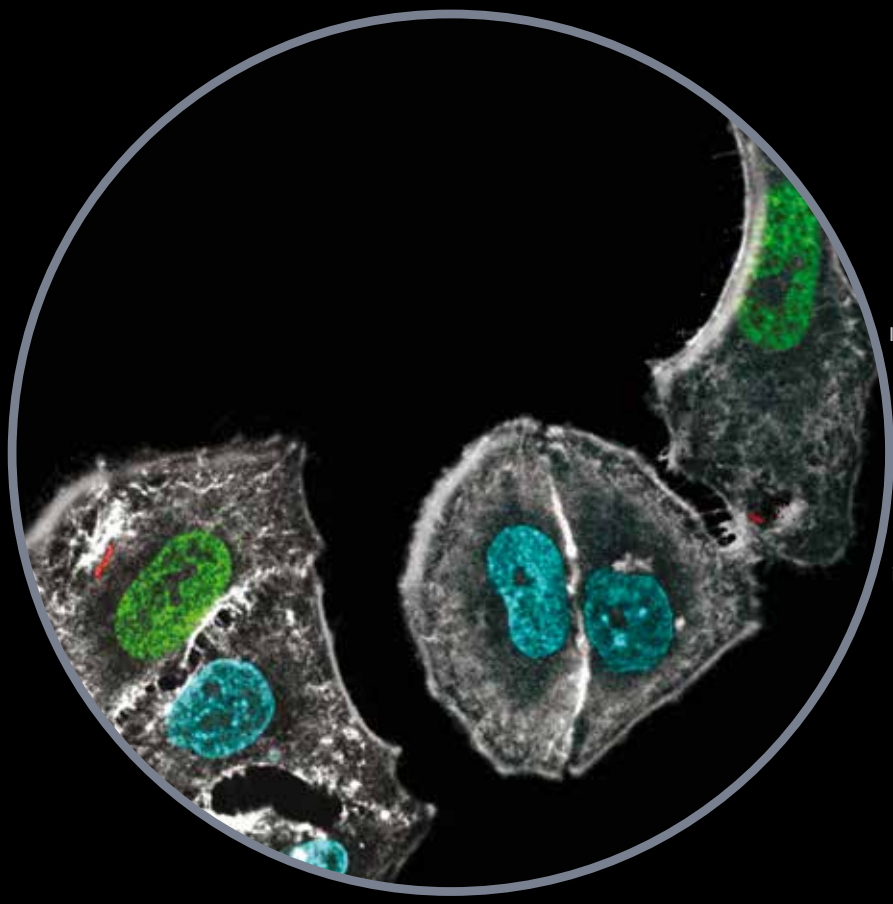
A MICROSCOPE THAT "SEES" ATOMS

In 2011, the Cascice project was selected for EquipEx funding under the French government's Investing in the Future program. With €7.5 million in funding, this Institut Pasteur-coordinated project is aiming to set up a platform featuring cutting-edge structural biology equipment. Platform development began in 2013. The first instrument purchased was a mass spectrometer, the only one of its kind in the Paris region, which can be used for the mass characterization of large molecular complexes that play an important role in cell function. The second investment has now been announced: an ultra-high-resolution electron microscope that can "see" the structures of these large complexes at atomic level. A dedicated building will be needed at the Institut Pasteur to house this equipment, which will be used by the scientists on campus and also by teams from other French or international research organizations.

View of the future Nocard building to house the ultra-high-resolution microscope.

Genomes and Genetics

With the continual discovery of new genes revealing new biological functions, genetics raises numerous questions and offers a vast array of research possibilities for the scientists in the Genomes and Genetics Department.



In these cells infected by *Legionella pneumophila* bacteria (in red), the modified DNA is shown in green. Non-infected cell nuclei are in blue.

15 research units
4 technological platforms

The department explores the genetic information of the human body and microorganisms such as yeast and bacteria. 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 human genes over time. The progress of these research programs is largely based on new sequencing and genotyping techniques.

LEGIONELLA: THE ART OF MANIPULATION

Intracellular pathogens adopt various strategies in order to circumvent immune defenses and proliferate freely. Some are able to modulate host cell gene expression to their own advantage. One of the ways they manage this is by initiating epigenetic modifications, in other words altering not the genes themselves (genetic modifications) but their environment. This is the strategy used by the *Legionella pneumophila* bacterium responsible for legionellosis, a disease characterized by acute pulmonary infection which is potentially fatal if untreated. Carmen Buchrieser's team in the Biology of Intracellular Bacteria Unit has identified an epigenetic mechanism that enables the bacteria to alter the gene expression of the cells they infect.
This process, revealed for the very first time, facilitates the survival and proliferation of *Legionella pneumophila* during infection. In total, 4,870 host genes are thought to be "reprogrammed" by the bacteria. Some of these genes, such as interleukin 6 or the TLR5 receptor, are directly involved in the innate immune response. The mechanism used by *Legionella pneumophila* is based on the action of an enzyme it produces that restricts access to several host genes by altering the structure and conformation of DNA – an ingenious strategy that shows yet again how pathogens are masters in the art of manipulation.

DENGUE: THE ROLE OF MOSQUITO GENETIC FACTORS

Dengue is the most widespread viral disease transmitted by insects in the world today. Most research into how the disease spreads had previously been carried out using laboratory insects. But scientists from Louis Lambrechts' team in the Insect-Virus Interactions Group have conducted a study using wild *Aedes aegypti* mosquitoes (the primary dengue vector) that they collected in Thailand. They tested the genetic predisposition of these mosquitoes to spread different variants of the virus found in patients in the same region. Their research enabled them to pinpoint a series of genetic factors that make mosquitoes more or less likely to transmit the virus. Surprisingly, the effect of some of these factors seems to depend on the virus strain: a factor conferring resistance on one virus strain may be a susceptibility factor for another strain. For Louis Lambrechts, these findings not only shed new light on the biology of dengue in its natural environment; they also have fundamental implications for the genetics of predisposition to infectious diseases in general, suggesting that the effect of host genetic factors may vary depending on the pathogenic agent. It therefore appears that genetic vulnerability to infectious diseases is not solely an intrinsic characteristic of the host but also depends on the pathogen.

THE HISTORY OF TUBERCULOSIS

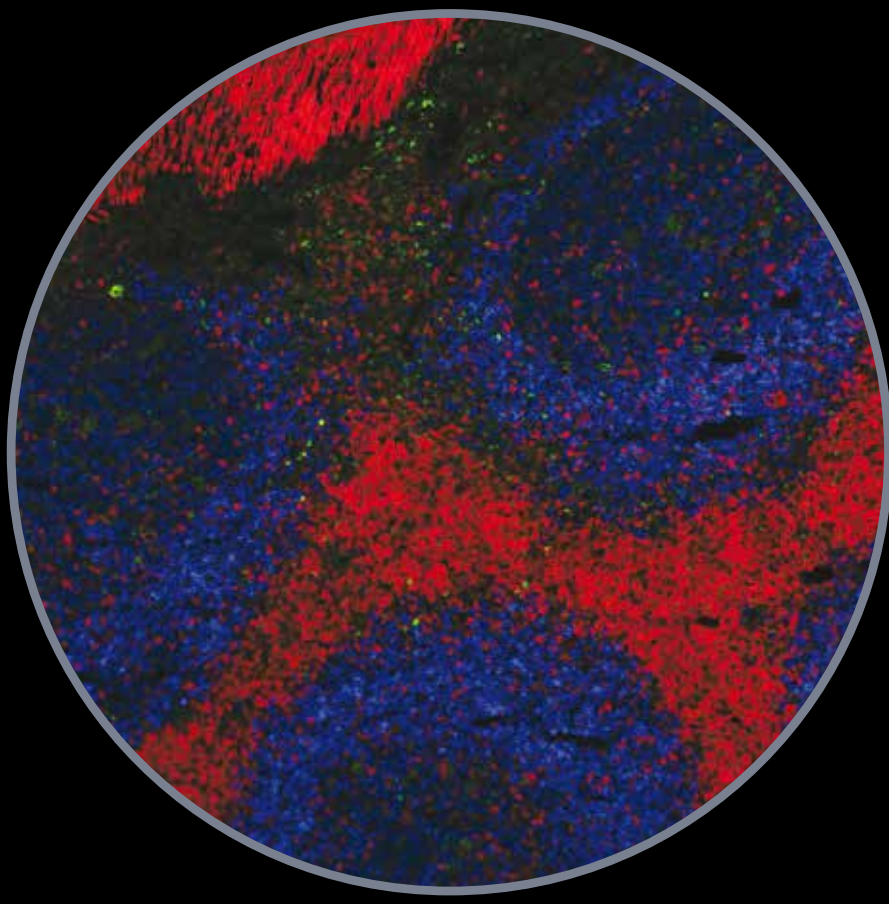
Given the vast number of mycobacteria species, why did *Mycobacterium tuberculosis,* "Koch's bacillus", evolve so successfully that around a third of the world's population currently carries the bacteria and 1.4 million people die every year from tuberculosis? In an attempt to answer this question, Roland Brosch's team in the Integrated Mycobacterial Pathogenomics Unit tried to trace the evolutionary history of the *Mycobacterium* genus. Working with a team from the Institut Pasteur in Lille and the Évry Génoscope, the scientists sequenced the whole genome of several strains of *Mycobacterium canettii,* which also causes tuberculosis but is only generally found in the Horn of Africa. Analysis of this data revealed that the strains of *M. canettii* are more genetically diverse and that their origins date back much further. The strains of *M. tuberculosis,* on the other hand, are highly genetically conserved and have evolved from a separate branch from the *M. canettii* strains. Comparing the genomic data for *M. canettii* and *M. tuberculosis* shows that *Mycobacterium tuberculosis* has undergone numerous mutations; it has lost some genes and acquired others by horizontal transfer. This data should now help the scientists identify genetic candidates that have contributed to the global dominance of *M. tuberculosis* by allowing it greater virulence and persistence in the host.

CNRS SILVER MEDAL

Lluis Quintana-Murci was awarded the CNRS Silver Medal in 2013. His Human Evolutionary Genetics Unit, which combines population genetics, epidemiology and human health, evolutionary biology, and human science, looks at genome diversity in human populations that have been subjected to different environmental pressures. This research helps improve understanding of how our history and environment have influenced our biological adaptation to pathogens and our current susceptibility to infectious diseases. It provides us with powerful tools to anticipate and tackle the long-term consequences of diseases.

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.



Peyer's patches seen from above. This lymphocyte population helps protect the intestine. In blue, B-lymphocyte aggregates; in red, T-lymphocytes.

14 research units
2 platforms

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, the formation of lymphoid organs, 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 behind them 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.

The department is also helping to lead a Laboratories of Excellence (LabEx) project called "Milieu intérieur" ("The environment within"), which began in 2012 and is supported by the French government's Investment in the Future program. The Milieu intérieur consortium carries out pioneering work on the human immune system. A cohort of 1,000 healthy donors has been recruited to help the teams identify natural variability in immune responsiveness and pinpoint the genetic and environmental determinants of a healthy immune system.

NANODOMAINS AND ASTROPHYSICS

To help fight off pathogens, our body elicits a complex immune response in which T-lymphocytes play a fundamental role. These T-lymphocytes must first be activated, which occurs when they recognize fragments of foreign bodies, or antigens, as they come into close contact with antigen-presenting cells. The Lymphocyte Cell Biology Unit, led by Andrés Alcover, is particularly focusing on the formation of this contact area, known as an immunological synapse, and the role it plays in activating lymphocytes. In this unit, the team led by Helena Soares recently demonstrated that T-lymphocytes redirect several intracellular vesicles to the synapse. When these vesicles arrive at the membrane, they deposit the signaling molecules they are carrying, and these molecules arrange themselves into elongated membrane domains known as nanodomains, which trigger a series of reactions that result in lymphocyte activation. To study these nanodomains more closely, the scientists[1] turned to astrophysics algorithms – programs that were initially designed to measure the distance between stars, which enabled them to map the positions and relative distances of signaling molecules and reveal possible interactions. This research demonstrates the importance of vesicular traffic in the formation of immunological synapses, a vital stage in lymphocyte activation.

1. In collaboration with the Imaging and Modeling Unit led by Christophe Zimmer (Cell Biology and Infection Department).

A TOXIN THAT ATTACKS THE CELL SKELETON

Buruli ulcer is a neglected disease prevalent in tropical regions. It is caused by *Mycobacterium ulcerans* bacteria, which spread locally and cause debilitating open wounds, sometimes covering entire limbs of affected patients. Caroline Demangel and her team in the Immunobiology of Infection Unit have been looking into the toxicity mechanisms of *M. ulcerans* for many years. It had previously been established that the skin tissue destruction in Buruli ulcer is caused by mycolactone, a lipid molecule produced by the bacteria. In 2013, the scientists identified how mycolactone acts at molecular level: it spreads in epidermal cells and deregulates the synthesis of the cellular skeleton, or cytoskeleton. This dynamic structure is vital in maintaining cell junctions and in coordinated cell migration for tissue repair in the event of injury. In cases of Buruli ulcer, the uncontrolled activation of cytoskeleton synthesis by mycolactone compromises both the cohesion of cutaneous tissue and its potential for healing and repair. The only currently available treatments – antibiotic therapy sometimes combined with surgery – are not compatible with field conditions. But this research paves the way for new therapeutic strategies that use functional inhibitors to stop mycolactone from acting on skin cells.

BUILDING AN IMMUNE BASE IN THE INTESTINE

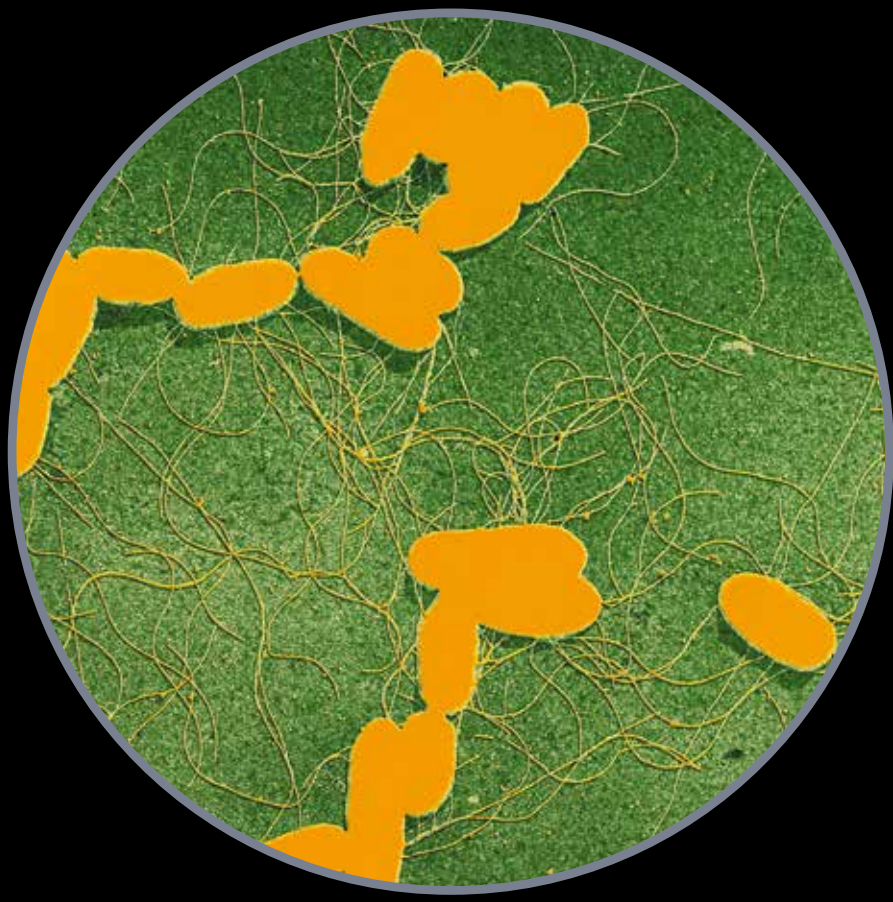
The epithelium of the small intestine is constantly in contact with a host of bacteria. Millions of T-lymphocytes colonize the epithelium and help protect it. Some of these intraepithelial lymphocytes (IELs) are "conventional", expressing TCRab receptors that are used in most adaptive immune responses. They acquire the molecules directing them to the intestine during migration to lymphoid structures associated with the intestine that collect bacterial antigens of intestinal origin. They escape through the thoracic canal and travel through the bloodstream to the epithelium. This immune reaction takes several days. Many IELs fall into a different category and express a TCRgd. They are highly cytotoxic and help maintain the integrity of the intestinal barrier by destroying infected or damaged epithelial cells. It was previously thought that they were programmed in the thymus so that they would already be activated on migration to the epithelium, constituting a first line of defense. But Delphine Guy-Grand, Antonio Bandeira and other scientists from the Immunology Department have demonstrated that, like conventional TCRab IELs, TCRgd IELs only acquire their cytotoxic function once they have been activated in lymphoid structures associated with the intestine, before they are colonized and spread in the epithelium. This major conceptual breakthrough will improve our understanding of immunity in the intestinal mucosa and influence our research into the elusive molecules that are recognized by these cells.

NEW GROUP

After infection, our body keeps a record of the immune strategy it used to defend itself. This "humoral memory" relies on antibodies, molecules produced by B-lymphocytes, which specifically target pathogens and protect against reinfection. These immune processes are the focus of a research project conducted by the Humoral Response to Pathogens Group set up in 2013 and led by Hugo Mouquet. The new team is aiming to characterize the molecular basis of the humoral response, particularly to the chikungunya and AIDS viruses, by producing specific antibodies. These antibodies could offer promising therapeutic possibilities for vaccine development.

Infection and Epidemiology

The Infection and Epidemiology Department is constantly seeking to stay in touch with clinical reality, remaining committed to public health issues while conducting fundamental research on infectious diseases.



Bacteria from the *Salmonella* genus belong to the Enterobacteriaceae family. Their long flagella can be seen on this colored image.

17 research units

The department investigates all elements of infectious diseases: pathogen reservoirs and transmission mechanisms, virulence factors, host immune response, tissue lesion development, infection risk factors, and therapeutic strategies. Its work involves several disciplines, including immunology, cell biology, epidemiology, microbiology, and virology. The department recognizes the importance of staying in touch with clinical reality; it conducts a number of clinical and epidemiological studies with hospitals in France and in the Institut Pasteur International Network so that its research can be successfully applied to humans. It is closely involved in public health, with research units in epidemiology and histopathology, nine National Reference Centers, four WHO Collaborating Centers, and the Laboratory for Urgent Response to Biological Threats (CIBU).

ELEVATORS FOR CELL NUCLEI

The group led by Thierry Rose in Jacques Thèze's Cellular Immunogenetics Unit carries out molecular-scale research to understand how the AIDS virus (HIV) manages to put CD4+ T lymphocytes – the "ringleaders" of the body's immune response – out of action, even though the virus only actually affects 0.5% of these cells. Using cutting-edge microscopy techniques, the scientists observed a new phenomenon which is altered in HIV patients, namely the rapid, transient formation of bridges between CD4+ T cell membranes and their nuclei. These bridges are part of the cytoskeleton and are known as microtubules. They are formed from the CD4+ T cell membranes on receptors which trigger a cascade of intracellular activation signals when activated, resulting in CD4+ T cell replication and thereby ensuring a constant supply of CD4+ T cells. The scientists have identified the very first stages in this process and demonstrated the essential role played by microtubules, which serve as "guides" or "elevators" for the transport mechanisms that carry the signaling molecules to the nucleus. Even more remarkable, the microtubules give them a "pass" to enter the nucleus. In HIV patients, these microtubules are unable to form, meaning that no link is created between the receptors and the nucleus, the signals cannot reach it, and the CD4+ T lymphocytes are unable to replicate. The scientists are now trying to pinpoint the factors responsible and demonstrate that they can be blocked.

ANTIBIOTIC RESISTANCE: *SALMONELLA* CAUSES CONCERN

Salmonella bacteria are one of the leading causes of food-borne infections. One strain of these bacteria known as *Salmonella Kentucky* is being closely monitored by a team led by François-Xavier Weill and Simon Le Hello from the Enteric Bacterial Pathogens Unit and the National Reference Center (CNR) for *Escherichia coli, Shigella* and *Salmonella.* This strain, which exhibits multiple resistance to several antibiotics, was first isolated in a patient coming back from a cruise on the Nile. Its rapid development, particularly in the Mediterranean Basin, has been a source of major concern for the scientific community for some time. In 2013, the unit published a paper on the expansion of the *S. Kentucky* contamination zones to India and South-East Asia. The paper also highlighted the bacteria's worrying tendency to acquire new resistance – some strains have proved resistant to all the classes of antibiotics used to treat severe salmonellosis, raising the risk of treatment options being exhausted. *S. Kentucky* had already been identified in poultry in Africa and the Middle East but recent studies have also pinpointed the bacteria in turkey farms in several European countries, heightening the threat of an epidemic in Europe. For the scientists, this study emphasizes the importance of monitoring *S. Kentucky* on national and international fronts. They are calling for this bacterium to be included in national *Salmonella* control programs in the poultry industry.

CERVICAL CANCER: THE IMPACT OF VACCINATION

Since the first cervical cancer vaccine came onto the market in 2006, the scientific and medical community has been analyzing its impact. The vaccine targets the two papillomavirus genotypes that are most likely to lead to cervical cancer. Didier Guillemot's team in the Pharmacoepidemiology and Infectious Diseases Unit is investigating the consequences of the possible replacement of the vaccine strains, which now circulate less widely, with non-vaccine strains. Working with the National Reference Center for Human Papillomaviruses, which is directed at the Institut Pasteur by Michel Favre, Isabelle Heard and Simon Wain-Hobson, the scientists have developed a mathematical algorithm for the transmission of different papillomaviruses after vaccination. Using this modeling tool, they concluded that the chances of genotype replacement strongly depend on the synergistic and competitive interactions between the different strains and the body's ability to eliminate the virus. The scientists are now planning to examine these two factors to develop a clearer picture of the impact of vaccination on the various viral genotypes in circulation. This research is part of a large-scale interdisciplinary program, the only one of its kind in the world, which involves monitoring a cohort of 30,000 students over more than ten years to gather data about their health, analyze various diseases, and explore prevention and treatment strategies. Find out more about the cohort at www.i-share.fr.

NEW TEAM

After a successful spell at Britain's Imperial College London, Simon Cauchemez arrived at the Institut Pasteur in November 2013 to direct the new Mathematical Modeling of Infectious Diseases Unit. His team is developing mathematical and statistical models to help better anticipate, assess and control infectious risks. The team is therefore well-placed to give advice to health authorities in the event of health emergencies. The methods developed also have a wide range of possible applications in microbiology. These new analytical methods will improve exploitation of the data gathered by teams on campus and in the Institut Pasteur International Network, and by external scientists.

Microbiology

As well as causing infectious diseases, bacteria can also serve as models to help us understand fundamental biological mechanisms. The research carried out in the Microbiology Department focuses on the molecular characterization of functions that help or hinder the interaction of pathogenic bacteria with their environment.

Visualization of *Helicobacter pylori* by scanning electron microscopy. This bacterium is responsible for diseases affecting the stomach such as chronic gastritis and gastric and duodenal ulcers, and it also plays an important role in the genesis of gastric cancer.

13 research units
2 collections
1 Biological Resources Center

The department's scientists study various microorganisms (bacteria and archaea) both at the cellular and molecular levels as model systems for fundamental research in areas such as genomics, genetics, and metabolism. They also focus on the mechanisms that render some of these microorganisms pathogenic and enable them to evade the host immune system, or to develop resistance to antibiotics. These studies improve our understanding of the life cycle of bacteria, which is vital if we are to develop new diagnostic tools and therapies to treat bacterial infections.

PARTNERS IN CRIME

Gastric cancer is currently the only cancer to be associated with a bacterial infection. This infection is caused by *Helicobacter pylori,* a micro-organism that colonizes the human stomach and lives there for decades, despite the changing and sometimes highly acidic conditions that characterize this environment. These bacteria employ various strategies, one of which involves modulation of the expression of some of their genes. This technique is the focus of the research done by Hilde De Reuse, head of the *Helicobacter* Pathogenesis Unit. The team is studying how the bacteria manage to reduce the production of some of their proteins under different conditions by destroying the RNA molecules used to make them. The scientists have identified two main protagonists in this process. The first is the RNase J enzyme, which degrades long RNA messenger molecules and stops them from being converted into proteins. This enzyme has a partner in crime, RNA helicase, a second enzyme which unfolds RNA, making it easier for RNase J to access the RNA molecules and carry out its work. These two enzymes form a functional complex, a sort of "molecular machine" called the RNA degradosome. It targets the enzyme urease, which is involved in the *Helicobacter pylori* resistance to gastric acidity. The bacteria therefore manage to survive by carefully dosing their urease activity to create optimal conditions in the hostile acidic environment of the stomach.

HOW DO BACTERIA BECOME PATHOGENIC?

Streptococcus agalactiae is an opportunistic pathogen that naturally occurs in the digestive and vaginal tracts. Carriage of the bacteria is normally asymptomatic, but in certain conditions they can cause severe infections. In France *S. agalactiae* is the leading cause of invasive infections (septicemia and meningitis) in neonates. So what makes these bacteria switch from commensalism to pathogenicity? This transition was previously only partially understood, but scientists from the Biology of Gram-Positive Pathogens Unit, led by Patrick Trieu-Cuot, have recently identified a mechanism used by *S. agalactiae* to regulate the expression of its main virulence factors. This is based on the "two-component system" widely used by bacteria to adapt to their environment. The scientists have demonstrated that *S. agalactiae* also uses a third component, known as Abx1. This bacterial membrane protein plays a vital role by keeping the CovRS two-component regulation system, the major regulator of virulence, in an intermediate state of activation, thereby allowing the infection to develop. When this system is locked in an activated or inactivated state, *S. agalactiae* becomes much less virulent. Surprisingly, Abx1 belongs to a widespread family of bacterial proteins. It could therefore also be involved in the adaptation and virulence of other human pathogens, such as *Staphylococcus aureus* ("golden staph"), a major cause for concern in hospitals.

VIRAL CHIMERAS

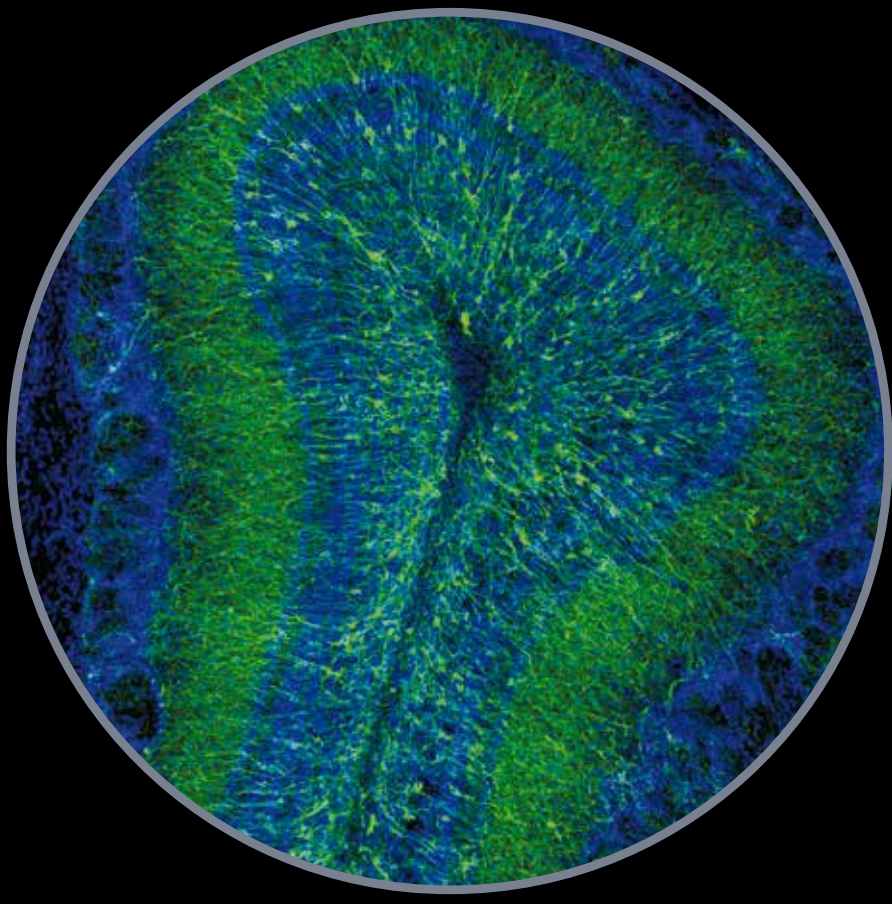
Viruses are the most abundant biological entities on our planet. They are as ancient as cellular organisms and astonishingly diverse. Unlike their cellular hosts, genomes of viruses can consist not only of DNA but also of RNA molecules, both single- and double-stranded. For a long time viruses with different genome types were considered to be unrelated, and the fundamental question of their origins remained unresolved. The recent study led by Mart Krupovic from the Molecular Biology of the Gene in Extremophiles Unit headed by Patrick Forterre has revealed an evolutionary link between viruses with RNA and DNA genomes. The scientists have shown that viruses belonging to these two different types can exchange genes, leading to the emergence of chimeric entities. Importantly, the initial acquisition of a gene from an RNA virus seemed to provoke an increased recombination frequency in the chimeric DNA viruses, thereby accelerating their evolution and expanding diversity. The realization that RNA and DNA viruses share a common genetic pool suggests that these viruses should be considered in the framework of an evolutionary continuum. Furthermore, the new evidence suggests that RNA-DNA recombination might have played an important role in the origin of small single-stranded DNA viruses, which are extremely abundant in the environment and include medically and agriculturally important pathogens.

MOBILOME

The term "mobilome" refers to all the mobile elements – viruses or plasmids – that can interact with the genome of a given microorganism. The links between the mobilome and microorganisms, particularly archaea, are being explored in a new project known as EVOMOBIL, led by Patrick Forterre from the Molecular Biology of the Gene in Extremophiles Unit. In 2013, this program was awarded a prestigious European Research Council (ERC) grant. The scientists are hoping to discover new viruses and mobile elements and to explore mechanisms that are not yet fully understood, such as the role of membrane vesicles in gene transfer. The project, conducted in partnership with Paris-Sud University, should also help shed light on the mobilome's impact on genome evolution.

Neuroscience

The Neuroscience Department attempts to explain the mechanisms of the nervous system in molecules, cells, synapses, and neural circuits. This fundamental research has led to many significant medical breakthroughs.



A cross-section of the olfactory bulb (slightly enlarged). Cell nuclei are shown in blue and neo-neurons in green.

7 research units

"There is no category of science that can be named applied science. There are science and the applications of science, bound together as the fruit of the tree which bears it." This quotation from Louis Pasteur perfectly sums up the scientific research conducted in the Neuroscience Department. Several teams defined their fundamental research areas while studying poorly understood human pathologies such as neurodegenerative diseases in children, deafness, autism, and addictions. Findings in recent years have helped shed light on how the brain functions in both its normal and pathological states. The scientists have identified genes that help them understand the brain's adaptability, as expressed in the extraordinary adaptability of chemical receptors, synapses, neural networks, and newly formed neuronal populations, and the highly adaptable behavior of individuals in their environment. With complementary skills in virology, genetics, structural biology and, more recently, high-resolution microscopy and animal behavior, the department's teams are attempting to improve their understanding of the links between molecular structure, neuronal physiology, and brain functions.

SANFILIPPO B: FIRST GENE THERAPY CLINICAL TRIAL

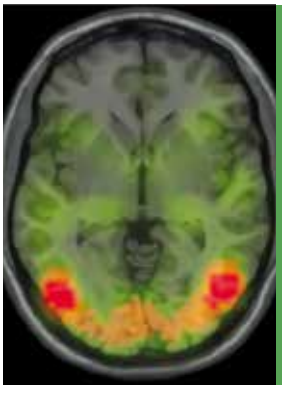
After more than ten years of collaborative research carried out by Prof. Jean-Michel Heard's team in the Biotherapies for Neurodegenerative Diseases Unit, a first clinical trial for Sanfilippo B syndrome was launched in October 2013. There is currently no cure or treatment for this disease, which is caused by a rare genetic mutation and affects around 1 in every 100,000 children. The first symptoms – hyperactivity and speech difficulties – occur at roughly 2 years of age and gradually lead to a loss of autonomy and social interaction. Premature death often follows before the age of 20. The mutation that causes the syndrome affects the catalytic and recycling activity of lysosomes, organelles that play an essential role in the inner workings of cells. The treatment is based on the development of a viral vector capable of delivering one of the four potentially mutated genes in Sanfilippo patients (corresponding to four essential lysosomal enzymes) to the patient's brain cells. This trial focuses on the B form of the disease. Cells incorporate the missing gene, provided by the viral vector, into their DNA, thus enabling them to produce the missing enzyme. Four young patients will be included in the trial. The treatment consists of several vector deposits in different areas of the brain and cerebellum. Because of the slow progression of Sanfilippo syndrome, it will be several years before the potential benefits of this treatment on the natural progression of the disease can be evaluated.

TOBACCO ADDICTION: THE ROLE OF GENETICS

Could our genes determine whether we'll become addicted to smoking? That appears to be the surprising finding of a study published in 2013 by Uwe Maskos and his Integrative Neurobiology of Cholinergic Systems Unit. The unit's scientists have demonstrated that in mice, the need for nicotine – the main addictive substance in tobacco – is strongly regulated by a genetic mutation that affects the nicotinic receptor in the neurons in our brain. When tobacco is consumed, nicotine binds to nicotinic receptors, activating the "reward circuit", a system that generates a feeling of well-being. For smokers, this circuit is constantly stimulated by nicotine and they feel withdrawal symptoms when they are deprived of tobacco. Any given individual's tobacco consumption is therefore closely linked to the sensitivity of these nicotinic receptors. The scientists' research has demonstrated that a genetic mutation leads to a marked loss in sensitivity to nicotine. As a result, mice with this mutation need a higher dose of tobacco – around three times as much – to experience the same pleasure from smoking as an individual without the mutation. The mutation is highly prevalent, affecting nearly 90% of heavy smokers and over 35% of Europeans. This finding could pave the way for the development of "personalized" smoking cessation treatments for individuals who carry this genetic mutation.

HIGH-FREQUENCY NEO-NEURONS

We have known for more than ten years that the adult brain is able to produce new neurons, ensuring a constantly new supply of these cells and maintaining our ability to learn throughout our lifetime. Pierre-Marie Lledo's team in the Perception and Memory Unit, which participated in this discovery, is continuing its research into the relationship between the properties these neo-neurons give to the brain, the electrical activity in neural circuits and the resulting behavior. In 2013, the scientists carried out behavioral tests on an animal model and observed that the brain's activity levels (concentration, distraction, etc.) could be characterized by different electrical frequencies. A high frequency of around 40 Hz is ideal for tackling difficult tasks such as recognizing a particular smell. The scientists explained this phenomenon with a second study, in which they found that high electrical frequencies correspond to the activity of the new neurons formed in the olfactory bulb of the adult brain. These new cells can work at high frequency because for the first four months of their life cycle they are not subject to the inhibition that affects all other cells. This constant stimulation enables them to establish connections with other neurons and to integrate and survive in the existing neural network.



THE BRAIN ON THE WEB

Roberto Toro, a member of the Human Genetics and Cognitive Functions Unit led by Thomas Bourgeron, has decided to make better use of the web as a tool for the neuroscience community by developing two interactive websites. The first, brainspell.org, indexes scientific publications according to the different brain regions they cover. Typing a keyword such as "vision", "music" or "autism" in the search engine will generate a 3D cross-section of the human brain regions involved. The second project, braincatalogue.org, was devised in cooperation with the National Museum of Natural History in Paris and the French Brain and Spinal Cord Institute. The museum has almost 2,000 vertebrate brains, one of the largest collections in the world. Over the next few years, they will be given a new lease of life as 3D imaging is used to provide access to the intricate workings of their anatomy. The long-term aim is to complete this database by encouraging a participatory approach.

Parasitology and Mycology

The Department of Parasitology and Mycology conducts research on the life cycle of parasites and their vectors, and of certain medically-important fungi. This research addresses global public health concerns and tackles the ongoing need for better prevention, control, and treatment.

A red blood cell infected by *Plasmodium falciparum,* the malaria parasite. In red, the infected erythrocyte; the parasite is illustrated in purple and the nucleus in blue. Transmission electron microscopy.

6 research units

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

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 brucei*, responsible for sleeping sickness. The *Anopheles* mosquito (the *Plasmodium* vector) is also studied, as is the tsetse fly (the sleeping sickness vector). Mycology research focuses on *Aspergillus fumigatus*, responsible for mycoses which can be fatal in immunodeficient patients, and other fungi that can kill and help control insect vectors. The department combines fundamental research on *in vitro* and *in vivo* models – including field work, particularly in Africa and Asia – with applied research, for example on the resistance of the malaria parasite to antimalarial drugs, and the identification of new antiparasitic drugs. Novel experimental models and 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.

MALARIA: THE MECHANISM OF RESISTANCE TO ARTEMISININ IS FINALLY DISCOVERED

Malaria affects several hundred million people and causes nearly 660,000 deaths each year. The disease is spread by mosquitoes carrying the *Plasmodium* parasite. Over the past ten years, parasites resistant to artemisinin derivatives, the most effective therapeutic molecules used to treat malaria, have emerged in western Cambodia. A major concern is that these will spread to sub-Saharan Africa, the region most affected by malaria. In this context, the teams led by Frédéric Ariey and Odile Puijalon at the Institut Pasteur in Paris, in cooperation with Didier Ménard at the Institut Pasteur in Cambodia (Phnom Penh), have made a major discovery: by comparing the genome of a strain of *Plasmodium* made resistant in the laboratory with sensitive parasites, they identified a molecular signature that indicates whether or not a parasite is resistant to artemisinin. This genetic mutation gives the parasite the ability to resist high doses of artemisinin. The scientific community had been searching for a molecular marker indicating this resistance for many years. This finding offers a reliable, effective method that can be used to improve detection of resistant forms of malaria, map their distribution, and respond quickly by adapting treatment plans.

MALARIA AND TOXOPLASMOSIS: THE IMPORTANCE OF VALIDATING VACCINE CANDIDATES

Plasmodium, the parasite that causes malaria, and *Toxoplasma,* the toxoplasmosis parasite, belong to the same group and both contain a protein known as AMA1. For many years, scientists believed that this protein was vital for parasites to be able to enter and infect host cells. Since the protein was discovered, several teams have used it to develop anti-parasite treatments, and it has become a major vaccine target for *Plasmodium.* But research carried out by Robert Ménard's team in the Malaria Biology and Genetics Unit has cast doubt on this theory. The scientists adopted a technique known as "reverse genetics", never used before in this field, to produce parasites that were totally lacking in AMA1. This enabled them to demonstrate that the lack of AMA1 had little effect on the ability of *Plasmodium* and *Toxoplasma* to invade host cells. The team also discovered that the AMA1 protein is used by parasites to adhere to host cells rather than enter them. This finding, which could have a major impact on the role of AMA1 as a vaccine candidate, emphasizes the importance of validating the potential of vaccine candidates with molecular genetics techniques.

CUTANEOUS LEISHMANIASIS: THE END OF TREATMENT BY INJECTION?

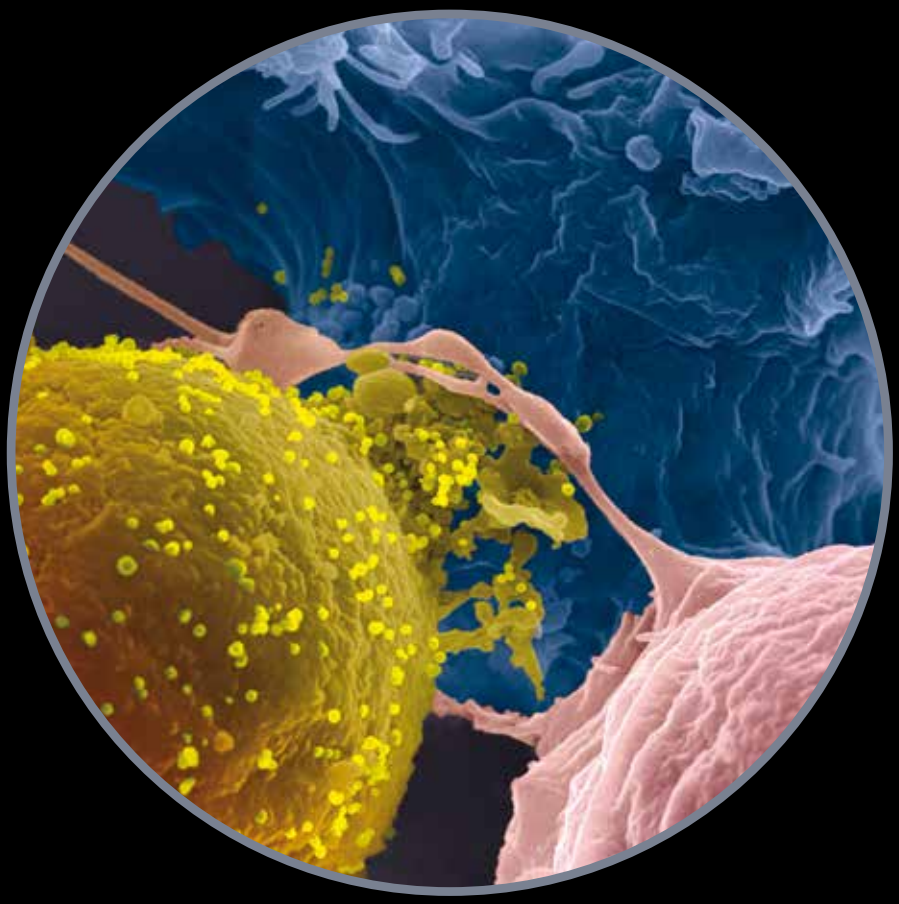
Cutaneous leishmaniasis is a parasitic disease that causes unattractive skin lesions which can lead to scarring. It affects 1.5 million people worldwide each year, particularly disadvantaged populations in southern countries, and children are especially at risk. Current treatments based on antimony salts contain toxic heavy metals and are administered by systemic or intralesional injection. Doctors are therefore often reluctant to use these treatments. A ten-year research partnership between the US Army Medical Research and Materiel Command, the Institut Pasteur in Tunis and the Institut Pasteur in Paris has demonstrated that a cream based on two antibiotics, paromomycin and gentamicin – known as WR 279,396 – is an effective, safe treatment for cutaneous leishmaniasis. A clinical study of 375 patients carried out at the Institut Pasteur in Tunis in coordination with the Institut Pasteur in Paris in 2013 showed a cure rate of 81% and few side effects in patients treated with WR 279,396, confirming the results of previous studies. The new treatment is easy to administer, making it much simpler to use in the field. This cream could become the first-line treatment for cutaneous leishmaniasis. It will be submitted for approval under the accelerated approval procedure of the US Food and Drug Administration (FDA).

AWARDS

In 2013, Philippe Bastin, Head of the Trypanosome Cell Biology Unit, was awarded the Pasteur Vallery-Radot Prize by the National Library of France and the Georges Zermati Prize by the Fondation de France. Philippe and his team are investigating *Trypanosoma brucei,* the parasite spread by the tsetse fly that causes sleeping sickness. Their research particularly focuses on the structure and function of the flagellum, an important organelle for the parasite. These prizes are recognition of the considerable progress made by the unit over the last five years in understanding how the parasite develops in the fly's salivary glands. They also award the team's innovative use of Trypanosoma as a model organism for investigating human genetic diseases caused by defects in cilia and flagella function.

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.



A cell infected by HIV.

21 research units

The department's 21 units focus their research on viruses, examining their molecular organization, mechanisms of proliferation within the cell, interactions with the host and the immune system, and determinants of pathogenicity. Some of the department's scientists concentrate on viruses that cause cancer, such as papillomaviruses, the hepatitis B and C viruses and the HTLV virus that causes leukemia. They also study retroviruses such as HIV, the AIDS virus; respiratory viruses such as influenza; and insect-borne viruses that are responsible for severe diseases such as dengue ("tropical flu"), yellow fever, Rift Valley fever, and chikungunya. To improve their understanding of infection mechanisms and their modes of propagation in organisms, our virologists are developing a number of partnerships within the Institut Pasteur and the Institut Pasteur International Network. The Virology Department also houses several National Reference Centers and WHO Collaborating Centers, thereby playing a major role in the epidemiological monitoring of infectious diseases.

AIDS: PATIENTS IN REMISSION

The ANRS EP 47 VISCONTI study published in 2013 describes 14 HIV-positive patients who received early treatment and have now brought their infection under control, seven and a half years after stopping antiretroviral therapy. This is the first described case of a group of patients who have achieved long-term remission from HIV infection. The project was coordinated by Asier Sáez-Cirión from Françoise Barré-Sinoussi's Regulation of Retroviral Infections Unit, and by Christine Rouzioux from Necker Hospital/Paris Descartes University. At a very early stage after infection, HIV can hide in latent form in some immune cells and stay there even after years of treatment. Patients in the VISCONTI cohort showed very low levels of these viral "reservoirs", leading the scientists to believe that early treatment can restrict the establishment of viral reservoirs and preserve immune responses. These results make a strong case for early use of antiretroviral treatment and have influenced international recommendations for treating HIV patients. They could play a major role in developing strategies to eradicate HIV or at the very least to achieve long-term, stable control of the infection without the need for treatment in most infected patients. The scientists are now trying to understand why only a small number of primary infection patients are able to achieve remission.

CORONAVIRUS: INSTITUT PASTEUR ON THE FRONT LINE

The year 2012 saw the emergence of a new virus called MERS-CoV, leading to an epidemic that has so far claimed more than 60 victims worldwide. This coronavirus, related to the SARS coronavirus, causes pneumonia that can rapidly progress to acute respiratory distress syndrome. The fatality rate is more than 50%. As soon as the first cases were recorded in 2012 in the United Kingdom and the Middle East, Sylvie van der Werf's team from the Molecular Genetics of RNA Viruses Unit and the National Reference Center for *Influenza* Viruses developed tests to detect the new virus. This team, which is on the front line in the fight against respiratory viruses in France, was then commissioned by the French Institute for Public Health Surveillance (InVS) to analyze samples from suspected cases of MERS-CoV infection, working alongside the Institut Pasteur's Laboratory for Urgent Response to Biological Threats. Two cases of the coronavirus were identified in France in 2013: the first patient was infected during a visit to the Middle East and the second via nosocomial transmission. Collaborative research has also been carried out to clarify the natural history of the infection in the French patients, to isolate and sequence the viruses responsible for the disease, and to identify how the virus is transmitted and how far it has spread. The scientists discovered that the second patient had an incubation period of 9-12 days, longer than initially reported. These results have been taken into account in the recommendations for monitoring people who have come into contact with infected patients.

WHY DON'T MOSQUITOES GET SICK?

Insects such as mosquitoes can spread many viruses that cause human diseases. But although these insects are persistently infected, they have virtually no symptoms. Carla Saleh's team from the Viruses and RNA Interference Unit has unraveled the intriguing immune mechanism that insects use to control viral replication so effortlessly and effectively. When the virus infects the host cell, it triggers a first wave of immune response, but this is not enough to limit viral replication. DNA fragments are then synthesized from the viral RNA using a cellular enzyme – a process which doesn't lead to viral replication but is used by the virus to produce a double RNA molecule from its genome. This double RNA sends a second alarm signal indicating infection, which triggers a second wave of immune response on top of the first, bringing viral replication under control. Insect cells offer an ideal environment for the development, spread and transmission of the virus. This strategy also stops the insect from using too much energy – rather than exhausting its energy reserves in an unlikely attempt to eliminate the virus, it manages to control viral replication just enough to stop it being harmful. A careful balancing act is therefore required to establish this state of persistent infection that seems to benefit both virus and insect.

FÉLIX REY IS AWARDED THE BEIJERINCK PRIZE

The M.W. Beijerinck Virology Prize is awarded every two years by the Royal Academy of the Netherlands to two virologists, a junior researcher from the Netherlands, and an internationally renowned senior scientist. Félix Rey, Head of the Institut Pasteur's Structural Virology Unit, was awarded the prestigious "senior scientist" prize in 2013 for his structural virology research. The award especially recognized his work on viral glycoproteins and the mechanism they use to induce fusion between viral and cell membranes when a cell is invaded by a virus. The atomic structures of viral glycoproteins are essential for the development of preventive vaccines and antiviral drugs.

Technological platforms

With 14 technological platforms divided into three clusters, as well as a Central Animal Facility, a Mouse Genetics Engineering Center, and a Center for the Production and Infection of Anopheles, the Institut Pasteur ensures that its teams have all the resources they need to perform cutting-edge research.

GENOPOLE

The Institut Pasteur Genopole houses a range of cutting-edge equipment and scientific expertise to support projects in the fields of genetics, genomics, population genomics, genomic epidemiology, transcriptomics, epigenetics, and bioinformatics.

When it comes to microorganisms, parasites, humans, or model organisms, high-throughput sequencing has revolutionized the analysis of genetic information. It is now possible to characterize microorganisms in a single step to identify virulence factors and antibiotic resistance, and to reveal the dynamics and 3D structures of genomes. In 2013, the Genopole was involved in the discovery of a molecular marker associated with resistance to artemisinin derivatives in the malaria agent. Sequencing all the coding regions (the exome) in humans is currently the most effective way of identifying the mutations that predispose individuals to some diseases or increase susceptibility to infections. Large-scale analysis of transcription and epigenetic modifications can improve our understanding of how organisms function in a normal or pathological state. A major part of this research focuses on analyzing data using computing techniques. The Genopole's bioinformaticians work with the Center of Informatics for Biology to develop and implement computing methods to analyze and process genomic and postgenomic data. The addition of a medium-throughput sequencer in 2013 has improved the Genopole's flexibility and its ability to meet the needs of the teams on campus.

At the Genopole, 19 scientists, engineers and technicians with a wide variety of skills are involved in fundamental research and public health projects. All four Genopole platforms have received official accreditation from the GIS IBiSA[1] and are partners of France Génomique, the national biology and healthcare infrastructure.

1. Scientific Interest Group for Biology, Healthcare, and Agronomy Infrastructures.

PROTEOPOLE

Pasteur-Proteopole, which received official IBiSA accreditation as a national platform in 2008, provides outstanding technological and methodological skills focused on the molecular study of macromolecules, and more specifically proteins. Its expertise covers several fields, including:

- protein production in prokaryotic and eukaryotic microorganisms, as well as in insect and mammalian cells;
- monoclonal and recombinant antibody engineering;
- identification and analysis of proteins and other macromolecules using mass spectrometry and analytical chemistry;
- biophysical characterization at the molecular level, including spectroscopy, hydrodynamics, surface plasmon resonance, and microcalorimetry;
- structural characterization at the atomic level, particularly using X-ray crystallography.

Pasteur-Proteopole provides research teams with modern tools for answering biological questions and pinpointing new areas for analysis. Since late 2012, the Proteopole has been divided into five platforms (Recombinant Proteins, Antibody Engineering, Proteomics, Molecular Biophysics, and Crystallography). Its current staff of 32 scientists and technicians provides a wide range of services to the research community, and is closely involved in a number of biological and methodological research projects in collaboration with laboratories from the Institut Pasteur and other French or foreign institutions, particularly in the field of structural biology of infectious diseases.

IMAGOPOLE

The Imagopole is an imaging center for the study of infectious, systemic and tumoral diseases, at both molecular and functional levels. It has four technological platforms (Dynamic Imaging, Ultrastructural Microscopy, Flow Cytometry, and the Center for Human Immunology) and 35 engineers, and offers access to around 40 imaging systems. The Imagopole has been awarded ISO 9001 certification and is recognized throughout the world for the quality and innovative nature of its work. It is involved in the France-BioImaging project, which is coordinating research into new imaging techniques by concentrating R&D efforts in a series of French centers of excellence. It is also part of the France Life Imaging project, which aims to coordinate and harmonize French preclinical and clinical imaging research.

Research

The Imagopole works to develop and apply methods for host-pathogen interaction research at the molecular and cellular levels, as well as for tissues and entire organisms. These techniques are also used in high-throughput screening to identify anti-infective molecules, and in ambitious projects such as the Laboratories of Excellence (LabEx) project "Milieu intérieur" ("The environment within"), which is aiming to shed light on the genetic and environmental factors that influence the variability of the human immune system.

Development

The Imagopole directs several funded projects which focus on the development of new molecular probes, new imaging and preparation methods for cells and tissues, and new biological models, as well as image analysis and database compilation. The Imagopole's teams are well equipped to carry out this research, with specializations in the fields of luminescence, phototoxicity, 3D imaging, superresolution, data processing, analysis, and statistics.

MOUSE GENETICS ENGINEERING CENTER

The discovery of new genes and genetic sequences of interest opens up the possibility

of generating new transgenic animals to analyze their biological functions and provide *in vivo* confirmation of expression profiles and gene regulation mechanisms. Each year, the Mouse Genetics Engineering Center (CIGM) produces several mouse strains that have been genetically modified using transgenesis – both "traditional" (random integration of an exogenous gene) and "targeted" (a specific deficiency or alteration at an endogenous locus) techniques – by microinjecting preimplantation stage mouse embryos. The center is involved in fundamental and applied research projects conducted mainly by Institut Pasteur units but also by other research institutions in France and abroad. The CIGM team comprises a head engineer and three technicians, all of whom have highly specific skills in embryonic stem cell biology and culture, microsurgery, and embryo microinjection, and can boast expertise in handling mice at all stages of development (from embryo to fetus and adult). Targeted transgenesis, which was initially based on microinjecting embryonic stem cells modified by homologous recombination, now includes new techniques that enable embryos to be microinjected with specific enzymes. In 2013, the CIGM broadened its experience in genetic modifications by using RNA from zinc finger nucleases (in rats) and Talen nucleases (in mice). The CIGM also moved into its new premises in the François Jacob building in 2013, where it will have more room for laboratories and a dedicated room in the building's new animal facility.

CENTRAL ANIMAL FACILITY

The use of animal models remains a necessity for the Institut Pasteur research programs. With a total capacity of 16,000 cages, the Central Animal Facility houses almost all the resources deployed for working on rodents and lagomorphs. It also offers technical operations such as the cryopreservation and the decontamination of mouse strains, the breeding of genetically modified strains, and the production of mouse strains with defined microbial flora. The 48-member team is led by three veterinarians, one engineer, and an operations manager.

The new animal facility in the François Jacob building, which opened in November 2012, will replace the previous facilities, which are gradually being renovated or closed. It features state-of-the-art, sophisticated equipment including a large high health status breeding and experimental area for rodents, with a total capacity of around 8,300 cages, and a restricted BSL3 area for rodents infected with biological agents from risk groups 2 and 3, with a capacity of 2,500 cages. The Central Animal Facility breeds more than 150 genetically modified mouse strains for the Institut Pasteur's research units. By the end of 2015, that number will have risen to 500. A former animal facility is currently being renovated to house a behavioral exploration platform for rodents and the Institut Pasteur's gnotobiology center. In accordance with new regulatory requirements, all animal protocols are examined by the Institut Pasteur Committee for Ethics in Animal Experimentation (CETEA).

CEPIA

The activities and organization of the Center for Production and Infection of *Anopheles* (CEPIA) aim to allow study of the interactions between the *Plasmodium* parasite, responsible for malaria and its mammalian (mice or cell lines) or insect (*Anopheles* mosquitoes) hosts. The platform mass-produces two *Anopheles* species (*A. gambiae,* African vector and *A. stephensi,* Asian vector). Moreover, regarding the human parasite *Plasmodium falciparum,* the CEPIA produces gametocyte stages and infects *A. gambiae* mosquitoes with the subsequent parasites. *A. stephensi* mosquitoes are mainly used to study the early stages of *Plasmodium berghei* and *yoelii* following the infectious bite in rodent models. A wide range of equipment, insectaries, CEPIA's animal facility and its biosafe laboratory are provided for the study of *Anopheles-Plasmodium*-vertebrate hosts. Thanks to funding from the Greater Paris region (DIM Malinf), the CEPIA has extended its logistics capacities for research into mosquito stages of *Plasmodium falciparum.* After the major work launched in 2012 to bring CEPIA's facilities into compliance, the reorganization and modernization efforts were continued in 2013 to optimize the platform's infrastructures and improve working procedures. This major reorganization was an opportunity for CEPIA to establish a development program for its *P. falciparum* research with the aim of increasing its research capacity and being able to take on new projects. The required renovations will be carried out in 2014 and new equipment will be set up. All this upgrade work is being carried out in connection with CEPIA's quality policy under its ISO 9001 certification.

CLINICAL INVESTIGATION AND ACCESS TO BIOLOGICAL RESOURCES PLATFORM (ICAREB)

The clinical investigation and biobanking platform ICAReB pursued its four major missions in 2013:

- to provide Institut Pasteur and external teams with bioresources, in full compliance with the ethical and regulatory framework. In 2013, from its stock of more than 70,000 human biological samples, the platform provided bioresources for around thirty teams working on the development of diagnostic tests for infectious or tropical diseases or investigating genetic predisposition to these diseases;
- to carry out research on bioresources, particularly by analyzing the freeze quality of the material stored;
- to develop its partnerships, especially with the WHO, in order to improve diagnosis of African trypanosomiasis (sleeping sickness): a biobank containing more than 47,700 samples from nearly 1,720 donors has been set up. Other partnerships have been formed with hospitals to investigate diseases such as listeriosis and hidradenitis suppurativa and to identify the microorganisms responsible for infectious syndromes of unknown etiology;
- to guide and advise institutes in the Institut Pasteur International Network as they set up their own biological resources centers.


Advion
Institut Pasteur

International

"Science knows no country, because knowledge belongs to humanity."

Louis Pasteur

Christophe Rogier

Director of the Institut Pasteur in Madagascar

“The southern hemisphere is where new questions and new challenges often arise.”

What attracted me to working in the Institut Pasteur International Network in the southern hemisphere? This is where people, often living in poverty, are most in need of the best that science can offer, where new questions and new challenges often arise. So this is precisely where we need to encourage a new generation of disciples that can follow in the footsteps of Pasteur, Calmette, Laveran, Nicolle, Yersin, Girard... and Françoise Barré-Sinoussi. And in the lab and in the field, this is where we can really judge whether the fundamental research that’s being carried out is still relevant.

Alejandro Buschiazzo

Director of the Protein Crystallography Unit

Institut Pasteur in Montevideo, Uruguay

"A series of streamlined procedures that help us work together rather than compete against each other."

I joined the Institut Pasteur in Montevideo in 2006 to develop its structural biology research. For me personally, this post was a turning point in my career. It was a huge challenge because I had to build everything from scratch. Our unit currently works really well. We specialize in key signaling and regulatory proteins in bacterial pathogens like *Leptospira* and in parasites like *Leishmania.* We're currently working on setting up collaborative projects with other International Network institutes in the Americas. In my view, the real strength of this network is that it offers a series of streamlined procedures that help us work together rather than compete against each other. It's only by pooling our expertise in different areas, sharing our ideas and working together in the field that we will be properly equipped to tackle the increasingly complex world of infectious diseases and the challenges they present us with.

An international institute

The Institut Pasteur is at the heart of the Institut Pasteur International Network, a unique network for global cooperation in public health, teaching, and research, with 32 institutes worldwide.

A NETWORK AT THE HEART OF GLOBAL HEALTH CHALLENGES

The Institut Pasteur International Network, a direct reflection of Louis Pasteur's vision, is a key global player in researching and fighting infectious diseases. From its very early days, this vast human and scientific community has played an active part in international research, public health, and training programs.

The institutes in the International Network are key partners for health authorities, research institutions, and international organizations. The International Network recognizes the importance of research in tackling global health challenges. This research, firmly rooted in the health needs of countries around the world, is a powerful tool in the fight against infectious diseases associated with poverty such as AIDS, tuberculosis, and malaria – all leading causes of child mortality and morbidity – and also chronic diseases such as cancer that are caused by infectious agents. Several teams in Africa and Asia are working to identify the emerging pathogens behind zoonoses and vector-borne diseases and to understand the risk factors for their emergence. Other research areas include resistance to anti-infective drugs and neglected infectious diseases in southern hemisphere countries, including rabies, arboviral diseases, viral hepatitis, leishmaniasis and Buruli ulcer.

COMMITTED TO FIGHTING INFECTIOUS DISEASES

In its response to the challenges presented by infectious diseases, the International Network has to adapt to constantly changing environments that are being transformed by demographic growth, increasing urbanization, economic developments, and environmental upheaval. The International Network is working to strengthen local diagnostic capabilities and introduce or support surveillance programs, in line with international health regulations. Laboratories are essential both for diagnosing diseases in individuals and for optimizing surveillance networks.

Teams in the International Network played a vital role in the epidemiological alerts for avian influenza in Cambodia and for the chikungunya virus in the Antilles-French Guiana region. These teams carry out their work with the input of national and international partners in the public and private spheres. The French Ministries of Foreign Affairs and Higher Education and Research also play an active and vital role. In cooperation with WHO, the International Network is involved in strengthening national diagnostic capabilities in each country. The French Development Agency (AFD) is supporting a project to assess the health risks caused by disturbances to ecosystems and economic developments in South-East Asia (the ECOMORE project – see p. 40). The US Department of Health is supporting the International Network in its fight against respiratory infections. Other key international partners include Rotary International District 1660, which has been supporting the International Network's research on

malaria since 2011; Monaco's International Cooperation Department; the Total Foundation and the Areva Foundation.
An increasing number of laboratories in the International Network are focusing on the links between infectious and chronic diseases (such as metabolic diseases and cancer) in response to a need pinpointed by health ministries and highlighted by epidemiological developments. With 32 institutes in 25 countries in a wide range of different environments, the strength of the Institut Pasteur International Network lies in its long-term approach and the unwavering commitment of its scientists. One of its priorities is to strengthen its human resources.

EVENTS IN 2013

Inaugurations

French Guiana – On December 14, 2013, a research building renovated under the European STRonGer program was officially opened at the Institut Pasteur in French Guiana during a ceremony attended by French Higher Education and Research Minister Geneviève Fioraso.
Uruguay – The Innovation Space at the Institut Pasteur in Montevideo was officially opened on November 29, 2013, at a ceremony attended by Uruguay's Education and Culture Minister Ricardo Ehrlich.
Guadeloupe – The Micropollutants Laboratory at the Institut Pasteur in Guadeloupe was officially opened on May 28, 2013. This laboratory was set up with funds from the European Regional Development Fund (ERDF), with the support of the Regional and Departmental Councils and the French government. It will be used for sampling and analyzing a number of pesticides, residues of medicinal products, and heavy metals.
China – On April 26, 2013, the Institut Pasteur of Shanghai – Chinese Academy of Sciences (IPSCAS) officially opened its new facility in the center of Shanghai, on the Shanghai Institutes for Biological Sciences campus, at a ceremony attended by French President François Hollande.

Partnership agreements

- On December 17, 2013, the University of Hong Kong (HKU) and the Institut Pasteur signed a new partnership agreement for the establishment of the HKU-Pasteur Research Pole.
- On June 11, 2013, the cooperation agreement between the Institut Pasteur and the Mexican National Council of Science and Technology (Conacyt) was renewed during the Franco-Mexican Forum for Research and Innovation.
- On March 12, 2013, the Institut Pasteur and the French Development Agency (AFD) signed a funding agreement for ECOMORE (ECOnomic development, ecosystem MOdifications, and emerging infectious diseases Risk Evaluation – see p. 40), a project which aims to assess how economic development and changing ecosystems are affecting the risk of infectious disease emergence.

80 international grants in 2013

66 grants funded by the Institut Pasteur International Division, including

4 PhD grants
2 postdoctoral grants
21 traineeship grants
23 study grants
16 conference grants

14 grants co-funded by the International Division and partners, including

11 grants from the Pierre Ledoux Jeunesse Internationale Foundation
2 grants from the Prince Albert II of Monaco Foundation
1 PhD grant from the Total Foundation

International teaching and training

Various teaching and training activities are organized each year within the Institut Pasteur International Network. These are aimed at local scientists, technicians, and students, as well as staff from other bodies such as ministries and universities who can use their newly acquired skills in national or regional structures. In 2013, sixteen courses and workshops funded by the International Network were run in eleven countries, including three in Africa, four in Asia, one in Latin America, and two in North Africa.

Lawrence Ayong

Head of a
Four-Year Group (G4)
Pasteur Centre in Cameroon

"The unique opportunity to freely explore my scientific dreams..."

After a PhD and post-doctoral training in molecular parasitology in the United States, I joined the Institut Pasteur in Korea as the leader of a team working on malaria drugs, before being selected to set up and head a new four-year group (G4) on molecular, immunological and pharmacological correlates between gametocyte carriage and resistance to antimalarial drugs at the Pasteur Centre in Cameroon. My research interests lie in antimalarial drug resistance, vaccine discovery, and the molecular epidemiology of malaria transmission stages. The G4 program in the Institut Pasteur International Network offers me the unique opportunity to freely explore my scientific dreams while living close to my family. It provides me with the exceptional prospect of developing new research themes in areas that are of major public health importance to my home country, and forming new partnerships within and beyond the Institut Pasteur International Network. The capacity building aspects of this G4 program will give my host institution, the Pasteur Centre in Cameroon, the human and infrastructural leverage that is needed to undertake world-class research programs in malaria and other human pathogens, and to contribute significantly to the kind of multicenter research collaborations that are being envisaged by the Malaria Team in the International Network.

- On November 6, 2013, the Institut Pasteur and the Saudi Ministry of Health signed a health cooperation agreement at a ceremony attended by the French Ambassador to Saudi Arabia, Bertrand Besancenot. The aim of this agreement is to develop scientific partnerships for infectious disease research and to host Saudi scientists at the Institut Pasteur.

Anniversaries

Tunisia - The Institut Pasteur in Tunis, a national Tunisian institute under the aegis of the Ministry of Health, celebrated its 120th anniversary.
Russia - The Institut Pasteur in Saint Petersburg celebrated its 90th anniversary and 20 years as a member of the Institut Pasteur International Network.
Cambodia - The Institut Pasteur in Cambodia celebrated its 60th anniversary on March 11, 2013.

A POLICY TO ATTRACT YOUNG SCIENTISTS

New four-year group program

In 2013, two four-year groups (G4s) were launched to allow young postdoctoral fellows to develop research programs within the International Network. One group is based at the Pasteur Centre in Cameroon (see profile on p. 39) and the other at the Institut Pasteur in Bangui.

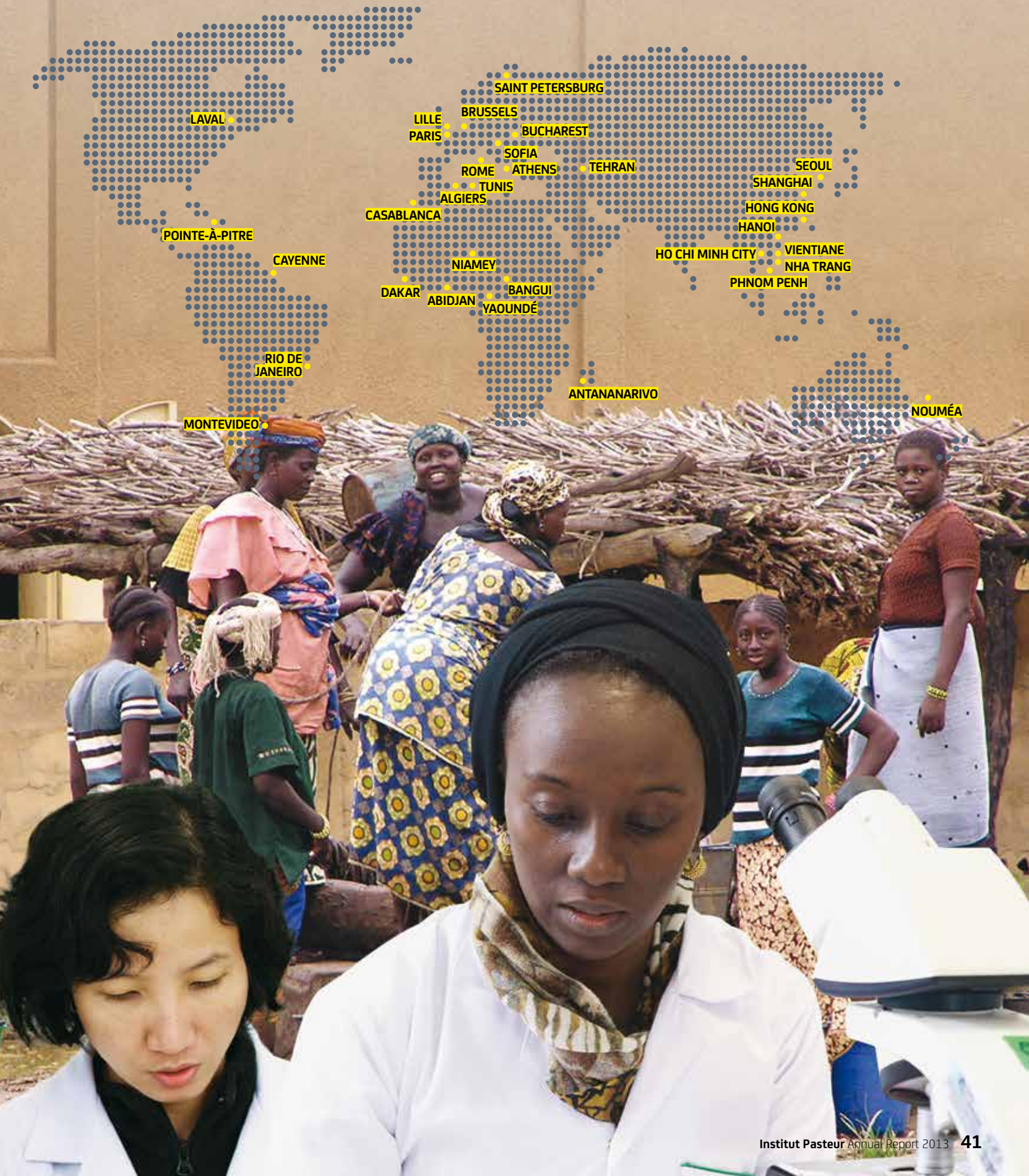
Training up scientists

One of the International Network's key missions is to offer training for young scientists. The Institut Pasteur has invested considerable resources to boost training opportunities at international level. The Calmette and Yersin fund supports an ambitious training program for international scientists and researchers. The aim is to develop continuing training, traineeships, and international PhD and postdoctoral programs in countries with limited resources. Each year, the Institut Pasteur awards international grants to scientists in the International Network so that they can attend courses or complete internships in Paris, at an institute in the International Network or at another research institute. These programs also give scientists the opportunity to complete their thesis or postdoctoral training at International Network institutes in countries in endemic areas. As part of its training policy, the Institut Pasteur International Network also runs international courses and offers training programs in partnership with universities specializing in science and medicine, or with local institutions.

Focus on... a regional project linking the environment and health

How can we analyze the impact of economic development and environmental changes on human health? That's the basic premise behind ECOMORE (ECOnomic development, ecosystem MOdifications, and emerging infectious diseases Risk Evaluation), a project which was launched in 2013 and has received €2.7 million in funding from the French Development Agency (AFD). The project is being developed in four South-East Asian countries (Vietnam, Cambodia, Laos, and Myanmar) and is coordinated by Yves Froehlich from his base at the Institut Pasteur in Cambodia.
In Vietnam, the aim is to measure the health impact of the move towards more intensive pig farming in terms of the risk of zoonoses and environmental pollution. In Cambodia, the focus is on how the newly extended road network is affecting the spread of diseases. In Laos, the scientists will be investigating whether workers in rubber plantations are at greater risk of contracting vector-borne diseases such as malaria, dengue, and chikungunya, so that they can be offered suitable protection. In Myanmar, economic development, the opening up of borders, and population movements mean that respiratory viruses such as SARS and avian influenza need to be monitored more closely, and diagnostic capabilities need to be improved. Across these four countries, the underlying idea is to set up scientific field studies in a bid to tackle these pressing public health issues that are closely linked to economic choices, environmental impact, and human and animal health.
Each priority topic is led by three institutes from the International Network with expertise in the field (the Institut Pasteur in Cambodia, the Institut Pasteur in Laos, and the National Institute of Hygiene & Epidemiology (NIHE) in Hanoi, Vietnam), together with government organizations in the countries concerned, such as Myanmar's National Health Laboratory. *"The region's economic development must be backed up by new tools, scientific evidence, and recommendations"*, concludes Maud Seguy, who coordinates the project at the International Division in Paris. *"The ECOMORE project provides us with an opportunity to offer our help and support to national authorities – just as Louis Pasteur envisaged the Institut Pasteur's role in the world."*

A global network



Teaching

"In the field of observation, chance only favors the prepared mind."

Louis Pasteur

Chiara De Pascalis

Student on the Pasteur-Paris University International Doctoral Program

"I can share my ideas and my curiosity for science."

I started my PhD with the Pasteur-Paris University International Doctoral Program in October 2013. It is a great opportunity for me to work at the Institut Pasteur, with its state-of-the-art research and its stimulating work environment. The atmosphere here is fantastic and very international: I have met new people with whom I can share my ideas and my curiosity for science. Even if a PhD can sometimes be challenging, I am really enjoying this privileged experience!

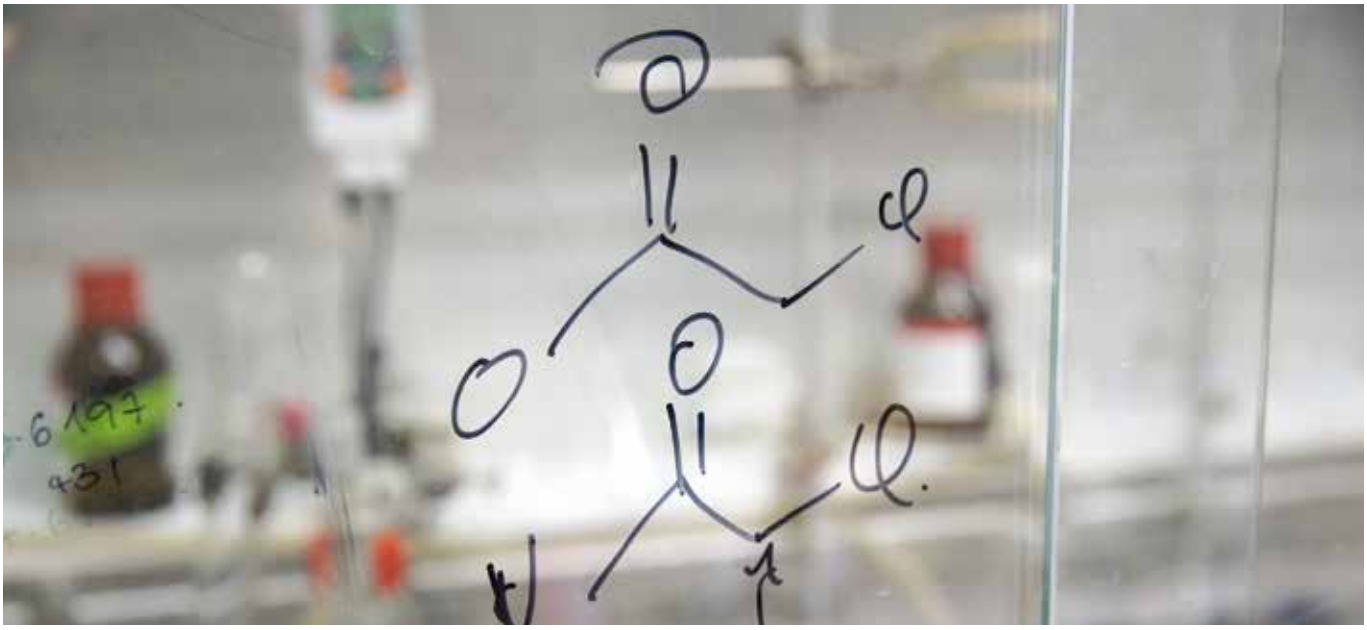
The transfer of values

The theoretical and practical courses offered at the Institut Pasteur Teaching Center are organized and taught by scientists from the Institut Pasteur or other organizations. The Institut Pasteur also offers training for young scientists from France and abroad who come to complete their Masters and PhD programs.

27 courses

500 students

220 PhD students



Since the early days of the Institut Pasteur, one of its main missions has been teaching and training. Each year, 500 people take the courses run at the Teaching Center and more than 300 young scientists come to the Institut Pasteur to conduct PhD or Masters research projects.

A DEDICATED ENVIRONMENT AND VARIED COURSE SELECTION

The Teaching Center, based in the former Pasteur hospital, offers outstanding facilities for theoretical and lab sessions in a wide range of disciplines related to microbiology, genomics, immunology, vaccinology, neuroscience, cell biology, and various areas of epidemiology. It offers some thirty courses each year, lasting between one and twelve weeks. The courses are aimed at current students and graduates from French and foreign universities and university teaching hospitals, as well as working professionals – scientists, doctors, and veterinarians – wishing to top up their training.

Many of the courses can be counted as part of a Masters degree program, either as second-year teaching units for the Masters offered at Paris Descartes, Pierre & Marie Curie, Paris Diderot, and Paris-Sud universities, or as part of the specialized Masters in Public Health run by the Pasteur-CNAM School of Public Health. Outside these university programs, they can be included in partner university degree programs. Most courses can also be taken by PhD students as part of their doctoral studies.

New courses are regularly set up to keep step with the latest developments in the field. In 2013, two new courses were launched: "Progress in stem cell biology" in partnership with the LabEx (Laboratories of Excellence) project "REVIVE", and "Genetics of human populations and genetic epidemiology" in partnership with the LabEx project "Milieu intérieur" ("The environment within"). The Institut Pasteur's technological platforms (especially the Imagopole) and the Center for Human Immunology offer valuable technical support for the courses run on the campus in Paris.

TEACHING STUDENTS FROM AROUND THE WORLD

The Teaching Center welcomes students, scientists, doctors, pharmacists, engineers, and veterinarians from all over the world. Each year, more than 200 foreign students from around 60 different countries come to take courses at the Institut Pasteur. With growing numbers of foreign students and lecturers, an increasing number of courses are taught in English. The Teaching Center is often the venue for courses run by Institut Pasteur scientists in partnership with the European Molecular Biology Organization (EMBO).

The Institut Pasteur is truly a higher-education hotspot for many young scientists. Each Institut Pasteur research laboratory is affiliated to a Doctoral school accredited by a Parisian university and is involved in supervision and training for doctoral students. Some 220 doctoral students conduct research projects in Institut Pasteur laboratories. The Pasteur-Paris University International Doctoral Program, which involves agreements with Paris Descartes, Pierre & Marie

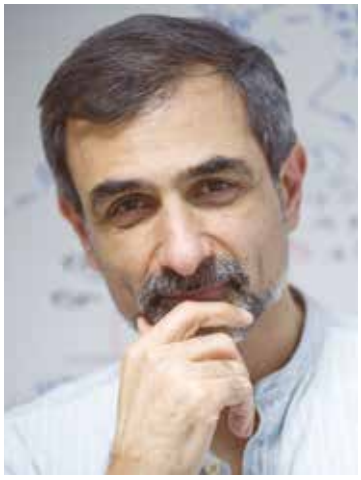
"The Teaching Center welcomes students, scientists, doctors, pharmacists, engineers, and veterinarians from all over the world."

60 nationalities represented

100 Masters interns

Curie, and Paris Diderot universities, is open to students who have completed courses at a foreign university. It is a three-year program leading to a PhD. The "François Jacob" class of 2013 included fifteen students from Spain, Hong Kong, India, Italy, Portugal, Romania, Serbia, and the United States (see profile on p. 43). Each year, a new set of students specializing in a wide variety of different fields are given the chance to meet and exchange ideas during joint activities organized by the International Doctoral Program, such as bibliography seminars and an annual retreat.

The specialized Masters in Public Health, recognized by the French *Conférence des Grandes Ecoles,* is run in partnership with the French National Conservatory of Arts and Trades (CNAM) and the French School of Public Health (EHESP) at the Pasteur-CNAM School of Public Health. It is geared towards health professionals, final-year students, doctors, veterinarians, pharmacists, biologists, staff members of health agencies, and personnel from international organizations. Following one semester of theory, the students complete a six-month internship in infectious diseases, either in France or in one of the institutes of the Institut Pasteur International Network, after which they write a dissertation. The oral defense takes place in December. The class of 2013 included 21 students, with around half coming from Algeria, Germany, Burkina Faso, Cameroon, Spain, Italy, Luxembourg, Chad, and Russia.



3 QUESTIONS FOR

Shahragim Tajbakhsh

Co-director of the new "Progress in stem cell biology" course

"Sparking interest among bright, motivated students, who will play a valuable part in our scientific networks and maybe become future Institut Pasteur scientists themselves."

Why was this course on stem cells set up?

This is the first course that takes a "multi-organism" approach to stem cells. We will be investigating stem cells in humans and mice, but also in *Drosophila,* zebrafish, chickens, and quails. The aim is to shed light on the strategies used by stem cells in organisms that function in different ways and have different life spans. The course will look at a wide selection of stem cells with varying properties, functions, and differentiation potentials, ranging from embryonic stem cells to induced pluripotent stem cells.

What makes the course unique?

When the other co-director, François Schweisguth, and I devised this course, we really wanted it to offer clear, comprehensive answers to the questions facing PhD students and postdoctoral fellows in the area of developmental biology. So we came up with the idea of a mentoring system, where experts from the Institut Pasteur and leading international specialists in the field could work with the students over a two-week period, offering theoretical guidance and also sharing practical advice and lab techniques. We decided to take on just a small number of students so that it would be easier for them to work directly with these renowned external experts – that's the major advantage of this course.

How did the first session in 2013 go?

Fourteen PhD students and postdoctoral fellows from around the world came to take this new course, and ten external scientists shared their expertise. With funding from the LabEx stem cell project "REVIVE", we were able to provide cutting-edge equipment for the laboratories, particularly in microscopy, right from year one. The highly skilled staff and comprehensive top-class facilities at the Institut Pasteur's Teaching Center were also incredibly important for the quality of the teaching we were able to provide. By offering such first-rate facilities, our aim is to spark interest among bright, motivated students, who will play a valuable part in our scientific networks and maybe become future Institut Pasteur scientists themselves.

PhD graduation ceremony

On September 30, 2013, the first PhD graduation ceremony was held at the Institut Pasteur for students who submitted and defended their theses during the year. Despite the formality of the occasion, there was a relaxed, friendly atmosphere. Proceedings were opened by Jules Hoffmann, 2011 winner of the CNRS Gold Medal and Nobel Prize in Physiology or Medicine, who gave a lecture about being a scientist and making new research discoveries, and spoke about his own career. The ceremony, attended by Institut Pasteur staff, family and friends of the PhD students, and representatives of partner organizations, is set to become an annual event. The next edition has already been scheduled for December 2014, with mathematician Cédric Villani as the guest of honor.

Health

"There are science and the applications of science, bound together as the fruit of the tree which bears it."

Louis Pasteur

Johann Cailhol

Doctor at the Institut Pasteur Medical Center

"An inspiring hub of intellectual activity."

I feel a sense of pride in working at the Medical Center here at the Institut Pasteur, where so many of the fundamental concepts and tools that we use on a daily basis were first developed. We receive patients from far and wide, all with their own needs and expectations. We do our best to live up to them. The competitive, high-level scientific environment at the Institut Pasteur, together with often complex clinical situations, results in an inspiring hub of intellectual activity.

Since the Institut Pasteur's work is firmly rooted in public health, it is in regular contact with both the French Health and Research Ministries as well as subsidiary agencies and bodies. It regularly submits reports on its collections of biological samples, which are vital for its scientific research, to the Ministry of Research. As a sponsor of clinical research projects, the Institut Pasteur works closely with the French Medicines Agency (ANSM), the competent authority that approves new projects.

National Reference Centers and WHO Collaborating Centers

The Institut Pasteur is home to 15 National Reference Centers (in Paris and Lyon) and 4 CNR-associated laboratories (in French Guiana and Lyon). These expert laboratories are appointed by the Minister of Health for a five-year period. They serve as observatories for communicable diseases throughout France. They work closely with the Institut Pasteur's Laboratory for Urgent Response to Biological Threats (CIBU) and provide support for health authorities in diagnosis, epidemiological surveillance, and research, playing an important role in the Institut Pasteur's public health activities.

At the Institut Pasteur, the CNRs are able to draw on the scientific environment of their host units and the various support structures such as the Laboratory for Urgent Response to Biological Threats (CIBU). The CIBU functions in a similar way to a CNR; it works 24 hours a day, 7 days a week and plays a vital role in emergency situations, offering essential support for the CNRs. 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 (OIE).

INFLUENZA VIRUSES

The 2012-2013 seasonal influenza epidemic was more intense and lasted longer than in previous years. The CNR for *Influenza* Viruses received 2,700 samples for analysis, half of which tested positive for one of the three viruses in circulation. Globally, the emergence of the MERS-CoV coronavirus in Saudi Arabia and the H7N9 influenza virus in China led to a concerted response from the international community to treat any returning traveler exhibiting severe respiratory symptoms. The CNR developed tools to detect these new viruses and also circulated technical guidelines and a positive test for MERS-CoV to the hospital laboratories responsible for investigating possible cases. The CNR helped detect two French cases in patients who were hospitalized in Lille. Scientific analysis of these two cases revealed evidence of human-to-human transmission, but transmission efficiency on a large scale remains very low.

RABIES

On October 31, 2013, the CNR diagnosed a kitten found on October 25 in Argenteuil, on the outskirts of Paris, with rabies. The scientists characterized the virus and demonstrated that it had been imported from Morocco; this was subsequently confirmed via an epidemiological investigation which revealed that the virus had been imported in late September. The local health authorities carried out an enquiry and found 44 people that had been exposed to the disease, 20 of whom were given post-exposure prophylaxis treatment. On August 5, 2013, another lyssavirus was identified in a bat from the Savoie region. This is the third time the Bokeloh bat lyssavirus has been isolated in Europe. Several members of the same family who had been exposed to the virus received post-exposure prophylaxis treatment. Three months later, no secondary cases had been reported. These two episodes show how important it is to continue monitoring rabies in humans and animals so that any risks can be identified as soon as possible and the public can be protected with appropriate measures.

FRENCH GUIANA AND ANTILLES

The Virology Laboratory at the Institut Pasteur in French Guiana hosts three CNR-associated laboratories, for arboviruses, *Influenza* viruses and hantaviruses. The CNR for Arboviruses had a busy year in 2013, with a long and intense dengue epidemic striking in French Guiana. Towards the end of the year, the chikungunya virus also emerged in the French Antilles and an epidemic was declared in December in Saint-Martin and Saint-Barthélemy. The CNR for *Influenza* Viruses recorded strains of A(H1N1) pdm09, B-Yamagata and, at lower levels, A(H3N2) in the first half of the year. The CNR strengthened its diagnostic capabilities following the international health alerts associated with the emergence of the MERS coronavirus and the H7N9 avian influenza virus. This also enabled it to identify other respiratory viruses in circulation, such as respiratory syncytial virus (RSV). Finally, the CNR for Hantaviruses continued its diagnostic work, pinpointing the Maripa virus as the cause of the fourth case of human infection by a hantavirus since 2008. The CNR carried out field research into this case to identify the rodents that may be serving as reservoirs for this virus, which proved fatal in three quarters of all cases observed in French Guiana.

ANAEROBIC BACTERIA AND BOTULISM

Botulism is a rare but severe disease caused by *Clostridium* bacteria, which produce toxins that block the signals sent by nerves to muscles, leading to respiratory failure and paralysis. In 2013, the CNR for Anaerobic Bacteria and Botulism carried out a biological diagnosis of ten botulism foci (fifteen cases). Most of them were caused by foodborne botulism; four others were cases of infant botulism. Although rare, infant botulism has been reported more regularly in recent years. For the first time, one of the isolated strains of *Clostridium botulinum A* in a neonate exhibited resistance to beta-lactams and cephalosporins. The CNR also works on animal botulism, identifying and typing the toxins to provide additional information alongside the initial analyses carried out by veterinary laboratories. In 2013, 177 veterinary samples and 176 foodborne samples were analyzed. Botulism types C and D, as well as the mosaic variants C-D and D-C, are prevalent in poultry farms and some cattle farms. Botulism remains a real concern in such farms, where several foci are detected each year and the disease represents a public health risk.

Medical Center

The Institut Pasteur Medical Center (CMIP) is the only entity within the institute in direct contact with patients through its international vaccination center and its outpatients clinic for infectious and tropical diseases, travel medicine, allergies, dermatology, and rabies treatment.

In addition to vaccinations, the Medical Center also provides travel advice for children and adults, with a special focus on vulnerable patients (i.e. patients living with HIV or organ transplants), as well as advice on the diagnosis and treatment of diseases contracted abroad. Other key orientations include HIV infection, infectious diseases such as Lyme disease, post-exposure rabies treatment (for which the Medical Center receives a grant from the Greater Paris Regional Health Agency), and dermatology, with a particular focus on hidradenitis suppurativa. Some of these diseases are monitored in cooperation with Necker-Enfants Malades University Hospital.

As part of its allergy consultation activities, the Medical Center also administers treatment for the largest national hereditary angioedema cohort. In addition, the Medical Center is involved in clinical research directly related to its medical focus areas: cohorts and therapeutic studies on HIV infection; the pathophysiology of hidradenitis suppurativa (in cooperation with Necker Hospital and the ICAReB Platform); vaccinology (for example, the interaction of yellow fever and measles vaccines in children); the epidemiology of multiresistant bacteria (in travelers upon their return) and the pathophysiology of post-infectious anosmia.

76,539 vaccines administered

2,393 consultations for rabies

12,203 consultations for infectious and tropical diseases

6,905 consultations for allergies

52,748 visits to the international vaccine center

Clinical research

The Institut Pasteur's public health mission is to promote the transfer of scientific discoveries from its research laboratories to human health applications.

FROM SCIENTIFIC TO CLINICAL RESEARCH: A PROFESSIONAL APPROACH

The Institut Pasteur's Clinical Research Department has the necessary expertise to conduct the entire clinical research cycle, from project start-up to business development.

The Institut Pasteur as sponsor

As a sponsor[1] for research on humans, the Institut Pasteur helps bridge the gap between fundamental research and clinical research. The Clinical Research Department represents the Institut Pasteur as a sponsor. Since 2009, the Clinical Research Department has processed 209 projects. In 2013, the Clinical Research Committee examined the regulatory, legal, and ethical compliance of 32 new clinical research projects. This figure is significantly down on 2012. The Institut Pasteur was the sponsor/legal representative for 66% of these projects (up by 3%). Of these, 28% (a 4% increase) concerned the Institut Pasteur International Network.

Developing innovative therapies: from preclinical to clinical trials

In 2013, major advances were also made in some of the large-scale projects led by the Clinical Research Department, such as the MAG-Tn3 project (for a therapeutic breast cancer vaccine), for which a clinical trial is currently being prepared, and the Sanfilippo B gene therapy project, which saw its clinical trial begin in September 2013. The first patient was enrolled in October 2013. Other projects are still in preclinical phase, such as the Anthrax project and the FP7 STOPENTERICS and ANTIFLU projects. The Clinical Research Department was involved in these projects in 2013, coordinating the production of batches for regulatory toxicology studies.

Training… and informing

A new course on clinical research (Clinical Research in the Institut Pasteur International Network – CREPIN) has been set up in the Institut Pasteur International Network to look at the specific needs and characteristics of southern-hemisphere countries. The first session of this multi-site course, subsidized by the International Division, was hosted by the Institut Pasteur in Cambodia in 2013. The fourth season of Clinical Research Department Workshops catered to a wide audience, providing another opportunity for discussion sessions on innovative and topical issues in the field of clinical research.

1. The sponsor is the body that initiates the project and takes responsibility for the research.

Expertise and resources

The future of the Institut Pasteur relies on the talent and skills of its staff, with their varied cultural backgrounds and complementary fields of expertise. Moving forward, and given its environmental and social responsibilities, the Institut Pasteur has also made its commitment to sustainable development a special priority. Thanks to its unique economic equilibrium, the Institut Pasteur is able to maintain its independence, its freedom of research, and its responsiveness.

Research applications

The mission of the Research Applications and Industrial Relations Department (DARRI) is to detect, promote, support, protect, and transfer inventions emerging 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.

With 51 invention disclosures submitted in 2013, the Institut Pasteur maintained a high level of innovation. It pursued its intellectual property strategy, focusing its efforts on extending and defending major patents – for example, a second key AIDS patent was extended until 2029. Research partnerships also continued to expand and develop. In 2013, business development activities as a whole generated proceeds in the region of €40 million, including part of the year's non-recurring revenues spread over several years.

PROMOTING AND DRIVING INNOVATION

The teams from the Research Applications and Industrial Relations Department met practically all the heads of the Institut Pasteur's research units and took part in all departmental meetings, with the aim of generating more invention disclosures. By the end of 2013, they had identified around 30 more potential invention disclosures, a third of which may result in patent filings.

BRINGING PROJECTS TO MATURITY

The Institut Pasteur continued its ongoing efforts to bring projects to maturity. The Pasteurinnov and Valoexpress calls for proposals were pursued during 2013. An invention disclosure consolidation program was also launched to improve patent protection for invention disclosures, and a program known as "Technophare" was introduced to support promising technological developments. The overall budget for these activities came to around €1 million (two thirds of which came from the Pasteur Infectious Diseases Carnot institute) plus the creation of seven dedicated positions.

TAPPING INTO EXTERNAL RESOURCES TO MAXIMIZE BUSINESS DEVELOPMENT POTENTIAL

Various new business development facilities and structures have been set up or are under development.

- The business development consortium CVT-Sud, in cooperation with the Research Institute for Development (IRD) and the International Cooperation Center of Agricultural Research for Development (CIRAD), has a portfolio of technologies from the Institut Pasteur with high business development potential.
- The Global Care consortium of Carnot Human Health Institutes has been set up under the aegis of the Institut Pasteur.
- The "Innovation in Vaccinology" strategic business development program is being set up under the joint responsibility of the Institut Pasteur and Inserm.

Another strategic business development program, for biomarkers and companion tests, is currently under preparation. The Institut Pasteur has volunteered to lead this program.

"A second key AIDS patent was extended until 2029."

CONSOLIDATING THE PATENT PORTFOLIO AND DEVELOPING AN INNOVATIVE PROTECTION STRATEGY

Some of the Institut Pasteur's patents were extended or consolidated. A continuation application for a second patent relating to the HIV-1 AIDS virus, filed with the US Patent and Trademark Office, was granted until 2029. These patents have enabled the Institut Pasteur to renegotiate the terms and conditions of some existing license agreements and to negotiate new agreements.

Given the technological development of high-throughput sequencing techniques and the likely impact on diagnostic approaches, an intellectual property development strategy for diagnostic kits based on this new technology has been introduced. A first pilot patent for a widely used diagnostic kit has been filed. Meetings held with scientists on the campus to identify new opportunities to generate intellectual property should lead to several new patents being filed in 2014.

STRONGLY DEFENDING THE INSTITUT PASTEUR'S RIGHTS

In conjunction with the Legal Affairs Department, work was once again carried out in 2013 to defend the Institut Pasteur's rights. Several specialists were involved in discussing this issue with some of our major partners to ensure that the Institut Pasteur enjoys a fair return for rights granted.

STRENGTHENING COLLABORATIVE RESEARCH WITH NEW PARTNERS

The Department had another busy year in terms of contracts, managing more than 170 agreements. These include 13 new license agreements, some offering potentially high returns over the next few years if successful,

51 invention disclosures

13 license agreements

29 priority patent applications

14 collaborative research agreements

and 14 new research cooperation agreements – a significant increase for the fourth year running. We continued to broaden our network of industry partners, particularly targeting technology firms. The year's highlights include the renewal and extension of an agreement with a major Japanese firm and the start of a partnership with an international company in the area of medical devices.

The strategic partnership between the Institut Pasteur and the Bioaster Technology Research Institute led to the signing of Bioaster's first ever consortium agreement in December 2013, based on a fair and balanced relationship between all parties. The terms of the agreement, negotiated by the Research Applications and Industrial Relations Department (DARRI), are now widely used in other consortium agreements.

SUPPORTING THE DEVELOPMENT OF YOUNG COMPANIES

The Institut Pasteur offers support for new companies based on technologies developed in its laboratories by hosting them on its Paris campus – particularly in the new François Jacob building – and taking a role in their governing bodies. In 2013, one of these companies launched a phase I clinical trial of its therapeutic AIDS vaccine.

Two of the Institut Pasteur's business start-up ventures won awards in the competition for innovative new companies run by the French Ministry of Research. An additional partnership with a new seed fund has been set up to provide the necessary capital for company set-up ventures. A national business incubator has also been launched for diagnostic projects. In 2013, the Institut Pasteur introduced an active management strategy for its holdings in the various companies based on research carried out on its campus.

PROMOTING BUSINESS DEVELOPMENT IN THE INSTITUT PASTEUR INTERNATIONAL NETWORK

The Institut Pasteur is becoming increasingly involved in the institutes in its International Network by actively contributing to partnership agreements (with the Institut Pasteur in Montevideo) and patent applications (the Institut Pasteur in Nouméa), sitting on expert committees (at the Institut Pasteur in Korea), and offering advice to many of the institutes (such as the Institut Pasteur of Shanghai).

Human resources

In 2013, the Human Resources Department focused its efforts on organizational developments, recruitment, and the employment of both young and older workers.

RECRUITMENT/TRENDS

As of December 31, 2013, the Institut Pasteur's workforce stood at 1,930 employees, with 73% on permanent contracts (a slightly lower proportion than last year). The number of employees on fixed-term contracts increased steadily. 70% of these fixed-term positions are held by young scientists, mainly PhD students and postdoctoral fellows, either recipients of research training grants or employed under an international agreement, or young foreign researchers living temporarily in France. These specific research positions are vital given the rise in project-based funding. The Institut Pasteur also employs staff under fixed-term contracts for specific assignments. This type of contract can be concluded for up to 36 months under French law and is particularly geared towards research activities.

The Institut Pasteur hosts a large number of employees from external research organizations (444 as of December 31). 85% of these staff members are permanent or contract researchers.

For several years now, the Institut Pasteur's recruitment policy has involved boosting numbers of managerial staff, maintaining similar levels of highly skilled technical employees, and cutting back on lower skilled positions. This reflects a need for increasingly highly qualified staff to provide the skills and expertise required to keep up with new technological developments (particularly for the high-tech platforms and the rapidly growing field of bioinformatics). The aim is also to pool and optimize some activities so that the Institut Pasteur can focus its human and material resources on its core mission of conducting and supporting research.

ORGANIZATION

Discussions on the development and harmonisation of the Institut Pasteur's information systems continued this year and involved all the support and operational departments. The aim is to introduce an ERP system incorporating all the features required for the pooling of information and data to the entire campus. The first practical HR applications (including time and activity management) should be implemented in spring 2014.

CHANGES TO THE HUMAN RESOURCES DEPARTMENT

In 2013, the first steps were also taken for the reorganization of the Human Resources Department. Discussions on this process began at the end of 2012 with the aim of establishing a closer working relationship between HR teams and Institut Pasteur staff based on service, advice, and support. This involves three main focus areas. Firstly, four pairs of HR employees are each assigned to a given number of research departments or other divisions in a bid to develop closer links with the campus community. They act as local contact people for the campus, supporting Institut Pasteur staff members for all their HR needs. Secondly, expert support is available in a comprehensive range of HR matters including human resources management, legal issues, training and recruitment processes, communications, and labor relations. Lastly, HR staff provides monitoring, administration, payroll, management and medical care services for Institut Pasteur employees.

At the end of 2013, the annual negotiations for the following year were also held, culminating in the signing of a memorandum of understanding on various overall and individual payroll measures including a general pay rise and a one-time bonus. The individual pay rise process has been separated from the annual appraisal system so that the appraisals can focus on past and future achievements and skills development. A computer application to deal with annual remuneration requirements has been developed for line managers with the help of the Information Systems Department.

Generation contract

A major agreement between the Institut Pasteur management and trade unions to promote employment of young and older workers was signed in 2013. This three-year "generation contract" sets targets for recruiting at least 30 young people on permanent contracts over three years and maintaining the proportion of older employees (aged 55 and over) on permanent contracts at or above 20% of the workforce. Several schemes have been introduced for welcoming and integrating new young staff members (an induction program, the appointment of mentors, training, and skills transfer), and efforts are also being made to support professional development (mid-career interviews, career change, training, etc.).

2,436
staff

INCLUDING

1,930
Institut Pasteur employees

+

444
employees from other research organizations

+

62
interns

INSTITUT PASTEUR EMPLOYEES

40%
men

60%
women

IN MANAGERIAL POSTS

51.6%
women

ON THE CAMPUS

60
nationalities

Sustainable development and social responsibility

In 2013, the Institut Pasteur, a member of the United Nations Global Compact since 2010, pressed on with its action plan to reduce greenhouse gas emissions and stepped up its “Green Campus” program.

For the **3rd** year in a row, the Institut Pasteur issued a “Communication on Progress” report, which is available on the UN website.

ONGOING COMMITMENT TO THE UNITED NATIONS GLOBAL COMPACT

In 2013, the Institut Pasteur reaffirmed its membership of the United Nations Global Compact. For the third year in a row it issued a "Communication on Progress" report summarizing the improvements made over the past year, which is available on the UN website. As part of its pledge to raise awareness of principles relating to human rights, labor rights, environmental protection and the fight against corruption within its sphere of influence, the Institut Pasteur organized a presentation on these principles for the directors of the institutes in the Institut Pasteur International Network in a bid to encourage them to engage in a similar initiative to the one adopted at the Institut Pasteur in Paris.

ACTION PLAN TO REDUCE GREENHOUSE GAS EMISSIONS

Following the greenhouse gas emissions assessment carried out in 2012, the Institut Pasteur has devised an action plan to limit or reduce its emissions. In connection with these efforts, a plan for the rationalization and renovation of the cold storage rooms on campus is currently underway. The aim is to identify equipment that should be permanently dismantled or replaced by equipment that uses more environmentally-friendly refrigerants such as R134a or R407c. In 2012-2013, €85,000 were invested to replace equipment that uses the refrigerant R22.

ENVIRONMENTAL CRITERIA IN CALLS FOR TENDER

After identifying the "environmentally responsible" suppliers in the Institut Pasteur's product catalog, the Procurement Department joined forces with the Quality, Environment and Sustainable Development Department to update the procurement policy, particularly by incorporating "sustainable development" criteria (low energy consumption, packaging materials and recycling potential, etc.) where possible into calls for tender for consumables and equipment such as printers.
Since January 2013, 80% of the calls for tender for overheads launched by the Procurement Department have included sustainable development criteria in the evaluation process for tenders. The first call to use this process involved the management of the Institut Pasteur's green spaces.

REDUCTION IN NOISE DISTURBANCE

The Institut Pasteur must comply with strict regulatory requirements for acoustic emissions. Given the increasing need for refrigeration facilities – the main source of noise disturbance on the campus – the Institut Pasteur's technical department launched a series of surveys in 2009. These formed the basis of an action plan to improve noise control by 2013. The measures implemented cost a total of €4 million. A new noise map will be drawn up in 2014 to determine the efficacy of these measures.

RECOVERY OF USED BATTERIES

In December 2013, the Institut Pasteur stepped up its efforts to collect used batteries from activities carried out on campus and also opened up the scheme to allow staff to recycle batteries from personal use on the Institut Pasteur site. For this scheme, the Institut Pasteur joined forces with an accredited environmental organization to make sure that it meets regulatory requirements while eliminating processing and disposal costs.

Donations and legacies – generous giving to support research

The Institut Pasteur would never have existed without the generous support of the public. Today, it still depends on donations, legacies, gifts, and sponsorship. This valuable public support is one of the four pillars of the Institut Pasteur's budget, giving its scientists the independence and freedom they need to carry out their work.

DONATIONS

Thank you!

The outstanding €23.4 million raised in 2013 reflects the trust that the Institut Pasteur's donors place in its scientists, and the hopes put on the Institut Pasteur's work. Despite the economic difficulties experienced by many French households and companies over the past year, the phenomenal efforts of the Institut Pasteur fundraising team resulted in a 15% increase of fundraising revenue in just one year. The bonds of solidarity and support connecting the Institut Pasteur's scientists to donors are stronger than ever, demonstrating that the Institut Pasteur's research remains a priority for the French public. In 2013, many individual donors once again chose to make a long-term commitment to the Institut Pasteur by setting up regular direct debit donations and more than 50,000 new donors pledged their support. Online giving showed a 30% increase and a surge of major donors gave more generously than ever. The funds raised from the Pasteurdon campaign, held in mid-October each year, stabilized in 2013, with pledges totaling €1 million. Companies also continued their generous giving in 2013: sponsors in all fields maintained their support for the Institut Pasteur and some even increased their commitment through bigger donations and/or longer pledges. Apprenticeship tax, which funds the Teaching Center's activities, stabilized at a high level, with €1.3 million collected. Public generosity is a vital pillar of the Institut Pasteur's funding and a guarantee of the independence of its research. The commitment of all donors, however modest their contribution, is vital for the continued success of the Institut Pasteur's research. We extend our heartfelt thanks to them for their ongoing and loyal support.

"The commitment of all donors, however modest their contribution, is vital for the continued success of the Institut Pasteur's research."

LEGACIES AND GIFTS

A year of contrasts

In 2013, while the number of new legacies received rose to nearly 110, the total amount accounted for a 30% decrease compared to 2012. The legacies bequeathed to the Institut Pasteur are increasingly shared with other institutions, which obviously affects the sums received by the Institut Pasteur. Overall the legacies and gifts recorded in 2013 totaled €34.6 million, up from €30.6 million in 2012. Once again, life insurance policies represented a major source of recurring income, raising almost €7 million in 2013. Like legacies and gifts, these policies are exempt from transfer duties.

Quality strategy recognized with unique certification

The Institut Pasteur's Legacies and Real Estate Assets Management Office is the only department of its kind in France to have received an ISO 9001 certification for its activities. This certification has been extended this year and the office is preparing for a three-year certification renewal in 2014.

New communication channels

More and more people are contacting the Legacies Office every year to find out how to give a legacy, gift or life insurance policy to the Institut Pasteur or to learn more about 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. In 2013, a redesigned and updated information brochure was published with the aim of providing clear and simple advice on the technical and practical details involved in offering a gift or legacy.

A promotional campaign was launched in both the mainstream and trade press that focused on legacies and gifts – two major sources of funding that played a fundamental role in the inception of the Institut Pasteur itself.

The third conference on philanthropic trusts was held at the Institut Pasteur in April 2013. More than 450 people attended the lectures and debates on public interest and charity. This conference is now widely recognized as the leading event for philanthropy professionals. The think tank on philanthropic trusts represents a unique platform for sharing views and ideas on questions relating to assets and tax in the area of philanthropy.

"The Institut Pasteur would like to pay tribute and extend its sincere gratitude to the generous benefactors who passed away during 2013, whose legacies, gifts or life insurance policies have made a major contribution to the research carried out in its laboratories."

Communications and fundraising

In 2013, the Institut Pasteur focused primarily on consolidating and developing the activities and programs launched in previous years, while also working on a new campaign based on the idea of “Incurable curiosity”. The Department of Communications and Fundraising also worked hard to promote the Institut Pasteur’s achievements and successes, and improve its visibility and reputation, resulting in a record year in terms of fundraising.

Throughout the year, the department also continued its efforts to raise awareness of the Institut Pasteur's activities, values, and achievements. After two years of preparations, a new website was launched at the end of July. This redesigned version of the Institut Pasteur website is more user-friendly and features a new editorial approach and graphic style to promote the Institut Pasteur's image and provide a more engaging user experience.
Out of the 33 press releases published in 2013, 24 focused on advances in research.
Finally, 2013 was a busy year for internal communications, with several highlights including Pasteurdon, a new President, and the reopening of the newly renovated lecture hall in the Émile Duclaux building in September.

PASTEURDON FEATURED ON NEW CHANNELS

Pasteurdon, the Institut Pasteur's annual fundraising event, supported by major French companies and organized in partnership with 19 French TV channels, benefited from increased media coverage in 2013. Alongside our long-standing partners, six new TV channels supported the campaign this year. Pasteurdon 2013 was a great opportunity to raise public awareness on science and biomedical research, and to emphasize the importance of donations to improve health. A dedicated Pasteurdon website was also launched, and exclusive content was available on the Institut Pasteur's Facebook and Twitter accounts. This content was widely featured on social networks through our media partners and their presenters.
Pasteurdon 2013 ran from October 12 to 14, with pledges totaling €1 million. For the third year in a row, actress Alexandra Lamy was the Pasteurdon patron.

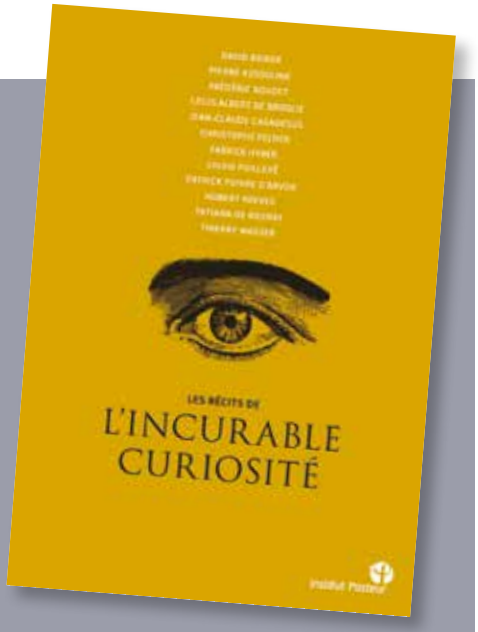
ACTIVE SPONSORS

Despite the ongoing economic crisis, many corporate partners and donors continued to support the Institut Pasteur, a recognized leader in its field. Sanofi renewed its partnership with the second edition of the Sanofi-Institut Pasteur Awards. Alongside loyal partners such as the Total Foundation, the Areva Foundation, and the Le Roch-Les Mousquetaires Foundation, new sponsors rallied to the Institut Pasteur's cause, including FIA-NET. The "Roulons solidaires" ("Riding in solidarity") campaign was held again this year during the Tour de France, in association with AG2R La Mondiale.

AT HOME WITH MR. PASTEUR

As well as offering guided tours, the Pasteur Museum is committed to raising awareness among the general public and the Institut Pasteur's staff about the unique history of its premises. In 2013, in partnership with La Poste, it hosted a special ceremony to celebrate the joint issue with Vietnam of a stamp dedicated to famed scientist Alexandre Yersin, marking the 150th anniversary of his birth. The museum was also involved in the official reopening of the renovated lecture hall, which has been named after Louis Pasteur's successor Émile Duclaux. Finally, a new Pasteur Museum brochure was published and is now available in the museum gift shop.

In 2013, the Institut Pasteur, a symbol of scientific excellence and the French philosophic tradition, celebrated its 125th anniversary. To mark this special anniversary, it launched a major campaign in September based on the idea of "Incurable curiosity", an allusion to the "virus" of curiosity inoculated by Louis Pasteur in each and every one of us. The three-pronged campaign included a short film, the publication of a collection of essays, and an extensive online presence. David Abiker, Pierre Assouline, Frédéric Boutet, Louis Albert de Broglie, Jean-Claude Casadesus, Christophe Felder, Fabrice Hyber, Patrick Poivre d'Arvor, Sylvie Poillevé, Hubert Reeves, Tatiana de Rosnay and Thierry Wasser all agreed to share their ideas on how curiosity can lead to discovery. Their thoughts are published in a short collection of essays entitled ***Les Récits de l'incurable curiosité*** (Tales of incurable curiosity). The collection was distributed free of charge in several FNAC bookstores in France. This campaign was honored by two industry awards: it won the corporate publicity campaign award from the Communication & Entreprise organization and received a mention in the 2013 Corporate Communication Strategies Grand Prix awards.

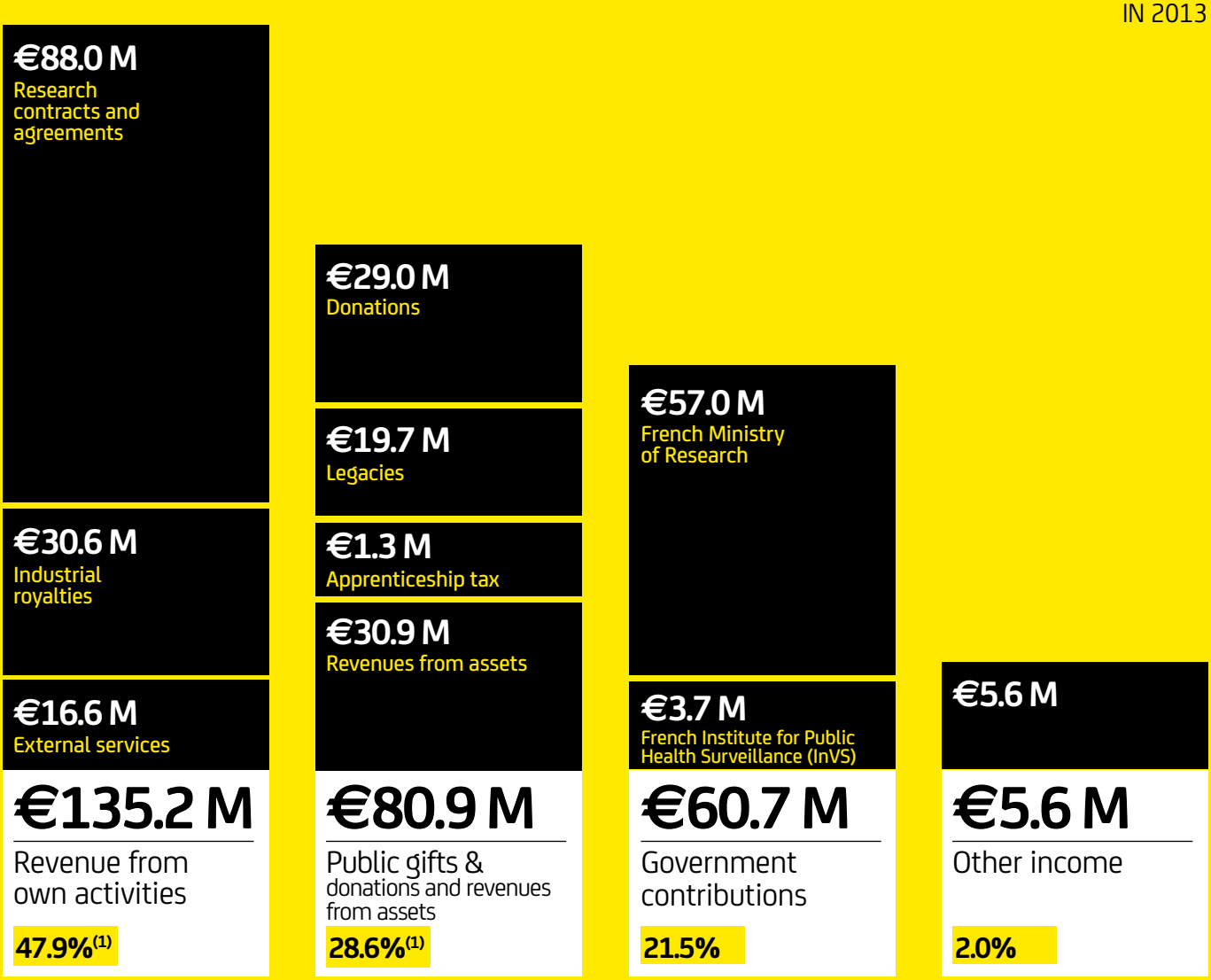


Financing structure

Current income

€282.4 M

IN 2013



REVENUE FROM OWN ACTIVITIES

Research contracts and agreements (€88 M accounting for 31.2% of income) are the income item with the highest growth rate over the past two years. They reflect the Institut Pasteur's success in tenders funded by the French National Research Agency (particularly under the Investing in the Future program) and the European Union (particularly with the European Research Council). R&D contracts with industry amounted to €7.5 M, a slight drop (by €0.2 M) on 2012's total. Other funds – received from private organizations (AFM [French Muscular Dystrophy Association], Ligue nationale contre le cancer [French Cancer League], Fondation de France, Fondation pour la recherché médicale [Medical Research Foundation], etc.) – amounted to €5.1 M, down by €0.9 M compared with 2012.
Industrial royalties (€30.6 M accounting for 10.8% of income) are essential for the Institut Pasteur. They are a direct result of the research carried out on campus. They fell sharply in 2013 owing to the cessation of income from the resolution of a litigation with a pharmaceutical company and the expiry of diagnostics patents.
External services (€16.6 M accounting for 5.9% of income) comprise activities linked to business development (expert assessments, advice for industrialists, etc.), public health activities carried out at the Medical Center, and services provided particularly to network institutes. This income rose by €1.0 M compared with 2012.

PUBLIC GIFTS & DONATIONS AND REVENUES FROM ASSETS

Revenues from assets (€30.9 M) include current financial revenue, rent from income property and agricultural revenue from estates registered among the Institut Pasteur's assets. They fell slightly (by €0.4 M) compared with 2012 as a result of a decrease in rent from rental properties (four properties were sold in 2012).
Public gifts & donations (€50 M) include all donations and legacies, and apprenticeship tax.
The overall fundraising figure came to €23.4 M in 2013, an increase of €3 M over the previous year due to the renewal of a sponsorship agreement begun in 2011 and an increase in international fundraising.
Legacies, as regards the share allocated to current revenue (€19.7 M), rose by €2.9 M compared with 2012. The amounts recorded as income correspond to legacy payments completed during the year.

GOVERNMENT CONTRIBUTIONS

These are made up of the grants from the Ministry of Research and InVS, which cover some of the cost (40%) of National Reference Center activities.

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.

Current expenses

€281.7 M
IN 2013

€121.2 M
Staff expenses

€93.3 M
Operating costs

€22.7 M
Depreciation

€43.2 M
Provisions and commitments to be achieved

€1.3 M
Financial costs

The structure of research spending shows that 76% of our budget is earmarked for infectious diseases (viral, bacterial and parasitic diseases).

Financial statements

In 2013, the operating deficit was stable compared with 2012, standing at -€23.7 M. The financial result (€24.3 M), comprising income from short- and long-term investments, enabled us to balance the current result for the financial year (+€0.6 M). Exceptional items bring the Institut Pasteur's net result to €36.4 M.

CURRENT OPERATIONS

Current revenue (see page 66) increased by 4.4% compared with 2012.
The highest rises were recorded on research agreements and contracts and support from our donors. Contributions from public authorities, which remain key to balancing the Institut Pasteur's current result, fell by €1.3 M.
Current expenditure was up by 4.2% from 2012, owing both to the development of research contracts and agreements and to increasing costs related to the modernization of buildings and IT facilities on campus. In terms of the Institut Pasteur's activities, research accounts for the majority of current expenditure, while the rest is allocated to public health and teaching.

EXCEPTIONAL ITEMS

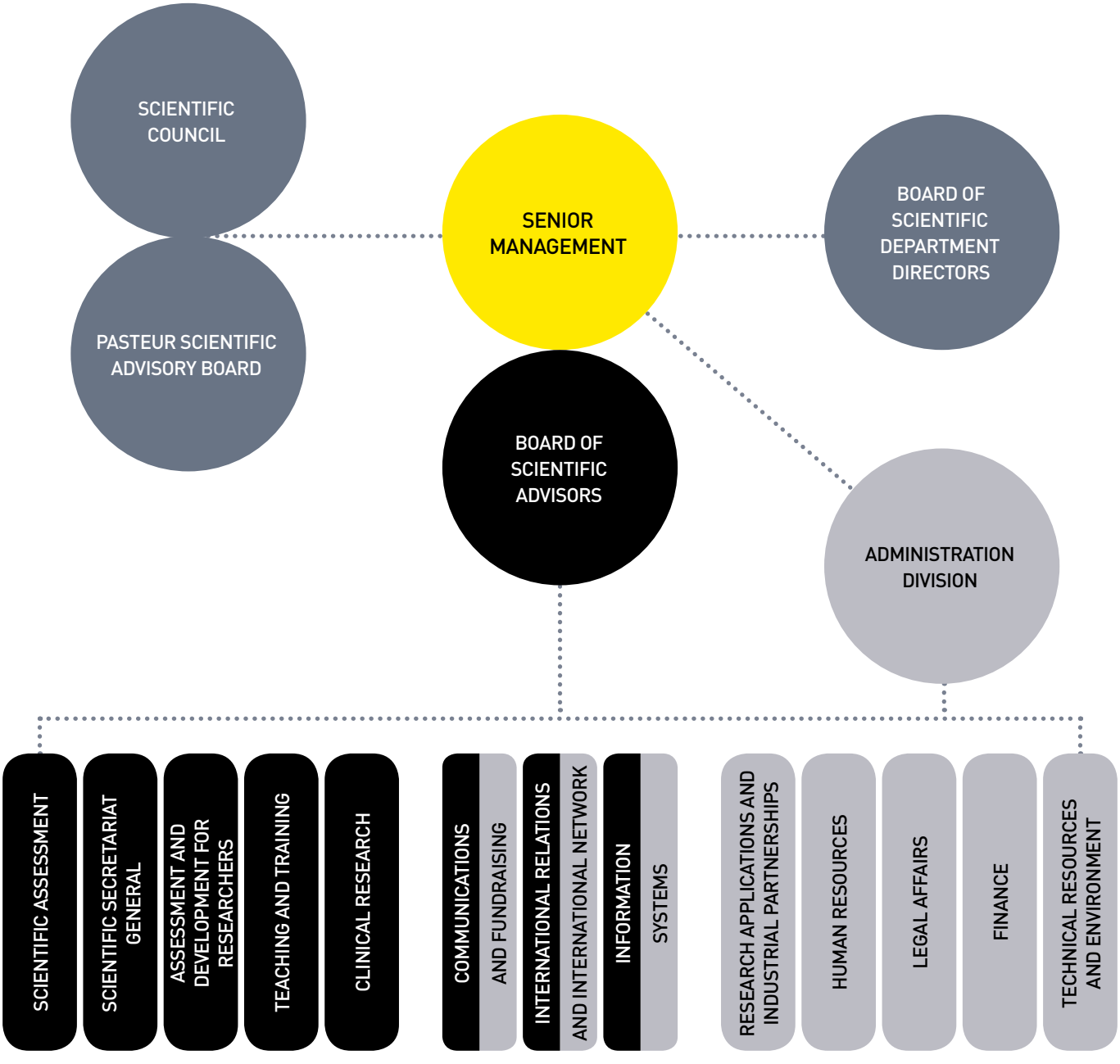
Exceptional operations relate to both a gift component (donations and legacies for the share exceeding €300,000) and a financial component (net valuation of financial assets resulting from capital gains or losses, realized or latent, based on the performance of the portfolio, with the balance of capital gains generated always exceeding the capital losses realized).
In 2013, the donations and legacies recorded as exceptional income amounted to €14.9 M, an increase of €1.1 M compared with 2012. The financial component showed a positive balance of €18.3 M, down from 2012 (-€7.8 M).
This year exceptional items also included capital gains of €2.6 M achieved from the sale of two rental properties.
Due to these exceptional items, the Institut Pasteur recorded a net result of €36.4 M.

General organization

The Institut Pasteur is governed by the Management, Board of Directors, and General Meeting.
The President, appointed by the Board of Directors, is responsible for overall policy and the smooth running of the institute.

Departments and governing bodies

March 2014



Board of Directors

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

April 2014

BOARD OF DIRECTORS BUREAU

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Vice-Chairman
DANIEL LOUVARD
Delegate of the President of the Institut Curie

Vice-Chairman
BERNARD GUIRKINGER
Suez Environnement

Treasurer
SOPHIE MANTEL
Head of Department in the Budget Division – French Budget Ministry

Secretary
ALAIN JACQUIER
Head of the Macromolecular Interaction Genetics Unit – Institut Pasteur

Standing invitees
BRUNO RÉMOND
Chairman of the Finance and Audit Committee, Chief Advisor to the French Government's Accounting Office

LIONEL ZINSOU
Chairman of the Appointments and Remuneration Committee, Chairman and Chief Executive Officer of PAI Partners

OTHER MEMBERS OF THE BOARD OF DIRECTORS

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

DOMINIQUE DEVILLE DE PÉRIÈRE
Directorate-General of Research and Innovation, French Ministry of National Education, Higher Education and Research

YVES FARGE
Chairman of the Society and Technologies Committee – Académie des technologies (French Academy of Technologies)

ALAIN FUCHS
Chief Executive Officer of the CNRS (French National Center for Scientific Research)

JEAN-PIERRE JOUYET
Chief Executive Officer of the Caisse des dépôts
Jean-Pierre Jouyet was appointed Secretary-General of the French Presidency on April 16, 2014.

CLAUDE LECLERC
Head of the Immune Regulation and Vaccinology Unit – Institut Pasteur

BENOÎT LESAFFRE
Vice-President – Paris-Est University

JEAN-BERNARD LEVY
Chief Executive Officer – Thalès

ISABELLE PELLETIER-DOUCEMENT
Biology of Enteric Viruses Candidate Unit – Institut Pasteur

ARMELLE PHALIPON
Molecular Microbial Pathogenesis Unit – Institut Pasteur

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

ANDRÉ SYROTA
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Vice-President Information Systems

ODILE GELPI
Head of the Biomedical Research Department

NATHALIE DENOYÉS
Vice-President Technical Resources and Environment

Management of the Institut Pasteur

The management team sets the Institut Pasteur's overall strategy. It is supported in its task by the Scientific Council and the Executive Board.

Scientific Council

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

April 2014

ELECTED PASTEURIAN MEMBERS

ANDRÉS ALCOVER (Vice-President)
Head of the Lymphocyte Cell Biology Unit

CHRISTOPHE D'ENFERT
Head of the Fungal Biology and Pathogenicity Unit

JEAN-PAUL LATGÉ
Head of the Aspergillus Unit

FRÉDÉRIC TANGY
Head of the Viral Genomics and Vaccination Unit

APPOINTED PASTEURIAN MEMBERS

PASCALE COSSART (President)
Head of the Bacteria-Cell Interactions Unit

CARMEN BUCHRIESER (Secretary)
Head of the Biology of Intracellular Bacteria Unit

LLUIS QUINTANA-MURCI
Head of the Human Evolutionary Genetics Unit

CHRISTOPHE ROGIER
Director of the Institut Pasteur in Madagascar

EXTERNAL MEMBERS

SØREN BRUNAK
Professor at the Center for Biological Sequence Analysis, Biocentrum-DTU (Technical University of Denmark), Lyngby, Denmark

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

JÖRG HACKER
Professor at the Deutsche Akademie der Naturforscher Leopoldina, National Academy of Sciences, Halle, Germany

RICHARD MOXON
Professor at the Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK

MICHEL C. NUSSENZWEIG
Professor at the Laboratory of Molecular Immunology, The Rockefeller University, Howard Hughes Medical Institute, New York, USA

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

CLAUDIO D. STERN
Professor in the Department of Cell & Developmental Biology, UCL, London, UK

GABRIEL WAKSMAN
Professor at the Institute of Structural and Molecular Biology at UCL and Birkbeck, London, UK

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25-28, rue du Docteur-Roux
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