



Institut Pasteur



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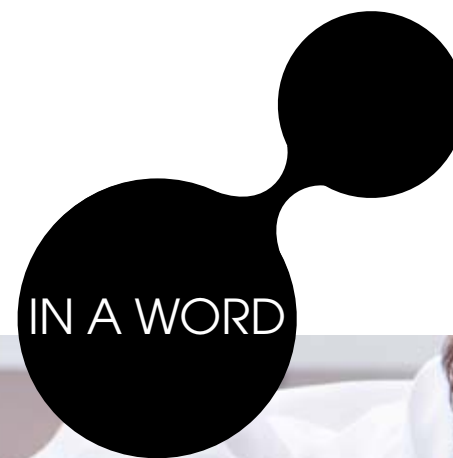
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www.pasteur.fr

For research,
for health,
for our future

2012
ANNUAL REPORT





Institut
Pasteur



For the past 125 years, scientists from the Institut Pasteur have been on the front lines in the fight against major public health challenges worldwide, battling diseases that threaten human populations. While leading the field of infectious diseases, the pioneering teams at the Institut Pasteur are also recognized for their excellence in neuroscience, developmental biology, genetics and genomics. Their research enables us to improve our understanding of living beings and develop new methods for the diagnosis, prevention and treatment of disease.

Serving public health

The Institut Pasteur's scientific strategy focuses on developing original and innovative topics, promoting interdisciplinary and multidisciplinary cooperation, and transferring scientific discoveries to applications. In order to ensure progress in understanding in the field, and to gain new victories in the fight against disease, Institut Pasteur teams have access to the technological resources they need to speed up and improve further the quality of their outstanding research.

At the cutting edge of biomedical research



2,400
staff



10
Nobel
laureates



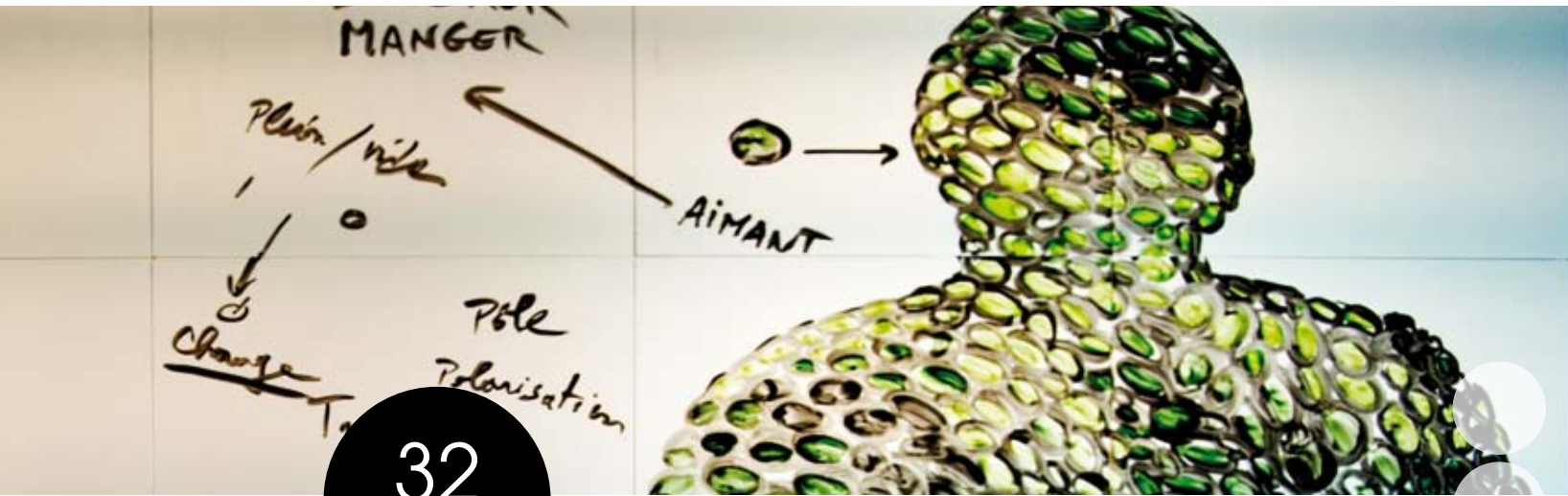
130
research units

With an international network of 32 institutes worldwide the Institut Pasteur plays a key role in the understanding, prevention and fight against a vast number of diseases, particularly infectious diseases. All of these institutes are linked through partnerships for scientific research, training and public health services. Additionally, the Institut Pasteur works in collaboration with major international players to further progress in the life sciences.

International presence

The Institut Pasteur has an international reputation for quality teaching that attracts students from all over the world who come to further their knowledge or top up their degree programs. Thirty courses with a strong emphasis on practical work are offered and are divided into three themes: Mechanisms of Living Organisms, Biology of Microorganisms, and Epidemiology and Public Health. These courses can be taken as part of Masters degree programs at various universities or as part of the specialized Masters run by the Pasteur-CNAM School of Public Health.

Teaching students from around the world



32
institutes
worldwide



500
students each year



60
nationalities

In order to guarantee the independence of its research policy, the private, state-approved Institut Pasteur has adopted a unique economic model. Its budget relies, as it always has, on funding from four sources: public generosity and patrimony incomes, government contributions, the development of business based on Institut Pasteur research and related contracts and agreements.

A unique economic model



€270.5
million budget
in 2012

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Interview with Jean-Pierre Jouyet

●● CHAIRMAN OF THE INSTITUT PASTEUR BOARD OF DIRECTORS⁽¹⁾



●●
By working together we can build
a truly great scientific facility
complete with sophisticated,
state-of-the-art equipment.

What events particularly stood out for you this year?

For the Institut Pasteur, the high point of 2012 was undoubtedly the inauguration of the new François Jacob building for research on emerging diseases with a ceremony attended by the French President on November 14. This marked the successful culmination of a lengthy project, completed on time and on budget despite the tough economic climate. I am delighted that our scientists will be able to use this unique facility to carry out their research on the different stages of disease.

For me, this building also epitomizes the Pasteurian spirit. I'm particularly proud that it has been named after François Jacob, who embodied the same values of humanity, freedom, knowledge, and audacity that the Institut Pasteur embraces today. One of the Institut Pasteur's strengths is its ability to take inspiration from its outstanding heritage, rich with scientific success and characterized by strong values, as it seeks to remain at the forefront of progress.

The building is also a valuable asset for Paris, proving that the French capital still has true global influence. Despite what the skeptics may say, our country has shown that by working together we can build a truly great scientific facility complete with sophisticated, state-of-the-art equipment. This new building will improve working conditions for the Institut Pasteur's scientists and give them the tools they need to fight the spread of viruses.

How is the Institut Pasteur's financial situation looking in the light of the ongoing economic crisis?

The Institut Pasteur has experienced some difficulties, but on the whole, as with many companies and institutions in France, the financial situation is sound. The efforts of all the teams and the work carried out by the management and the Board of Directors to modernize the Institut Pasteur's campus and working methods have proved effective, keeping us in a good position in recent years. I would particularly draw attention to the fact that, despite the economic downturn, the Institut Pasteur has continued to set the bar ever higher and has not shelved any of its projects. We have managed to stabilize our operating expenditure, allowing us to increase the overall budget for our research units by 7% in 2012. Given the current context, that's a feat that many institutions would struggle to emulate. We must pursue our efforts to modernize both the campus facilities and the Institut Pasteur's procedures and management policies and practices. Our reputation as one of the world's leading research organizations depends on it.

What were the main issues addressed by the Board of Directors in 2012?

In April 2012, the Board of Directors started a recruitment process for a new President, who will start work on October 1, 2013. The Board Members wanted this to be a gradual transition and were keen to maintain transparency at all times so that the management team led by Alice Dautry, in which the Board of Directors has the utmost confidence, could continue working as normal until the new President takes office.

The Board of Directors has continued to oversee the management of assets, including the ongoing redistribution of real estate, and has closely followed the Institut Pasteur's international activities. One of the Institut Pasteur's major strengths is its network of over 30 institutes worldwide. The most recent institute was opened in Laos in

January 2012 and was visited by the French President, who emphasized the Institut Pasteur's important economic role as an employer of local people who are committed to their institute.

What are your thoughts on the Institut Pasteur for 2013?

In 2013, the Institut Pasteur will celebrate its 125th anniversary. My hope is that the efforts of the people who work for the Institut Pasteur will be truly valued more than ever, that it would continue to reach out to the world, and that its thirst for knowledge would become ever greater. I want to see younger generations becoming passionate about joining the Institut Pasteur, about working together in this legendary place; I want to see them devoting themselves to our institute. During a televised documentary about the Institut Pasteur, a scientist said something that particularly struck me. She explained that her aim at the Institut Pasteur was to find those little extras that together could lead to great things.

And that is my wish for the Institut Pasteur.

(1) Until May 1, 2013.

●●
I want to see younger generations
becoming passionate about joining
the Institut Pasteur, about working
together in this legendary place...

Interview with Alice Dautry

●● PRESIDENT OF THE INSTITUT PASTEUR



What are your thoughts on the past year?

The year 2012 has been one of consolidation, with the continuation of several programs that have been launched over the past few years, against a particularly turbulent economic and political backdrop. Despite these difficulties, the Institut Pasteur has continued to demonstrate its expertise in France and within its international network. The year has also seen the successful conclusion of some major projects. And this is the last time that I'll be contributing to this Annual Report as President, because after eight years my term is coming to an end in October 2013.

What have been the highlights of 2012?

The major highlight of 2012 was undoubtedly the long-awaited inauguration of the François Jacob building on November 14 at a ceremony attended by French President François Hollande. This plan for a center dedicated to research on emerging diseases was first mooted seven years ago, and it was successfully completed with the support of the Board of Directors. The Institut Pasteur has boosted its capabilities to deal with the threat of emerging diseases by building one of Europe's largest research centers in the field, complete with state-of-the-art equipment. The building was named after the esteemed Professor François Jacob, an eminent Institut Pasteur scientist and 1965 Nobel medicine laureate who was also Chancellor of the Order of the Liberation and a Member of the French Academy. François Jacob, who attended the inauguration ceremony, sadly passed away in April 2013. I am particularly pleased that the Institut Pasteur was able to honor him in this way. The Institut Pasteur has been involved in the fight against emerging diseases for many years, especially through its international network of 32 institutes. In Laos, a new Institut Pasteur was inaugurated in January 2012, marking the culmination of a long-term project to set up effective facilities in South-East Asia for research on pandemic risks. This new institute is part of our South-East Asia network, which already includes three institutes in Vietnam and one in Cambodia. In November 2012, the French President visited the new Laos institute, which now hosts teams from Japan, Luxembourg, and France alongside the young Laotian scientists.

What have been the main scientific achievements?

The Institut Pasteur's scientific strategy for 2012 focused on recruiting teams of top scientists. As an international institution, the Institut Pasteur in Paris continues to attract scientists at the forefront of their

fields. The year also witnessed some major scientific achievements. A team of scientists led by Fabrice Chréten in collaboration with Shahragim Tajbakhsh demonstrated that stem cells are capable of remaining in a dormant state for several days in post-mortem tissues. This groundbreaking discovery opens up new possibilities for preserving stem cells, which can be used in the treatment of many diseases. Thomas Bourgeron's team also carried out significant research on autism, demonstrating the importance of synaptic genes in the onset and development of this syndrome. Given the increasing resistance to malaria treatments observed in recent years, Institut Pasteur teams across the world have stepped up their efforts in this area. In 2012, scientists identified new molecules that can halt the development of the *Plasmodium falciparum* parasite. This is a major breakthrough that offers real hope for the future. And finally, one of our teams working on fibrosis (abnormal wound healing) pinpointed the cells involved in the formation of diseased tissue. This paves the way for new therapy options for chronic fibrotic diseases.



The Institut Pasteur has boosted its capabilities to deal with emerging diseases by building one of Europe's largest research centers.



New partnership agreements have been signed...

The Institut Pasteur signed two major international cooperation agreements in 2012. The first aims to promote the effective implementation of the International Health Regulations drawn up by the World Health Organization (WHO) in 2007. Under this agreement, the institutes in our international network will have a key role to play in their respective countries in improving epidemic response. The second agreement establishes a partnership with the International Cooperation Center of Agricultural Research for Development (CIRAD), with the aim of strengthening our international cooperation in infectious diseases and zoonoses (diseases that can be passed from animals to humans).

The Institut Pasteur continues to enjoy truly global reach...

Our international strategy has three main components: encouraging international partnerships; developing the best tools and resources, both in human and technological terms; and teaching, training and transferring knowledge. Firstly, we enjoy long-term cooperation with major international scientific bodies, including several universities

across the world, particularly in the United States, and also the Wellcome Trust and various French partners. We offer ongoing support to the international research community – in 2012, we launched a new recruitment program for top-level scientists to encourage them to take a leading role in their own countries and set up their own research teams. Following the first call for applications, two scientists were selected to set up teams in African institutes of the Pasteur Network. We have also focused our efforts on setting up high-security laboratories fitted with the sophisticated equipment and technologies needed for research projects, particularly in the field of infectious diseases. The final element of our strategy involves teaching and training, since we have a duty to prepare the scientists of the future. In 2012, we recruited around ten students from across the world who will be joining us in Paris to complete their PhD.

Institut Pasteur scientists have also received various awards...

Our scientific achievements were recognized in 2012, with Philippe Sansonetti receiving the Inserm "Grand Prix" for his research on microbial infection, and Christine Petit being awarded The Brain Prize 2012. The European Research Council also selected four research teams to receive Starting Grants and two to receive Advanced Grants.

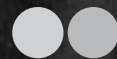
Did individuals and companies continue to support the Institut Pasteur in 2012?

Absolutely. Gifts and sponsorship have almost doubled in five years, despite the ongoing economic crisis. More than ever, the Institut Pasteur enjoys the support of a very large number of sponsors, companies, donors, and legators, whose gifts help fund both our research programs and also projects such as the new François Jacob project. Our relationship with our donors is so important – together we can achieve great things. During this year's Pasteurdon, our annual fundraising event, the digital terrestrial network channels once again offered their support. Our Pasteurdon patron, Alexandra Lamy, was simply amazing and was really committed to the cause, even missing film shoots to be with us! Finally, the Sanofi-Institut Pasteur Awards for innovative biomedical research were set up and will take place again this year.

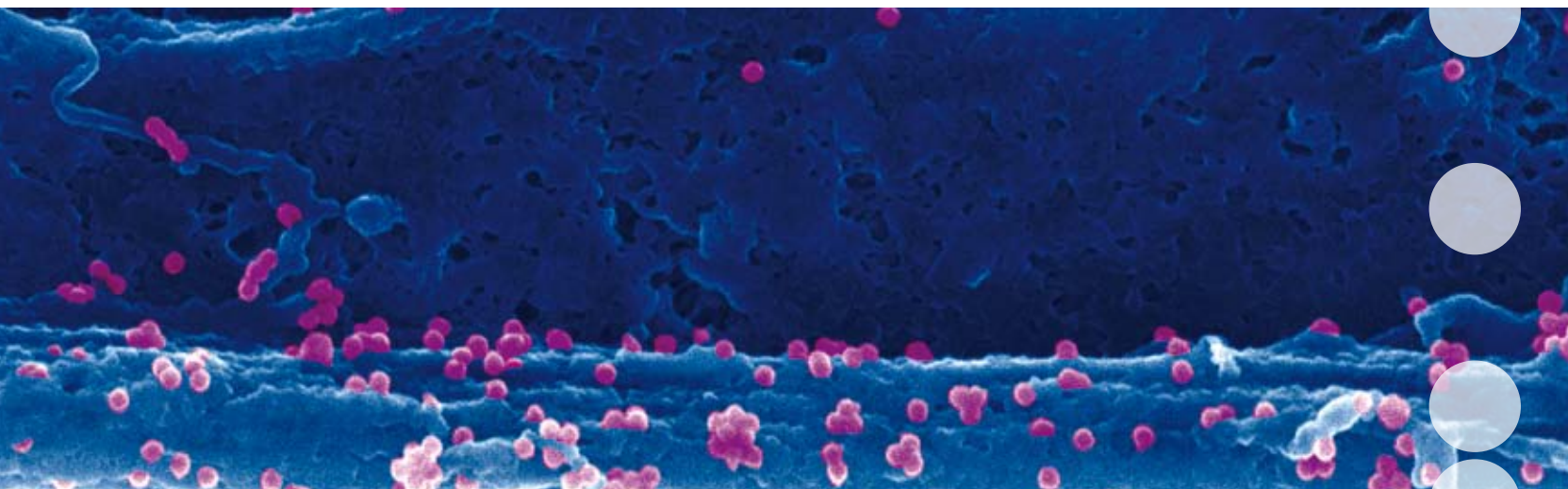
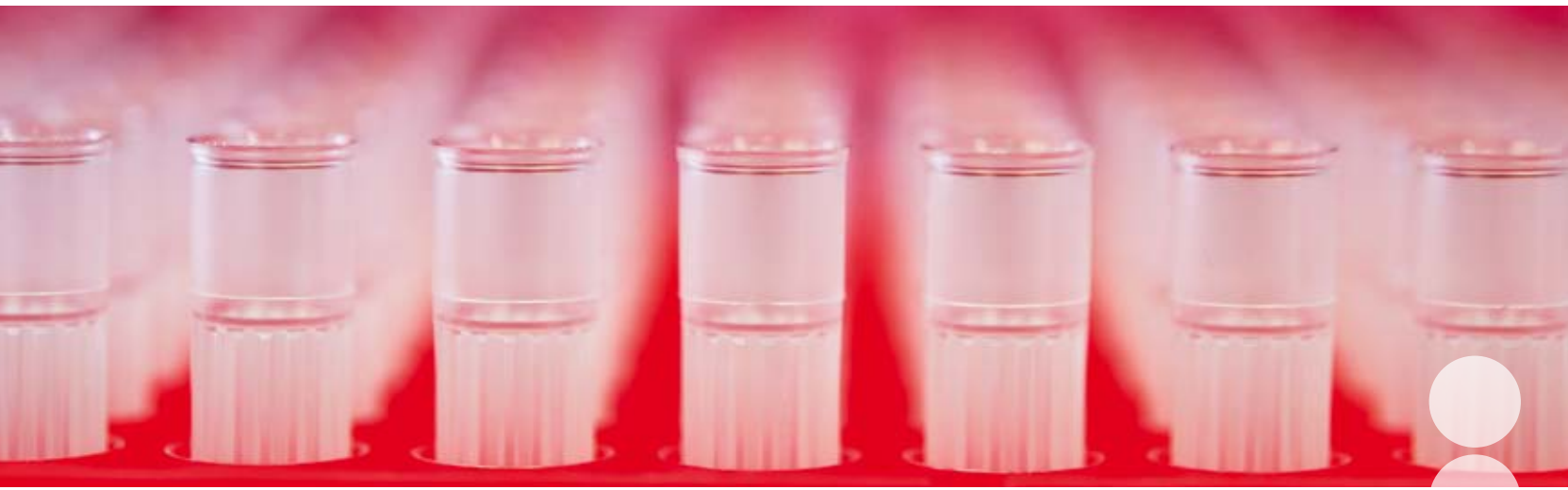
Do you have a final word for the scientists?

I'm so proud of the work all our teams have achieved since I took over as President of the Institut Pasteur in 2005. The Institut Pasteur has experienced major changes in its science, its organizational set-up, and its facilities. The research results of our teams, including the institutes in the International Network, have been published in leading international journals. Today the Institut Pasteur is at the forefront of progress – but it hasn't got there by chance. The key is to create the right dynamic, to find a balance while allowing that degree of unpredictability that can spark progress. I firmly believe that the Institut Pasteur is ready to embrace any challenges that come its way, so I'd like to encourage our scientists just to go for it!

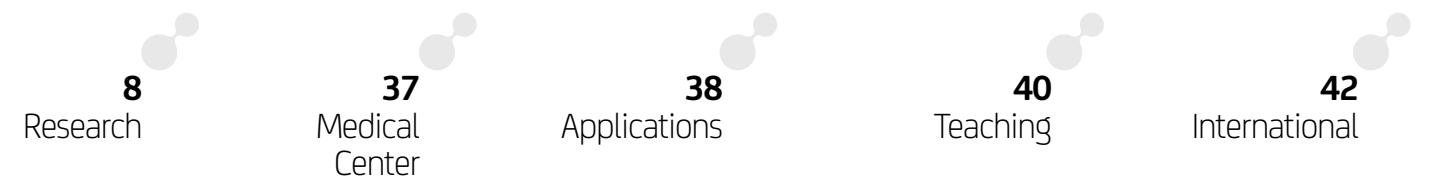
Our relationship with our donors is so important – together we can achieve great things.



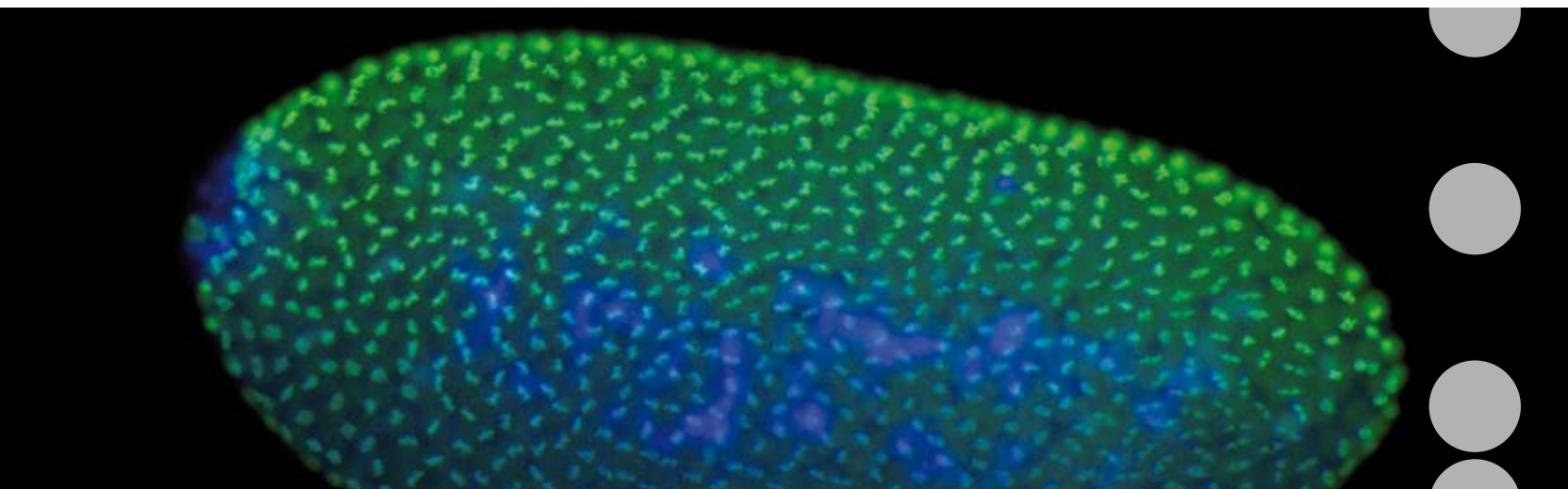
Scientific discovery for sustainable health



The dynamics and infrastructure of research at the Institut Pasteur are geared towards providing research teams with the resources required for the realization of ambitious, innovative projects. The ongoing investment in cutting-edge technologies and close cooperation with partners from the Institut Pasteur International Network, along with the application of discoveries and transfer of values, constitute the pillars of high quality laboratory research.



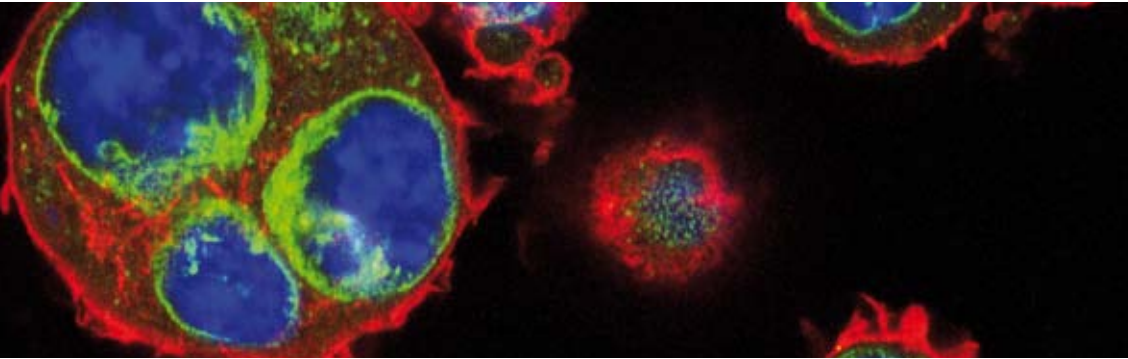
Multidisciplinary research



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The Cell Biology and Infection Department studies the mechanisms regulating 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.

Cell Biology and Infection



Drosophila cells, examined here to investigate one of the mechanisms of tumorigenesis. The DNA is shown in blue, the edges of the nuclei in green, and the actin cytoskeleton in red.

Understanding infection mechanisms requires extensive research into how cells function both during infection and in the balance between the commensal flora and host.

The Cell Biology and Infection Department strives to develop the analysis of the interface between microorganisms and cells/tissues. The department has three major priorities:

- foster the integration of cell biology, cell microbiology, genomics, and imaging, to enable more effective analysis of bacterial, viral, parasitic, and prion infections;
- develop expertise in tissue microbiology and use increasingly sophisticated *in vivo* imaging techniques to improve understanding of infection at the whole-animal scale;
- promote close links with other departments, in particular immunology and microbiology.

These activities are closely related to the development of new techniques such as imaging, image analysis, genomics, and post-genomics.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

NONINVASIVE NANOSCOPY

Traditional techniques to observe cellular and molecular structures using optical microscopy offer relatively low resolution, typically limited to 200 or 300 nanometers. Since most viruses are smaller than this, more detailed imaging techniques are needed to identify their internal structure. The Imaging and Modeling Group led by Christophe Zimmer, in collaboration with Pierre Charneau's Molecular Virology and Vaccinology Unit, developed a new optical microscopy technique that offers ten times the resolution of traditional microscopes and respects the biological function of the visualized molecules. This new technique is based on two recent imaging methods – PALM super-resolution microscopy (which forms a high definition image from thousands of low-definition shots) and FLAsH fluorescence labeling. The scientists used this technique to observe the AIDS virus, providing evidence that the capsid containing the viral genome remains intact until HIV enters the cell nucleus, contrary to a widely held belief. This suggests that the capsid might play an important role in the viral replication cycle. This new non-invasive observation approach opens up unique possibilities for studying microbial complexes and their interactions with host cells.

12 RESEARCH UNITS

2 TECHNOLOGICAL PLATFORMS

AMOEBIASIS: A NEGLECTED PARASITIC DISEASE

The Cell Biology of Parasitism Unit, led by Nancy Guillén, focuses its research on amoebiasis, a parasitic disease that causes bloody diarrhea and is a major killer world-wide with high impact in the poorest regions. In 2012, the unit became a partner in the national "Para-Frap" Laboratory of Excellence. Two major recent breakthroughs of the unit correspond to the analysis of the evolutionary history of parasite species and of genetic regulation as a means of understanding infectious diseases. The scientists focused on the RNA of *Entamoeba*, the parasite that causes amoebiasis, and were able to discover novel regulatory RNAs as key factors of virulence. The scientists also worked with clinicians, observing human intestine fragments to identify how amoebas cross the intestinal barrier. Using living tissue imaging, they conclude that amoebas likely cross the human intestinal barrier by taking advantage of the dense collagen structure for their motility thereby triggering the inflammatory process at the origin of the disease. This discovery opens up new possibilities for research into other intestinal diseases such as colon cancer, which is also associated with a poorly regulated inflammatory process.

FOLLOWING THE BACTERIAL TRAIL

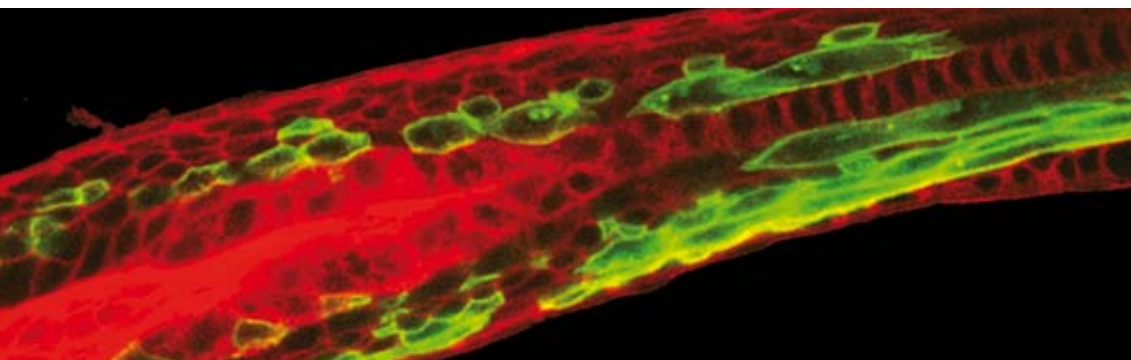
Over the past few years, the Dynamics of Host-Pathogen Interactions Group, led by Jost Enninga, has developed a technique using fluorescence microscopy to visualize and identify the location of invasive bacteria in human cells. This process allows scientists to track the movements of bacteria, in the cytoplasm or cell compartments known as vacuoles, in real time at single-cell scale. Working in conjunction with Roland Brosch's unit, which specializes in mycobacteria, the scientists investigated the intracellular localization of *M. tuberculosis*, the causative of human tuberculosis. Contrary to what was believed, they demonstrated that *M. tuberculosis* does not remain in the phagolysosomes, cell vesicles where they were thought to proliferate while resisting destruction by the host. Instead, they rupture this compartment to reach the cytoplasm. This causes the infected cell to die quickly through necrosis. The scientists identified that the mechanism used by the bacteria to rupture the phagolysosome involves a protein known as ESAT-6, whose last ten components seem to be particularly vital. This research reveals a promising therapeutic target – a drug that blocks ESAT-6 would stop the bacteria from accessing the cytoplasm, thereby preventing the infectious process.

2012 Inserm "Grand Prix"

Philippe Sansonetti, Head of the Molecular Microbial Pathogenesis Unit (Institut Pasteur Inserm 786) and a professor at the Institut Pasteur and the Collège de France, has been awarded the 2012 Inserm "Grand Prix" for his research on microbial infection. This award is a fitting tribute for a scientist whose research has helped further our knowledge of human physiology and made a major contribution to progress in therapeutics and human health in general. Philippe Sansonetti's pioneering work involved updating the genetic bases of virulence in bacteria, particularly *Shigella*, which causes dysentery; he also studied all the various stages of the infection process.

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.

Developmental and Stem Cell Biology



A hair follicle observed using fluorescence techniques. In green, stem cells and cells produced by their division, which are distributed all along the follicle as it grows, from bottom to top.

The aim of the department is to understand how a highly integrated multicellular organism such as a human being develops from a single cell, the fertilized egg. Using mainly model organisms, four main research objectives have been defined:

- identifying embryo cell movements, cell polarity and shape changes for tissue and organ formation, and the information exchanges used during this process;
- determining how the identity of each cell is established and maintained through specific programming mechanisms during prenatal development and in adults;
- establishing the role of 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 the resistance of the host to infectious diseases and/or congenital and metabolic diseases.

In 2012, a junior research group was added to the department. In the near future, other recruitments are planned in connection with the LabEx (Laboratories of Excellence) project "REVIVE", set up as a result of investment by the French government. This ten-year funding will be used to build and coordinate a network of stem cell experts from the Institut Pasteur and Paris region with the aim to develop a globally recognized hub for regenerative medicine.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

A THERAPEUTIC TARGET FOR MULTIPLE SCLEROSIS

In multiple sclerosis (MS) patients, some white blood cells known as T lymphocytes are abnormally activated and produce too many cytokines, the messenger molecules in the immune system. These cells also express viral proteins that are not caused by infection but come from old viral sequences that have been incorporated into human DNA during evolution. These viruses are not normally expressed because the cell is able to maintain them under control using a regulatory protein, HP1, which binds to structural proteins in the genetic sequences. This type of regulation is epigenetic in nature, as it affects structural proteins and not the DNA sequence itself. By establishing a new parallel between these two pathological events – the overproduction of cytokines and the expression of viral sequences – Christian Muchardt's team in the Epigenetic Regulation Unit made the surprising discovery that the deregulation of cytokine production is also linked to the protein HP1. This protein blocks cytokine genes, but in MS patients its binding site on the structural proteins is destroyed and the blocking effect is absent. These observations provide new therapeutic options based on the development of chemical compounds that are able to correct the defective epigenetic mechanism and may therefore represent promising drug candidates for MS.

12 RESEARCH UNITS

1 MOUSE GENETICS ENGINEERING CENTER

A DIVERSITY OF BEHAVIORS AMONG STEM CELLS

Adult organs contain stem cells with regenerative properties. When these stem cells are at rest, they are in a state known as "quiescence". But after physical activity or injury, they "wake up" and multiply to repair the damaged muscle tissue. In 2012, Prof. Shahragim Tajbaksh and his team in the Stem Cells and Development Unit demonstrated that as well as quiescent stem cells, resting muscles also have dormant cells, which are in a deeper state of rest with a reduced metabolism. Quiescent stem cells express lower levels of a protein known as Pax7 (Pax7-low cells), whereas dormant cells express higher levels of this protein (Pax7-high cells). After severe damage to the tissue all of these cells wake up, they divide by producing either a daughter stem cell and a daughter differentiating cell, using a different DNA segregation process for Pax7-high and Pax7-low cells, or by producing two identical daughter cells. Ultimately, these different types of division lead to fully functioning muscle fibers after regeneration and restoration of the stem cell pool. Working in cooperation with Prof. Fabrice Chrétien's team (see p. 20), the scientists then demonstrated that the muscles in deceased patients are able to retain their regeneration capacity for many days post-mortem. Remarkably, these stem cells are in a dormant state, presumably to survive in the hostile conditions. Prof. Tajbaksh, who received funding from the European Research Council, explains that "reducing the metabolic activity of stem cells enables them to remain alive; after injury or when conditions become favorable again, they can choose to divide in different ways."



A new team

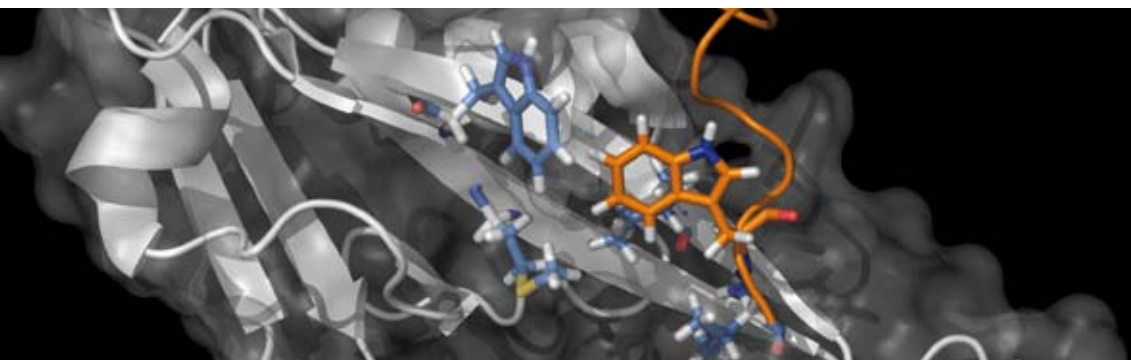
In 2012, the new Morphogenesis Regulation in Higher Vertebrates Group (Institut Pasteur/CNRS), led by Jérôme Gros, joined the department. The team is focusing on the general concepts underlying embryogenesis, using limb formation as a model. Using chicken and quail embryos, the scientists observe the development of embryonic structures dynamically at the single cell level. By combining traditional embryology with cutting-edge techniques in molecular genetics, cell biology, photon microscopy, and biophysics, they can monitor the behavior and molecular regulation of cells labeled by fluorescence in the developing embryo. The scientists hope that this research will help shed light on the origins of limb malformations.

WHY OUR CELLS ARE NOT ALL IDENTICAL

When a cell divides, the genetic information and different molecules it contains are generally distributed evenly between the two daughter cells. One exception to this rule is the Numb protein, which is inherited by just one of the daughter cells in what is known as asymmetric cell division. This mechanism is vital for humans. It is involved in the self-renewal of stem cells, and if inactivated it can lead to tumors. The mechanism of action of Numb in asymmetric cell division had not been fully determined. Scientists in the Drosophila Developmental Genetics Unit led by François Schweisguth have been focusing on this phenomenon using a model organism, the *D. melanogaster* fly. In 2012, they demonstrated how Numb regulates the activity of Notch, another protein located on the cell surface that was well known for its vital role in embryo development and whose dysfunction can disrupt the formation of the digestive tract, skin, and nervous system. In the daughter cell that inherits it, Numb prevents a build-up of Notch on the membrane, blocking activation. To carry out this research, the scientists developed a fluorescent probe that allowed them to observe Notch activation in real time in a single daughter cell within a whole living organism. This fundamental research helps shed light on the complex mechanisms that regulate stem cell production.

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.

Structural Biology and Chemistry



A rabies virus molecule (structure in orange) interacts specifically with a neuron protein (in gray), disrupting the cell's life/death balance.

The Structural Biology and Chemistry Department studies the three-dimensional structure of molecules (proteins, RNA, and DNA) so as to understand 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 biological complexes;
- molecular modeling, which is vital for determining and manipulating structures.

In 2012, two new teams joined the department, one focusing on proteomics and the other on nerve impulse transmission.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

SPOTLIGHT ON PROTEINS

Since July 2012, Julia Chamot-Rooke has been in charge of the Structural Mass Spectrometry and Proteomics Unit and related Proteomics Platform. This new team is developing innovative analysis methods to identify, characterize, and quantify proteins that play an important role in human health. There is renewed interest in proteins in the scientific community. They are responsible for the vast majority of cell functions, and are also major targets for the damage that occurs in cancer cells. The progress in mass spectrometry and huge volume of genomic data generated in recent years have given rise to the field of proteomics. While traditional methods are based on analyzing small protein fragments, the scientists in this unit use mass measurements for whole proteins, significantly reducing data loss. Scientists in the unit recently used this cutting-edge technology to analyze *Neisseria meningitidis*, the bacterium that causes meningitis, providing a new characterization of a chemical modification on one of its proteins that plays a vital role in the virulence and spread of the bacterium.

13 RESEARCH UNITS

4 TECHNOLOGICAL PLATFORMS

ANALYZING NERVE IMPULSES

In 2012, the new Molecular Mechanisms of Membrane Transport Group, led by Nicolas Reyes, joined the department. This team is investigating the transmission of nerve impulses in the brain and spinal cord. The scientists are particularly focusing on the transport of glutamate, a small chemical compound that transmits nerve impulses between neurons. Glutamate is a vital neurotransmitter in humans but it can become toxic at high concentrations. During a stroke, for example, a high build-up of glutamate between neurons can lead to nerve cell death. Excess glutamate has also been found in patients with neurodegenerative diseases such as Parkinson's and Alzheimer's, although a causal relationship has not been confirmed. Nicolas Reyes' team is looking into the molecular mechanism by which neurons capture glutamate, thereby regulating its extracellular concentration to ensure that the brain works properly. The scientists are adopting an innovative multidisciplinary approach combining X-ray crystallography, calorimetry, fluorescence spectroscopy, and electrophysiology. In 2012, Nicolas Reyes received funding from the European Research Council for this research under its highly selective programs for young researchers.

NEURON LIFE AND DEATH CONTROLLED BY A VIRUS

Some viruses are capable of hijacking cell mechanisms for their own benefit. One example is the rabies virus, which needs the neurons it infects to be kept alive so that it can spread throughout the body. The team led by Nicolas Wolff in the Nuclear Magnetic Resonance Unit, in cooperation with a virology team led by Monique Lafon, is using this model to understand the molecular and cellular mechanisms involved in neuron survival, which is partly regulated by the association of two cell-produced enzymes, MAST2 and PTEN. These two proteins form a complex that is involved in maintaining the delicate balance between cell life and death, known as cell homeostasis. The scientists discovered that one of the rabies virus proteins interferes with the formation of the MAST2/PTEN complex. When elucidated by nuclear magnetic resonance, the atomic structures of these proteins show that the viral protein cleverly mimics the interaction determinants of MAST2 and PTEN, and that it successfully competes with PTEN to bind to MAST2. The cell enzymes are transferred outside the nucleus, preventing them from carrying out their function, and the neuron is kept alive. This research illustrates the important notion that a protein can only be active if it is in the right place at the right time and has the right partners to allow it to carry out its work in the cell.



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.

Genomes and Genetics



A *Vibrio cholerae* colony. In blue, the bacteria whose chromosomes have been merged.

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 investigating the evolution of infectious agents and the selective pressures they have exerted on human genes over time. The progress of these research programs is largely based on new sequencing and genotyping techniques.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

DENFREE: A GLOBAL CONSORTIUM TO CONTROL DENGUE

DENFREE is a high-profile international program for dengue research, coordinated at the Institut Pasteur by Anavaj Sakuntabhai, Head of the Functional Genetics of Infectious Diseases Unit. The focus of the project is to improve understanding of dengue, which is spreading to new regions, with the aim of better containing and controlling dengue epidemics. The project consortium is composed of 14 partner institutions from eight countries in Europe, Asia, and Latin America. It has received €6 million in funding from the European Union. "The DENFREE project should enable us to study dengue from several different angles, investigating epidemiological, immunological, climatological, and geographical factors," explains Anavaj Sakuntabhai. The dengue virus is spread by mosquitoes, with symptoms ranging from mild aches and pains to fatal hemorrhagic fever. Individuals can also be infected with dengue without going on to develop the disease. Asymptomatic cases are one of the main focuses of research in the DENFREE program. Can infected patients who do not present any symptoms still spread the disease? How do they manage to resist the virus? "One aim is to develop an accurate rapid diagnostic kit so that we can systematically test the family and neighbors of patients with severe symptoms of dengue fever and identify healthy carriers more easily," explains Anavaj Sakuntabhai. "In the long term we hope to build predictive models to forecast epidemics and develop effective mosquito control methods."

14 RESEARCH UNITS

4 TECHNOLOGICAL PLATFORMS

GENE EXPRESSION: QUALITY OVER QUANTITY

To meet their needs, cells produce proteins from their DNA. This involves a series of tightly regulated stages, including the production of an intermediate molecule known as RNA (in its transcription stage), which then matures and is translated into proteins. If the cell fails to follow these vital processes correctly it can lead to serious consequences such as the development of tumors. These "quality control" mechanisms in gene expression are the focus of research by scientists in the Macromolecular Interaction Genetics Unit, led by Alain Jacquier. The team has already identified several regulation processes and made various surprising, unexpected discoveries. For example, in eukaryotic organisms such as humans, transcription does not only take place in genes but in virtually the whole genome, including regions without genes. The corresponding RNA is eliminated so quickly by means of specially devised quality control mechanisms that it is completely undetectable. The unit's scientists have recently joined forces with a team from the CNRS in Gif-sur-Yvette to demonstrate that these mechanisms can be responsible for the degradation of up to two thirds of some RNA, despite its abundance. This research shows how vital quality control mechanisms are, and why the cell expends so much energy on them.



New platform

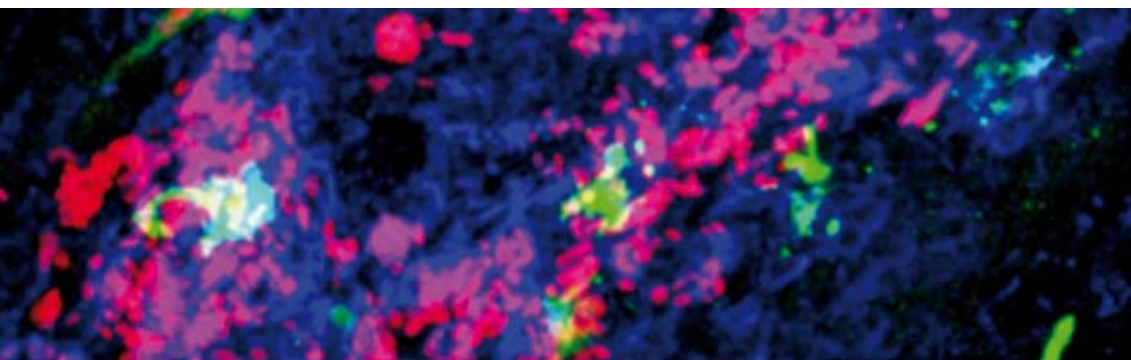
The new Eukaryote Genotyping Platform, set up in 2012 and led by Béatrice Regnault, is the first Institut Pasteur platform to focus on superior organisms. It uses two high-throughput techniques – genotyping on microarrays (to detect genetic variations) and sequencing (reading genes "letter by letter") – to identify the genetic anomalies that cause disease and pinpoint genes that confer susceptibility to or protection from given diseases. This cutting-edge sequencing equipment is widely believed to be the technology of the future in this field. To help the scientists use the equipment, the team has developed an automated process whereby they can create their own custom experiment profile.

OPTIMIZING BACTERIAL GENOMES

The Bacterial Genome Plasticity Unit, led by Didier Mazel, is investigating why the genomes of some bacterial species are divided into multiple chromosomes. The scientists have taken as their model the bacterium that causes cholera, *Vibrio cholerae*, which has become a paradigm for bacteria with multiple chromosomes. In 2012 they published a seminal article explaining how the splitting of the bacterial genome may confer selective advantages on *V. cholerae*, and unveiled some of the molecular mechanisms used for genome maintenance. To carry out their research, they extensively remodeled the genomic structure of *V. cholerae* to create mutants with variable genomic architecture, including a mutant with a single chromosome. It was already known that *V. cholerae* DNA relied on epigenetic modifications – inherited changes that are not determined by genes – for its growth. By analyzing these mutants, the scientists were able to clearly demonstrate that this epigenetic regulation takes place at the stage of chromosome duplication. They also demonstrated that the bacteria benefit when their genome is partitioned into small chromosomes as the impact of damage to their DNA is limited. By improving their understanding of how bacterial genomes are organized, the scientists will be able to identify optimal chromosome arrangements that could lead to new developments in synthetic biology.

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.

Immunology



Skin infection by *Leishmania major* (red). Although only some cells (shown in green) are able to activate an immune response against the parasite, the defense mechanism can be triggered remotely in all the cells (blue).

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. 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"), supported by the French government's program for Investment in the Future, initiated in 2012 and lasting for eight years. The Milieu intérieur consortium will carry out pioneering work on the human immune system. In 2012, it led the recruitment of a cohort of 1,000 healthy donors, which will help the team establish the natural variability in immune responsiveness, and identify the genetic and environmental determinants of a healthy immune system.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

THE BIRTH OF OUR BLOOD CELLS

Adult blood cells are produced by hematopoietic stem cells (HSCs) in the bone marrow. But new HSCs that are born during embryo development have to undergo various stages of maturation before they are able to form the body's different blood cells. In 2012, Ana Cumano's team in the Lymphopoiesis Unit showed that this maturation process involves the expression of small surface proteins, known as histocompatibility antigens. These proteins exist in all adult cells, but not in embryonic cells. Adult cells infected by viruses lose these surface antigens and are targeted by natural killers, cells in the immune system whose role is to eliminate any "naked" cells. In embryonic stem cell transplant patients, these same natural killer cells notice immature HSCs without histocompatibility antigens and eliminate them, jeopardizing the success of the therapy. This research has major implications for the use of embryonic stem cells or cells from embryonic tissue for cell therapy. It also sheds light on how adult stem cells are formed, providing information that can help improve protocols for *in vitro* HSC production and bone marrow transplant therapy.

13 RESEARCH UNITS

2 TECHNOLOGICAL PLATFORMS

REMOTELY CONTROLLING INFECTION

CD4 T-lymphocytes are cells in the immune system that have a vital role to play in combating many pathogens, particularly intracellular parasites. T-lymphocytes physically interact with infected cells, and where the two come into contact the T-lymphocytes produce molecules called cytokines. These molecules tell the infected cell to destroy the parasite-invaders. The Dynamics of Immune Responses Unit, led by Philippe Bousso, used innovative *in vivo* imaging approaches to investigate this mechanism, discovering that the cytokines produced by the CD4 T-lymphocyte not only act on the infected cell that has come into contact with the lymphocyte, but also on neighboring cells. The team measured the scope of action of this cytokine at around 100 micrometers. This means that CD4 T-lymphocytes can control an infection "remotely", even if they only interact with a small proportion of the infected cells. The results of this research shed new light on the immune response mechanisms that are employed to control intracellular pathogens.

FIBROSIS VS. WOUND HEALING: SCIENTISTS IDENTIFY "BAD" CELLS

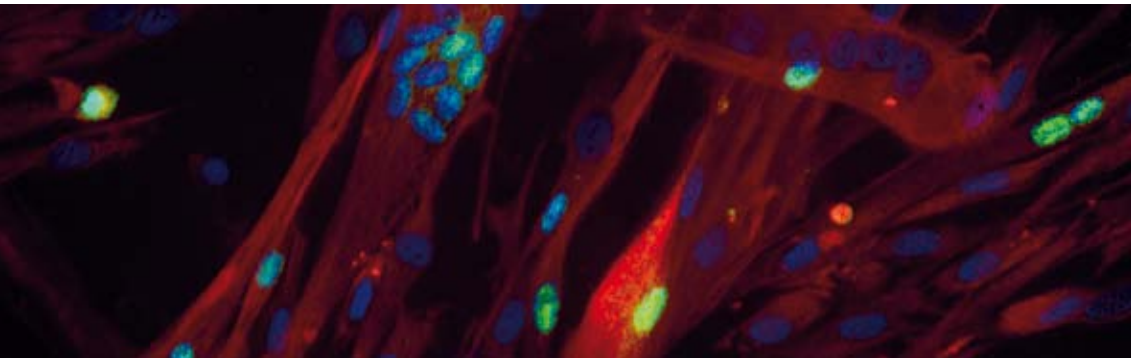
A team of scientists led by Lucie Peduto in the Lymphoid Tissue Development Unit recently addressed a subject that does not get much attention from immunologists at the Institut Pasteur: fibrosis. This pathological process results from excessive wound healing, and can be fatal when it affects vital organs. It is caused by the production of scar tissue, occurring when internal organs are subjected to repetitive trauma, infection or inflammation, ultimately preventing it from functioning properly. Little is known about the underlying mechanisms that govern the production of scar tissue, and developing treatments is a delicate task, requiring scientists to alter the action of scar-tissue-producing cells, fibroblasts, without affecting their vital role in wound healing. The unit's scientists discovered a population of fibroblasts that are directly responsible for the excessive production of scar tissue. They demonstrated that in skin and skeletal muscle that have been severely injured, over-productive fibroblasts are temporarily generated following the activation of progenitor cells found around vessels. Excessive production of scar tissue could be avoided by eliminating these cells. This discovery paves the way for new therapies for some fibrotic diseases, such as systemic sclerosis or liver fibrosis, which involve chronic activation of these "pathological" fibroblasts.

Exploring living beings, cell by cell

In 2012, the Immunology Department received new equipment that was of particular interest to the Institut Pasteur's scientists. The technology can generate gene expression data for an individual cell, opening up possibilities for investigating biological phenomena on a quantal scale. This new micro-fluidic PCR contains 96 wells for cells on one side, and 96 wells for reagents on the other, and with a series of micro-valves that can be opened to combine the two, it enables scientists to run up to 9,216 assays at once. This new technology offers a wide range of options including gene expression analysis, genotyping, digital PCR, and mutant detection. Several scientists from the Institut Pasteur's research departments have already begun using the new equipment.

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.

Infection and Epidemiology



A myotube (created from the merging of several stem cells) obtained *in vitro* from muscle stem cells taken 17 days after the patient's death.

The department's research looks at 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 through translational research. It is closely involved in public health, with research units in epidemiology and histopathology, nine National Reference Centers and three WHO Collaborating Centers, the Laboratory for Urgent Response to Biological Threats, and the Genotyping of Pathogens and Public Health Platform.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

STEM CELLS... POST MORTEM

In 2012, scientists from the Histopathology Unit led by Fabrice Chretien joined forces with the Stem Cells and Development Unit led by Shahrugim Tajbakhsh, demonstrating that the stem cells in some of our organs can survive for up to 17 days after we die. In a hostile environment, these cells can drastically reduce their metabolism and enter a dormant state. This process requires cellular organization to be stripped to the bare minimum, with very few mitochondria (the organisms that produce energy in cells) and very low stores of energy. These "dormant" stem cells still maintain their potential for cell division and can reactivate this function for organ/tissue repair or growth when conditions become more favorable again. They can also regain their ability to differentiate into fully functional adult cells. Stem cell transplants are already used to treat diseases such as leukemia, but this therapy is hampered by a lack of compatible cells and cell preservation difficulties. The scientists' discovery therefore represents a major breakthrough. These stem cells offer real hope for treating diseases that require a transplant and also raise the possibility that we might one day use them to repair a diseased heart or lung.

16 RESEARCH UNITS

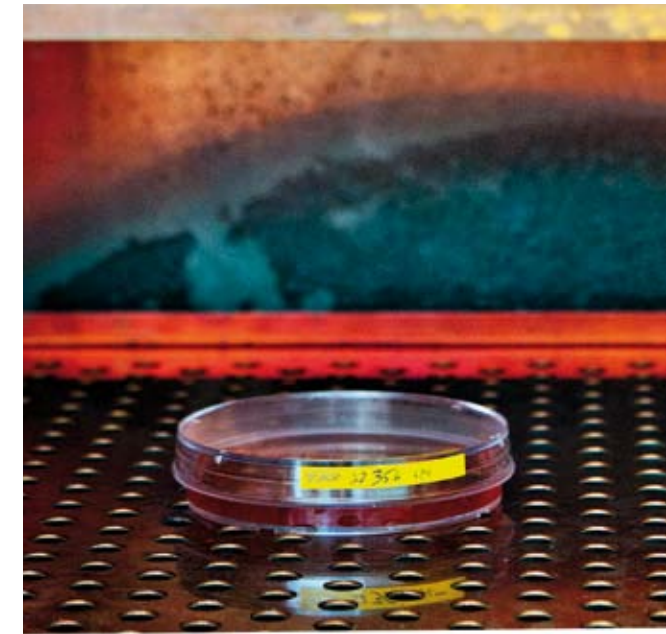
1 TECHNOLOGICAL PLATFORM

LYCHEE PICKING – A CAUSE OF MENINGOENCEPHALITIS?

Arnaud Fontanet and his team in the Epidemiology of Emerging Diseases Unit have been investigating childhood encephalitis epidemics in northern Vietnam for several years. In malnourished children in Asia, this disease can be very severe, with a mortality rate of around 25%. The causes of these epidemics, which strike at the beginning of the rainy season each year, were previously unknown. But in 2012, the unit's scientists published research demonstrating a strong correlation between the onset of epidemics and lychee picking in June and July. The most affected areas are those where lychee picking is most widespread. Moreover, in years when the fruit are harvested a few weeks late, the epidemics are delayed by the same time. The team is now looking into the theory of a virus that might spread more easily in hot and humid conditions, when lychee harvesting takes place. The lychee picking season brings together different groups of people, who live in close contact for several weeks, creating a breeding ground that appears to encourage the spread of the virus. Working with the teams led by Jean-Claude Manuguerra and Marc Eloit, the scientists are now focusing on identifying the virus responsible in order to determine suitable preventive measures and effective medication.

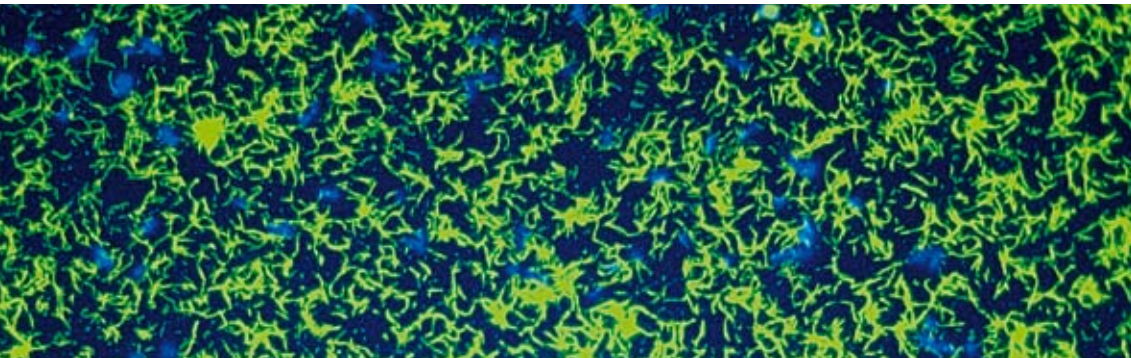
IMMUNE CELLS DIFFER BETWEEN TISSUES

The pioneering work of Ilya Mechnikov highlighted the importance of macrophages, cells in the immune system that help defend the body against infectious agents. These cells do not form a homogeneous population, and although immunologists recognize the existence of subpopulations, the primary influence on macrophage properties and functions comes from their immediate environment. Professor Jean-Marc Cavaillon and his team in the Cytokines and Inflammation Unit demonstrated this by investigating the macrophages in pulmonary alveoli. The scientists had already shown that, unlike others, these macrophages are unable to trigger the normal physiological mechanism to resolve inflammation during an infection – they can be constantly activated by microbial products and do not manage to moderate the process. The team has recently demonstrated that this property is a result of the specific immune environment in the lungs, which are rich in some cytokines (the immune system's messenger molecules) and B lymphocytes (antibody-producing white blood cells). These findings show that future therapeutic approaches, particularly for treating septicemia (widespread inflammation caused by an infection), will have to account for the specific behavior of cells in different tissues.



As well as causing infectious diseases, bacteria can also serve as tools to help us understand biological mechanisms. The Microbiology Department studies bacteria as both pathogenic agents and experimental models.

Microbiology



Immunofluorescence detection of *Escherichia coli* bacteria (in blue) and its surface structures ("hairs" or pili, shown in green) used to form biofilms.

The department's scientists study various microorganisms (bacteria and archaea) as model systems for fundamental research in areas such as genomics, genetics, and metabolism. They also focus on the mechanisms that enable some of these microorganisms to be virulent and escape destruction by the host immune system, and to develop resistance to antibiotics. This work can improve our understanding of how pathogens live and interact with the environment. Understanding the molecular mechanisms of virulence is essential for the development of new diagnostic tools and therapies – antibiotics and vaccines – to treat bacterial infections.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

A NEW GENE TRANSFER MECHANISM

Bacteria can incorporate mobile genetic sequences known as genomic islands into their chromosome, enabling them to resist certain antibiotics or acquire a virulence factor. But little is known about the mechanisms used to transfer these genomic islands between bacteria. The *Yersinia* research unit, led by Élisabeth Carniel, investigated this phenomenon in cooperation with Didier Mazel from the Bacterial Genome Plasticity Unit, using as their model the high-pathogenicity island of the *Yersinia pseudotuberculosis* bacterium, which causes severe septicemia in humans. The scientists demonstrated that this island was transferred spontaneously in virtually normal environmental conditions (low temperature and iron-deficient environment). As they were working to identify a mechanism specific to the island, they unexpectedly discovered a general, previously unknown genetic material transfer process. This process, which they named GDT4 (Generalized DNA Transfer at 4°C), uses a plasmid (a short DNA molecule separate from the bacterial chromosome) that can insert itself almost anywhere in the chromosome and direct transfer to other bacteria. The notable feature of GDT4 is that the plasmid does not use homologous sequences on the bacterial DNA to integrate into the chromosome; this makes it a more universal mechanism than others that have been described. This surprising discovery could offer scientists a novel gene transfer tool.

13 RESEARCH UNITS

A SECRETION MECHANISM INHERITED FROM A BACTERIOPHAGE

The *Clostridium difficile* bacterium is the leading cause of post-antibiotic nosocomial diarrhea. It secretes two toxins that account for its virulence. Although the factors regulating expression of the toxins had already been identified, the details of their secretion had remained a mystery for a long time. This is no longer the case thanks to the work of the Pathogenesis of Bacterial Anaerobes Laboratory led by Bruno Dupuy. The team recently demonstrated that *C. difficile* uses an original secretion mechanism, previously only observed in bacteriophages (bacterial viruses) to destroy its host bacteria. The bacteriophage produces a holin protein that is inserted into the membrane to form a channel, allowing a bacteriophage endolysin to be secreted. This enzyme destroys the bacteria and releases phage particles. *C. difficile* uses a similar mechanism to secrete its toxins. One of the genes of phage origin located on the bacterial chromosome near the toxin genes codes for a protein similar to a holin. This "cousin" is assembled in the membrane and allows the toxins to be secreted without killing the bacteria. Given the emergence of antibiotic-resistant *C. difficile* strains, the discovery of this secretion mechanism could pave the way for the development of therapeutic agents that block secretion of the bacterium's main virulence factors.

ANTIBIOTIC RESISTANCE: THE STRATEGY OF STAPHYLOCOCCUS AUREUS

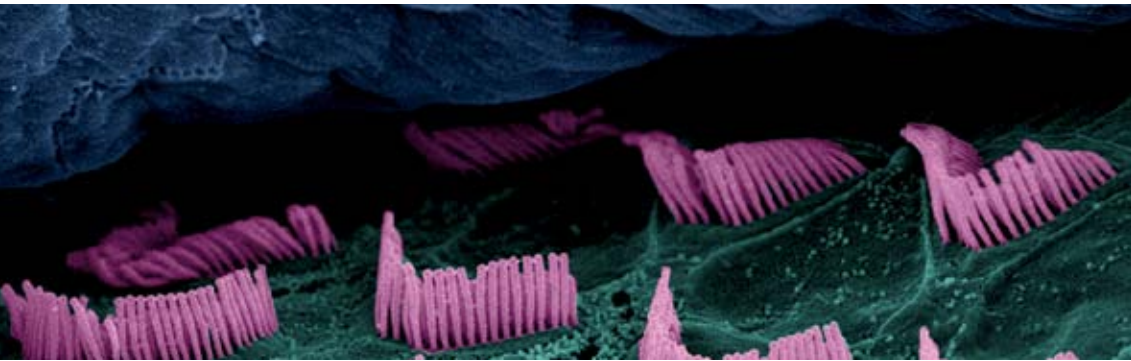
Staphylococcus aureus ("golden staph") is a highly pathogenic bacterium of major cause for concern in hospitals as it can lead to a wide range of infections, ranging from skin lesions (boils, paronychia, impetigo, etc.) to acute pneumonia or septicemia. The threat of this bacterium is compounded by the fact that some strains are developing multiple antibiotic resistance. The mechanisms used by staphylococcal bacteria to acquire resistant genes were previously unknown. But Tarek Msadek's team in the Biology of Gram-Positive Pathogens Unit made a major breakthrough in this field in 2012. The scientists identified a mechanism whereby *Staphylococcus aureus* uses specialized machinery to capture foreign DNA potentially carrying antibiotic-resistant genes in its environment. This process is linked to the activation of an *S. aureus* gene known as *sigH*, through two possible mechanisms identified by the team. After experimentally activating the *sigH* gene, the scientists transformed a non-methicillin-resistant *S. aureus* strain into a methicillin-resistant strain similar to those responsible for nosocomial infections. These findings suggest that inhibiting the *sigH* gene could be a promising approach towards preventing the occurrence of *S. aureus* strains with multiple antibiotic resistance.

Pasteur Vallery-Radot Prize

In 2012, Jean-Marc Ghigo, Head of the Genetics of Biofilms Unit, was awarded the Pasteur Vallery-Radot Prize. This annual prize, funded by the National Library of France from the legacy of Jacqueline Pasteur Vallery-Radot, the wife of Louis Pasteur's grandson, is awarded to Institut Pasteur scientists under the age of 50 in recognition of the quality of their research. Jean-Marc Ghigo and his team are investigating the life of bacteria in communities known as biofilms. Bacterial biofilms are generally beneficial but are also responsible for health problems, particularly in hospitals, where they can develop on medical instruments and cause multiple infections. The unit's work focuses on identifying the molecular mechanisms involved in the formation of biofilms and analyzing the biological properties of this original bacterial lifestyle.

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 significant medical breakthroughs.

Neuroscience



The inner ear in scanning electron microscopy. The auditory sensory cells with their ciliary tufts are shown in pink. They convert the sound wave into an electrical signal that can be processed by the brain.

“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.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

LEARNING AND MEMORY: THE ROLE OF NEO-NEURONS REVEALED

In 2003, the Perception and Memory Unit, led by Pierre-Marie Lledo, revealed the existence of new neurons formed in adult brains. This discovery debunked the established theory that the number of nerve cells was fixed at birth and any loss was irreplaceable. But the function of these new neurons remained a mystery. By adopting an experimental approach combining genetics and optical techniques (optogenetics) to stimulate neo-neurons in mice by a brief flash of light, the very same scientists recently demonstrated the role played by these cells in learning and memorizing complex tasks. The mouse models were able to memorize information more quickly and to remember exercises up to 50 days after experiment completion. By contrast, the neo-neurons generated just after birth did not offer any advantage for learning or memory. This emphasizes the importance of neo-neurons produced by the adult brain for cognitive and behavioral processes. The research illustrates how the brain can adapt to new sensory and intellectual stimulation throughout an individual’s lifetime. It also demonstrates that the constant acquisition of neo-neurons helps individuals distinguish between two recent memories. More generally, this research opens up promising possibilities for new therapeutic protocols to combat the development of neurological and psychiatric disorders.

7 RESEARCH UNITS

AUTISM: SPOTLIGHT ON INTERNEURONAL COMMUNICATION

Autism was the focus of a major national campaign in France in 2012. We still know relatively little about the syndrome and what causes it. The Human Genetics and Cognitive Functions Unit led by Thomas Bourgeron has been investigating the genetic causes of autism spectrum disorders for many years. The unit’s scientists recently demonstrated that genetic mutations affecting a gene known as SHANK2 appear to be directly involved in the disease. SHANK2 produces a protein located in the synapses, the contact points between neurons that allow them to communicate with each other. Mutations in this gene can reduce the number of synapses, impairing communication between nerve cells. This confirms the neurobiological basis of autism spectrum disorders. The same team also developed a neurobiological and behavioral characterization of a SHANK2-mutant mouse. This mouse model provided *in vivo* confirmation of the drop in the number of synapses and enabled the team to pinpoint specific anomalies in some regions of the brain. The mutant mice did not present any major physical problems or memory impairment but were hyperactive and anxious and had difficulties interacting socially. The development of animal models is a major step forward in understanding the many causes of autism, and paves the way for new treatments.

OBSERVING THE INTRICACIES OF NERVE IMPULSES

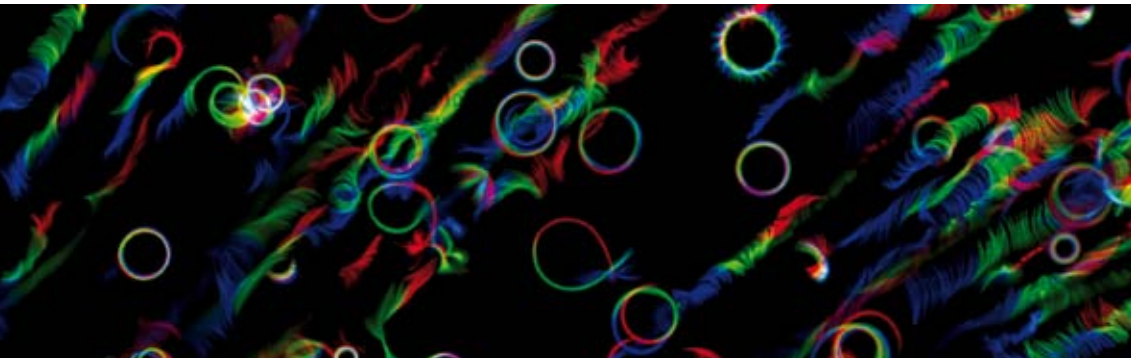
The human brain is a highly complex network of billions of nerve cells that are interlinked by trillions of connections. Each neuron sends nerve impulses to the other cells along what is known as an axon, a long projection extending from the neuron’s cell body. The axon is connected to other neurons via dendrites, slender protrusions that form an area of exchange known as the synapse. Each neuron can form more than a thousand synapses with its surrounding neurons. The work of the Dynamic Neuronal Imaging Unit, led by David DiGregorio, focuses on decrypting the communication that goes on in this complex system. The scientists use a novel approach involving electrophysiology and optical techniques to monitor the transmission of nerve impulses at the scale of a single synapse. They recently demonstrated the unique behavior of neurons in the cerebellum, which is involved in motor function. Unlike the brain’s other neurons, these cells are more highly stimulated when they receive impulses that are dissociated in time and space, from dendrites spaced far apart from each other. The scientists believe that this surprising process could allow the brain to fine-tune cerebellum activation and control movement precision.

2012 Brain Prize

In 2012, Prof. Christine Petit won the prestigious Brain Prize, awarded by the Grete Lundbeck European Brain Research Foundation in Denmark. This 1 million euro prize, shared with Karen Steel from the Wellcome Trust Sanger Institute, recognizes Prof. Petit’s seminal work on hereditary deafness that has led to the identification of the genes involved, elucidation of defective mechanisms, and discovery of new properties of the auditory sensory organ. This research has made a major contribution to our understanding of the different types of deafness, helping in the prescription of auditory and conventional prostheses and cochlear implants. Christine Petit is a professor at the Institut Pasteur and the Collège de France and holder of the genetics and cell physiology chair. At the Institut Pasteur she leads a joint Institut Pasteur–Inserm–Pierre-et-Marie Curie University unit.

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

Parasitology and Mycology



Circular movement of *Plasmodium*, the malaria parasite, on a glass slide.

The department studies three key eukaryotic parasites responsible for severe diseases of major health and economic burden in developing countries: *Plasmodium* species, which cause malaria; *Leishmania* species, the leishmaniasis agents; and *Trypanosoma brucei*, responsible for sleeping sickness. The *Anopheles* mosquito – the *Plasmodium* vector – is also studied. Mycology research focuses on *Aspergillus fumigatus*, responsible for mycoses which can be fatal in immunodeficient patients, and *Cryptococcus neoformans*, which causes severe respiratory infections. The department combines fundamental research on *in vitro* and *in vivo* models, 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 nature of parasitism and transmission by vectors, clarify host invasion mechanisms, and determine the virulence factors, pathology, and survival strategies of these organisms.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

PARAFRAP: A NETWORK TO FIGHT PARASITIC DISEASES

Major parasitic infections such as malaria, sleeping sickness, leishmaniasis and amoebiasis cause millions of deaths worldwide each year. The ParaFrap project (the French alliance against parasitic diseases) was officially launched in October 2012 as part of the French national “Laboratories of Excellence” research network. The alliance involves 14 internationally renowned French scientific institutes, two private biotechnology firms, and various partner research groups from endemic regions. Its aim is to unify and structure research efforts in parasitic diseases. ParaFrap’s scientific director Artur Scherf, who heads the Biology of Host-Parasite Interactions Unit at the Institut Pasteur, together with his deputy directors Stanislas Tomavo (University of Lille Nord de France–CNRS) and Frédéric Bringaud (University of Bordeaux–CNRS), launched the consortium with the research and higher education cluster at the University of Lille Nord de France, which is piloting the project. The aim of ParaFrap is to develop long-term inter-institutional and scientific links through joint research and training programs and technical platforms to pool expertise. Existing partnerships with pharmaceutical companies will be maintained and extended to other research sectors concerned by ParaFrap.

8 RESEARCH UNITS

1 CENTER FOR THE PRODUCTION AND INFECTION OF ANOPHELES (CEPIA)

FOUR YEARS TO DEVELOP A NEW ANTIMALARIAL VACCINE CANDIDATE

With 220 million cases worldwide each year, malaria is a major public health concern, despite high-profile campaigns promoted by WHO to control the disease. One of the major obstacles in the fight against malaria is the fact that *Plasmodium* parasites are acquiring resistance to the drugs currently available. It is becoming vital to develop new molecules that can be used in future treatments in order to avoid a therapeutic deadlock. This is the goal of the MaPI project, coordinated by Jean-Christophe Barale from the Parasite Molecular Immunology Unit. The project was launched in 2012 and is based on validating two new therapeutic targets, the proteins SUB1 and SUB2, which are used by parasites to enter and exit liver and red blood cells in humans. The aim is to identify and optimize a new antiparasitic molecule within the next four years that can block the action of SUB1 and SUB2. MaPI is funded by the French National Research Agency and involves several teams from the Institut Pasteur in Paris and Cambodia, and an industrial partner, Sanofi. The scientists will adopt an integrated, multidisciplinary approach, including iterative cycles of synthesis and biological evaluation of new chemical compounds both *in vitro* and in animal models. The chemical compounds will then undergo compliance testing to ensure they are safe for humans, and testing on multi-resistance “field” parasites from patients in Cambodia. Clinical trials will then be started on the most promising antimalarial candidates.

A HIGHLY VIRULENT SUGAR

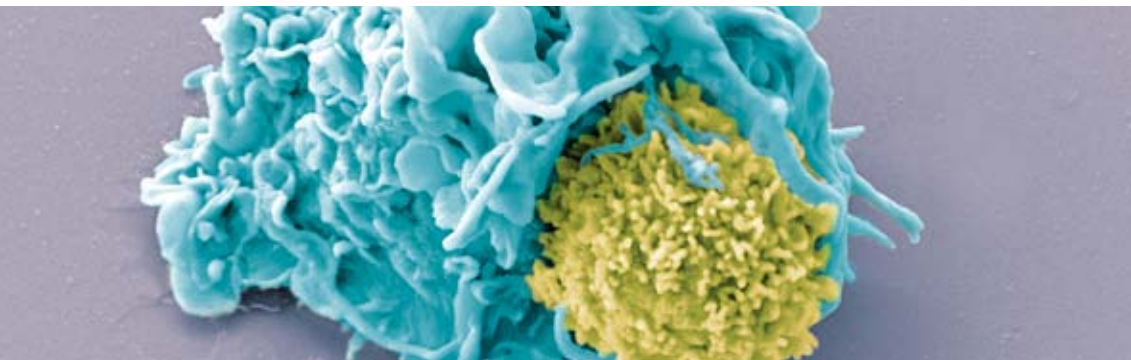
Aspergillus fumigatus is a naturally occurring fungus that can cause often fatal respiratory infections in humans. Jean-Paul Latgé and his team from the *Aspergillus* Unit are focusing on one of the key stages in the fungus’ development, the synthesis of its cell wall. Working in cooperation with teams from the University of Perugia (Italy) and Radboud University Nijmegen (Netherlands), the scientists recently found that one of the components of this cell wall acts as a powerful virulence factor. This complex sugar molecule, or polysaccharide, prevents the immune system from functioning properly. In 2012, the scientists developed a precise description of how this sugar works. They observed that the polysaccharide inhibits the action of interleukin-1 (IL-1), a molecule that normally activates the immune system during an infection. It triggers the synthesis of a protein that can replace IL-1 on its receptor, IL1-RA, blocking the signal to recruit cells involved in the body’s defense. It acts in a remarkably similar way to the drug anakinra, used to treat several autoimmune diseases. The scientists are now working to identify the virulence determinants of the polysaccharide, with the aim of screening chemical compounds that can inhibit its action.

Award

Each year, the French Foundation for Medical Research grants 14 science awards in recognition of groundbreaking research in the major fields of biomedical research. In 2012, Odile Mercereau-Pujalon, Chair of the Parasitology and Mycology Department, won the Jacques-Piraud Award for infectious diseases. She heads the Parasite Molecular Immunology Unit, where her research focuses on the malaria parasite. Her three main lines of investigation are the mechanisms involved in the emergence of drug resistance; the molecular basis of rosetting, a virulence factor responsible for severe forms of malaria in African children; and the development of much-needed innovative drug candidates.

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.

Virology



Contact between a lymphocyte, in yellow, and an antigen-presenting dendritic cell, in blue.

The department's 21 units focus their research on viruses, examining molecular organization, mechanisms for proliferation within the cell, interactions with their host and the immune system, and pathogenicity determinants. The department's scientists focus on viruses that cause severe diseases: cancer, such as papillomaviruses and the hepatitis B and C viruses; retroviruses such as HIV, the AIDS virus; the HTLV virus, which causes leukemia; respiratory viruses such as influenza; and insect-borne arboviruses that are responsible for diseases such as dengue ("tropical flu"), yellow fever, Rift Valley fever and chikungunya. To improve their understanding of the infection mechanisms of these viruses and their modes of propagation in organisms, virologists are developing a number of partnerships within the Institut Pasteur and with 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.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

THE IMPORTANCE OF BEING (RELATIVELY) FAITHFUL

Viruses multiply by reproducing their genetic code, which is usually carried by an RNA molecule. RNA polymerase, a large protein complex, has the task of "photocopying" this RNA, but it can make mistakes, and these can be passed on to descendants. The scientists in the Viral Populations and Pathogenesis Unit, led by Marco Vignuzzi, are focusing on these mechanisms. They had previously produced mutant viruses with "hyperfaithful" RNA polymerase, which made fewer mistakes than non-mutant viruses when duplicating RNA. But the scientists observed that this higher fidelity did not confer an advantage on the viruses; instead, it actually prevented them from adapting to their environmental conditions, weakening their virulence and making them less able to infect their host. In 2012, the team continued its work in collaboration with American crystallographers; this time they generated "hypermutant" viruses whose RNA polymerase made more mistakes when copying the RNA. But once again, these mutations didn't benefit the viruses – they developed serious mutations, which ultimately impaired their viability. The level of fidelity of RNA polymerase therefore appears to result from a long-standing optimization process. Varying this fidelity could enable scientists to weaken viruses, for example as part of a vaccine strategy.

21 RESEARCH UNITS

DENGUE ANTIBODY SHOWS PROMISE

The dengue virus has four forms, known as serotypes, each of which has its own specific properties. If an individual is protected against just one of these serotypes, there is a higher risk of infection by the other three, and a greater chance of developing severe, even fatal forms of the disease. Vaccine strategies to prevent dengue must therefore target all four viral serotypes. Félix Rey's team in the Structural Virology Unit joined forces with the Molecular Prevention and Therapy of Human Diseases Unit to provide the first characterization of an antibody capable of neutralizing all four serotypes of the dengue virus at once in mice. By using high-resolution crystallography to perform comparative analyses, the scientists visualized the way the antibody binds to the virus on the specific recognition sites of each serotype. This antibody recognizes the virus surface protein, although its binding affinity and neutralizing effect vary depending on the serotype. In all four cases, the antibody triggers the same inactivation mechanism by binding to the surface protein, irreversibly disrupting the architecture of the virus and rendering it permanently harmless. This is a major breakthrough in the development of an effective vaccine that could offer prevention against all forms of dengue.

A GLOBAL SCIENTIFIC STRATEGY: "TOWARDS AN AIDS CURE"

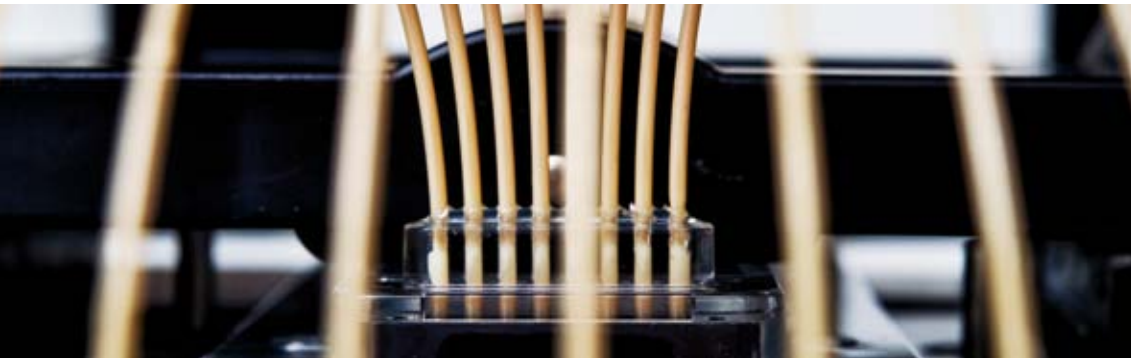
Since HIV was discovered at the Institut Pasteur thirty years ago, research efforts have led to remarkable progress in preventing and treating infection. But a cure for AIDS remains elusive. Recent advances in research have raised new hopes, with the development of therapeutic approaches which, at the least, enable patients to control the virus without the need for treatment. The International AIDS Society (IAS) has launched the global initiative "Towards an AIDS Cure", led by Prof. Françoise Barré-Sinoussi, Head of the Regulation of Retroviral Infections Unit and laureate of the Nobel Prize in Medicine in 2008. The initiative aims to coordinate and speed up AIDS research. July 2012 saw a major milestone with the publication of a scientific strategy by a group of around thirty of the world's leading researchers. This strategy sets out seven integrated research priorities, involving both fundamental and clinical research, in a bid to tackle the problem of HIV persistence in patients on antiretroviral therapy. Working groups are now being set up to promote partnerships between pharmaceutical companies in relation with public research and to investigate ethical questions, the cost-efficacy ratio, and patients' perceptions of potential future strategies.

Viruses and cancer

Prof. Antoine Gessain, Head of the Oncogenic Virus Epidemiology and Pathophysiology Unit, was awarded the 2012 René et Andrée Duquesne Prize. Antoine Gessain's research focuses on viruses that cause cancer and related diseases. His team works on HTLV-1, a human oncogenic retrovirus that causes severe leukemia and tropical spastic paraparesis, a chronic neurological disease. It is also investigating HTLV-3, a new human retrovirus that it discovered, as well as human herpesvirus type 8 and emerging viruses. Much of this research is carried out in close cooperation with the institutes in the Institut Pasteur International Network.

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.

Technological platforms



GENOPOLE

When it comes to microorganisms, humans, or anything in between, high-throughput sequencing has revolutionized the analysis of genetic information. Its capacity for large-scale sequencing of microbial genomes provides data for population genomics studies, sheds light on evolution, and enables epidemiological monitoring of pathogenic strains. Applications include characterizing microorganisms in a single step to identify virulence factors and antibiotic resistance, and revealing the dynamics and 3D structure of genomes. Metagenomic and metatranscriptomic data mining paves the way for the discovery of new pathogens, particularly viruses, and can help prevent their emergence. 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 transcriptional analysis combining sequencing and DNA microarrays has improved our understanding of how organisms function in a normal or pathological state. It also enables scientists to address fundamental questions in microbiology and in the field of genetic and epigenetic programming during embryo development, throughout the cancer process, and during stem cell differentiation. Another 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 post-genomic data.

At the Genopole, 33 scientists, engineers and technicians with a wide variety of skills are involved in fundamental research and public

health projects. All five Genopole platforms have received official accreditation from the GIS IBISA* and are partners of France Génomique, the national biology and healthcare infrastructure.

PROTEOPOLE

Pasteur-Proteopole, which received official IBISA accreditation as a national platform in 2008, focuses its outstanding technological and methodological skills on the analysis of macromolecules, and more specifically, proteins. Its wide-ranging areas of expertise include:

- protein production in microorganisms (prokaryotes/eukaryotes) and in insect and mammal 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: spectroscopy and hydrodynamics, surface plasmon resonance, and microcalorimetry;
- structural characterization at the atomic level, particularly using X-ray crystallography.

By leveraging synergies between different methods of analysis, Pasteur-Proteopole can provide research teams with answers to vital questions and also pinpoint new areas for analysis. Since late 2012, it has been divided into five platforms (Recombinant Proteins, Antibody Engineering, Proteomics, Biophysics of Macromolecules and their Interactions, and Crystallography and X-Ray Diffraction), with 32 scientists providing a wide range of services. They are closely

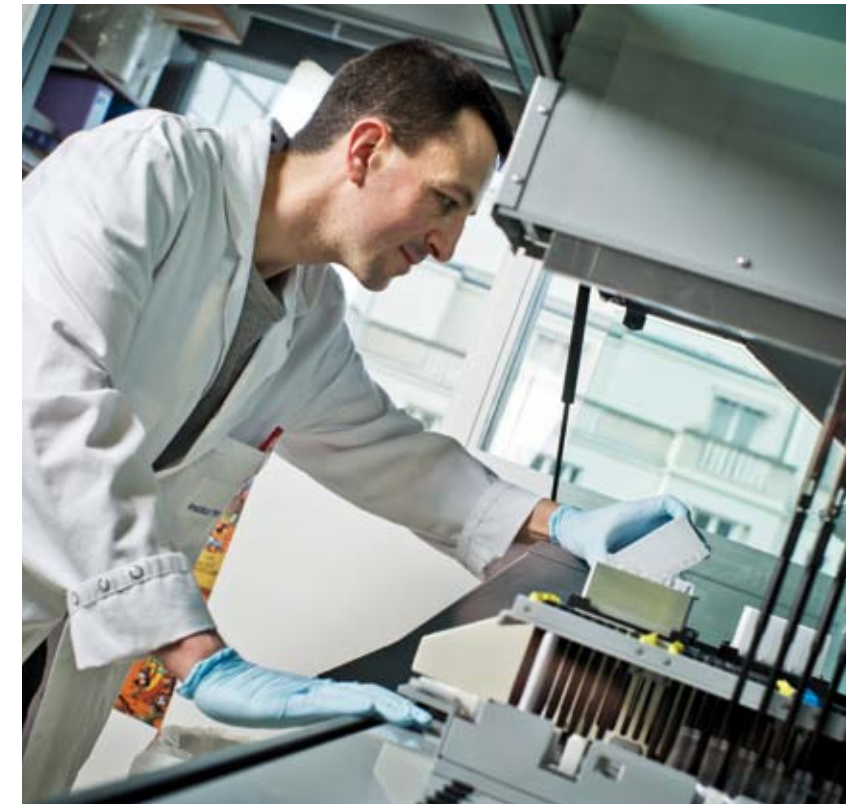
*Scientific Interest Group for Biology, Healthcare, and Agronomy Infrastructures.

In 2012, the Dynamic Imaging and Ultrastructural Microscopy Platforms moved into their new premises in the François Jacob building.

involved in a number of biological and methodological research projects in cooperation with Institut Pasteur units and other French or foreign institutions, particularly in the field of structural biology of infectious diseases.

IMAGOPOLE

The focus of the Imagopole's work is to study infectious, systemic and tumoral diseases, at both molecular and functional levels. It has 35 engineers and is divided into four technological platforms: Dynamic Imaging, Ultrastructural Microscopy, Flow Cytometry, and the Center for Human Immunology. Some 500 scientists from the Institut Pasteur and other research institutions spend almost 40,000 hours using the Imagopole's 40 imaging systems each year. In 2012, the Dynamic



Imaging and Ultrastructural Microscopy Platforms moved into their new premises in the François Jacob building. The Imagopole is IBISA accredited and has ISO 9001 certification.

INFECTION IMAGING

The Imagopole develops and offers methods for research into host-pathogen interactions at molecular and cellular level, as well as in tissues and even entire organisms. Mathematics, bioinformatics, and statistics are used to analyze data.

DEVELOPMENT

The Imagopole is currently leading two major projects. The aim of the first project, which received Carnot-Fraunhofer funding, is to develop a new technique combining optics and genetics – optogenetics – that will enable scientists to stimulate a single target cell in dense tissue. The second project, Fuel, focuses on optimizing optical techniques used to detect infection. It involves amplifying the fluorescent signal emitted by bacteria by transferring the light signal to nanoparticles. This project is funded by the Pasteur Infectious Diseases Carnot Institute.

MOUSE GENETICS ENGINEERING CENTER

The discovery of new genes and genetic sequences opens up the possibility of generating transgenic mice to research biological functions and provide *in vivo* confirmation of expression profiles and genetic



regulatory mechanisms. Each year, the Mouse Genetics Engineering Center (CIGM) creates several mice lines that have been genetically modified using “traditional” and “targeted” transgenesis techniques. “Traditional” transgenesis involves microinjecting transgenes into mouse embryos for integration into the mouse genome. Genetic modification via “targeted” transgenesis focuses on homologous recombination in embryonic stem cells (ES cells). It enables precise manipulation of the mouse genome, thus providing a large number of mutant mice in which genes of interest have either been inactivated (KO mice) or inserted into the genome (KI mice). In 2012, CIGM performed the first microinjections of RNA from zinc finger nucleases (in rats) and Talen nucleases (in mice). This new method can be used to generate KO/KI animals without needing to use ES cells. The four members of the CIGM team have complementary and 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). The platform is involved in fundamental and applied research projects conducted by various Institut Pasteur units as well as other research institutions in France and worldwide.

CENTRAL ANIMAL FACILITY

The use of animal models remains a necessity for the Institut Pasteur’s research programs. The Central Animal Facility houses almost all the resources deployed for work on rodents. It also handles technical operations such as cryopreservation and the decontamination of

strains, development of genetically modified strains, and the production of mice strains with defined microbial flora. The new animal facility in the François Jacob building became operational in November 2012. It features state-of-the-art, sophisticated equipment (including an automated washroom) as well as a large high health status breeding and testing area for rodents. This new facility increases the Institut Pasteur’s capacity for rodents infected with biological agents, which are used to research the diseases they cause. The next stage will be the renovation of one of the old animal facilities and the closure of several others in an effort to rationalize resources and improve quality of service. In accordance with new regulatory requirements, all animal protocols are now examined by the Institut Pasteur Committee for Ethics in Animal Experimentation (CETEA).

CEPIA

The activities and organizational set-up of the Center for the Production and Infection of Anopheles (CEPIA) are geared to research interactions of the *Plasmodium* parasite, the malaria agent, with its mammalian hosts (mice or cell lines) and insect hosts (mosquitoes of the *Anopheles* genus). The platform mass-produces two species of *Anopheles*: *A. gambiae*, the African vector, and *A. stephensi*, the Asian vector. CEPIA also produces gametocyte-stage cultures of the human parasite *P. falciparum* and experimentally infects *A. gambiae* with these *P. falciparum* gametocytes. *A. stephensi* mosquitoes are mainly used to analyze the early stages of development of *P. berghei* and

P. yoelii following an infectious bite in rodent models. *Anopheles-Plasmodium*-vertebrate host interactions are studied using a wide range of equipment, insectaries, and a biosafety laboratory. Funding from the Greater Paris region (in connection with the “DIM Malinf” research area for infectious diseases) has enabled CEPIA to strengthen its logistics capabilities for research into the mosquito stages of *P. falciparum*. In 2012, major work was launched to bring CEPIA’s facilities into compliance, with the aim of optimizing the platform’s infrastructures and operation and improving the procedures for *Anopheles* production and infection. This work is part of a quality procedure that has also led to CEPIA securing ISO 9001 certification.

CLINICAL INVESTIGATION AND ACCESS TO BIOLOGICAL RESOURCES PLATFORM

The clinical investigation and biobanking platform ICAReB pursued its three major missions in 2012:

- to provide the Institut Pasteur teams with bioresources (human biological samples) in full compliance with the ethical and regulatory framework that governs biobanking;
 - to carry out research on bioresources by analyzing the freeze quality of the material stored;
 - to develop its partnerships, particularly with the WHO, in order to improve diagnosis of African trypanosomiasis (sleeping sickness).
- The platform built up a biobank of 47,000 samples from 2,000 donors. Other partnerships were set up with hospitals to investigate listeriosis and hidradenitis suppurativa and to identify the microor-



As observatories for communicable diseases, the National Reference Centers (CNRs) and WHO Collaborating Centers (WHOCCs) under the responsibility of the Institut Pasteur play an important role in its public health activities.

National Reference Centers and WHO Collaborating Centers



National Reference Centers (CNRs) are expert laboratories that serve as microbiological observatories for communicable diseases throughout France. They are closely involved in the fight against infectious diseases, and offer support to health authorities in diagnosis, epidemiological monitoring, and research on communicable infectious diseases. Seven of the 15 CNRs hosted by the Institut Pasteur are also WHO Collaborating Centers (WHOCCs), and one CNR/WHOCC has been designated as a reference laboratory for the World Organization for Animal Health. At the Institut Pasteur, each CNR is part of a research unit, enabling it to draw on the scientific environment of its host and the various support structures such as the Genotyping of Pathogens and Public Health Platform and the Laboratory for Urgent Response to Biological Threats (CIBU).

PAPILLOMAVIRUS AND CERVICAL CANCER

In 2012, the National Reference Center for Human Papillomaviruses (HPV) analyzed and published the data from the external quality control exercise. This was achieved in partnership with the French Agency for the Safety of Medicines and Health Products (ANSM), with the aim of assessing the capability of microbiology and anatomic pathology laboratories to detect different DNA concentrations of HPV 16 and

HPV 18, the main papillomaviruses that cause cervical cancer. One of the CNR's tasks is to measure the impact of vaccination against HPV 6/11/16/18 (the Gardasil vaccine). In connection with this research, it completed its genotyping study of HPVs in Pap smears in non-vaccinated women undergoing cervical cancer screening. Data on prevalence and viral ecology are currently being analyzed. The HPV CNR is also involved in the DyPAVIR study, designed to estimate HPV prevalence and distribution in 5,000 female students and to characterize infection dynamics over a three-year period in 1,000 of these students. The CNR is also involved in various research projects to analyze the immune response to the Gardasil vaccine and/or the prevalence of HPV in girls and in men having intercourse with men and undergoing HIV treatment, and to identify the etiology of precancerous lesions and oral cancer in non-drinkers and non-smokers.

HANTAVIRUSES

The National Reference Center for Hantaviruses was approached in connection with the global alert issued by US health authorities in late August 2012 after visitors to Yosemite National Park were infected by the Sin Nombre hantavirus. The CNR received samples from 68

patients with suspected infection by this hantavirus, but no cases of recent infection were detected.

In the endemic zone for the Puumala hantavirus (the north-eastern quarter of France), 2012 saw high circulation of the virus, with 168 cases of recent infection detected by the CNR. On average over the past ten years, there have been around a hundred cases a year. The most recent periods of high activity were in 2005 and 2010.

FRENCH GUIANA AND ANTILLES

The Virology Laboratory at the Institut Pasteur in French Guiana, in association with the CNRs for Arboviruses, Influenza Viruses and Hantaviruses, is involved in epidemiological surveillance for these viruses in the Antilles-French Guiana region and in monitoring circulating viruses. The year 2012 saw the co-circulation of three dengue serotypes (1, 2, and 4), with a predominance of serotype 2 in French Guiana (89%) and serotype 4 in the Antilles (75%). Influenza viruses circulated throughout the entire year in the Antilles-French Guiana region. The Hantavirus CNR in French Guiana did not diagnose or document any cases of human infection. In cooperation with the Virus-Host Interaction Laboratory at the Institut Pasteur in French Guiana, the Virology Laboratory also fully sequenced the hantavirus identified in French Guiana, named the Maripa virus. This research demonstrated that the virus is phylogenetically close to the Rio Mamore virus that was isolated in Bolivia.

INVASIVE MYCOSIS

In spring 2012, the French Institute for Public Health Surveillance (InVS) and the CNR for Invasive Mycoses and Antifungals were notified of grouped cases of severe infections (with an overall mortality rate of 80%) in hematology departments, caused by a rare fungal species. The CNR rapidly identified the pathogen responsible, *Saprochaete clavata*. A national alert issued by the InVS in association with the CNR showed an epidemic peak of 15 cases, mostly in severely immunodeficient patients. Since the *S. clavata* genome was not yet known, the Genotyping of Pathogens and Public Health Platform fully sequenced the 17 clinical strains isolated during or prior to the epidemic peak. This novel approach enabled the scientists to develop rapid genotyping tests and demonstrate the existence of a clone that was responsible for the epidemic. At the same time, the InVS focused on determining the potential source of the infection. This episode is a successful example of multidisciplinary collaboration between a CNR, a genomics platform, and the InVS; this joint effort enabled vital information to be contributed to the urgent investigation of this severe case of invasive fungal infection.



New terms

The year 2012 saw the start of the new five-yearly term for National Reference Centers (2012–2016), under the aegis of the French Institute for Public Health Surveillance (InVS) and the French Ministry of Health. The Institut Pasteur is responsible for 15 of the 47 research areas selected by the health authorities. Two research units at the Institut Pasteur in French Guiana also host four laboratories associated with the CNRs in mainland France (by ministerial decree of December 30, 2012).

Accreditation

In 2012, the Institut Pasteur officially launched the accreditation process for CNRs under ISO 15189. This initiative is part of ongoing efforts since 1999 to implement the provisions of the Good Laboratory Practices Guide (GBEA). The aim is to achieve the highest level of reliability required by health authorities for these expert reference laboratories to carry out their tasks, particularly in the area of microbiological diagnosis in human health.

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

Clinical research



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 PROMOTER

In promoting research on humans, the Institut Pasteur helps bridge the gap between the fundamental research carried out in its units and clinical research. The role of the Clinical Research Department is to represent the Institut Pasteur as a promoter. Since 2009, the department has overseen 186 projects. In 2012, the Clinical Research Committee examined the regulatory, legal, and ethical compliance of 46 new clinical research projects on humans or healthcare products. Twenty-four percent of these projects involved the Institut Pasteur International Network. The Institut Pasteur was the promoter/legal sponsor for 63% of these projects. This growing role as institutional promoter demonstrates the Institut Pasteur's strategy to commit to translational and clinical research and to accept the responsibilities that come with this type of research as regards the human subjects involved.

DEVELOPING INNOVATIVE THERAPIES: FROM PRECLINICAL TO CLINICAL TRIALS

The year 2012 also saw significant progress made on several major projects led by the Clinical Research Department:

- Sanfilippo B gene therapy: the start of regulatory preclinical trials (production of the first technical batch, toxicology study in animals).

- RMV-HIV: completion of the phase I clinical trial of an HIV vaccine candidate; the results are currently being analyzed.
- MAG-Tn3: development of the final formulation of the breast cancer vaccine candidate; regulatory toxicology study carried out.

The Clinical Research Department is also involved in two anti-infective therapy projects funded by the European Union (FP7): the STOPENTERICS project against shigellosis, with a forthcoming clinical trial promoted by the Institut Pasteur, and the ANTIFLU project against influenza (preclinical activities coordinated by the Clinical Research Department).

TRAINING... AND INFORMING

For the fourth year running, the "Research on Human Beings and Applied Ethics" program trained scientists in the regulations for research on humans. Targeted educational initiatives were implemented to train PhD students and scientists in ethics.

The third season of Clinical Research Department Workshops met with great success. This new series of six twice-monthly training and information sessions is designed to give scientists a better grasp of the regulations behind the development of clinical research protocols and to meet the growing demands that govern the submission of publications and access to national and international funding.



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, rabies treatment and allergies.

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, and dermatology, with a particular focus on hidradenitis suppurativa. Some of these diseases are monitored in collaboration with Necker University Hospital.

Noteworthy, the Institut Pasteur Medical Center provides the greatest number of allergy consultations for adults in France. It also administers treatment for the largest national hereditary angioedema cohort.

In addition, the Medical Center carries out clinical research directly related to its medical focus areas: cohorts and therapeutic trials on HIV infection; the pathophysiology of hidradenitis suppurativa (in

80,594 VACCINES ADMINISTERED

2,129 CONSULTATIONS FOR RABIES

7,201 CONSULTATIONS FOR ALLERGIES

51,400 VISITS TO THE INTERNATIONAL VACCINE CENTER

collaboration with Necker Hospital and the ICReB Platform); vaccinology (interaction between yellow fever and measles vaccines in children); the epidemiology of bacterial resistance in travelers returning from abroad and the pathophysiology of post-infectious anosmia.



Research applications

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

With 48 invention disclosures submitted in 2012, the Institut Pasteur has maintained a high level of innovation by national and international standards. Following on from its successful project proposals submitted under the French government's Investing in the Future program in 2011, a major aim for 2012 was the implementation phase of these new business development opportunities. Efforts also focused on extending and defending the Institut Pasteur's intellectual property rights, with one important patent being extended up to 2029. Finally, research partnerships have continued to develop, increasing fourfold in the past three years. Overall, business development activities in 2012 generated proceeds in the region of €46 million.

ENCOURAGING INNOVATION

In 2012, the teams from the Research Applications and Industrial Relations Department met practically all the directors of the Institut

48	INVENTION DISCLOSURES
19	PRIORITY PATENT APPLICATIONS
13	LICENSE AGREEMENTS
40	RESEARCH PARTNERSHIP AGREEMENTS

Pasteur's research units, with the aim of generating more invention disclosures. By the end of the year, around 40 potential invention disclosures had been identified.

BRINGING PROJECTS TO MATURITY

The Institut Pasteur continued its ongoing efforts to bring projects to maturity. Some 20 projects were targeted in 2012 in order to enhance their value and appeal for future industry partners.

REALIZING BUSINESS DEVELOPMENT POTENTIAL

Various new business development facilities and support structures were set up:

- 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), will pool resources to identify business development synergies and improve the licensing potential of Institut Pasteur technologies.
- The Global Care consortium of Carnot Human Health Institutes will promote the Institut Pasteur's business development at international level to encourage partnerships with foreign stakeholders.
- The strategic business development program for vaccines will coordinate efforts to bring projects to maturity in this field in France.
- Bioaster, the Technology Research Institute specializing in infectiology and microbiology.

CONSOLIDATING THE PATENT PORTFOLIO

Some of the Institut Pasteur's patents were extended or consolidated. A patent for the HIV-1 AIDS virus was granted a continuation by the United States Patent and Trademark Office up to 2029. Other patent groups were strengthened both in the US and Europe, for example the "DNA Flap" portfolio, relating to a key technology to improve gene insertion and expression.

DEFENDING THE INSTITUT PASTEUR'S RIGHTS

In conjunction with the Legal Affairs Department, work was carried out 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 RESEARCH PARTNERSHIPS

The Legal Affairs Department had another busy year in terms of contracts, managing around 150 agreements. These include 13 new license agreements, some offering potentially high returns over the next few years if successful, and 40 research cooperation agreements – a significant increase compared with the previous year. We continued to broaden our network of industry partners, particularly targeting technology firms.

SUPPORTING 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 2012, one of the newest of these companies, Pathoquest, confirmed the relevance of its work by developing an original and promising intellectual property portfolio.



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 serves as a training center for young scientists from France and abroad who come to complete their Masters and PhD programs.

In 1889 the Institut Pasteur offered the world's first microbiology course, "Technical Microbiology", and it has made teaching a core mission ever since. Today the Institut Pasteur is truly a higher education hotspot, with 500 students and healthcare professionals taking courses at the Teaching Center each year. The Institut Pasteur also hosts young scientists from all over the world – in 2012, 220 PhD students conducted research projects and around a hundred Masters students completed internships.

A DEDICATED ENVIRONMENT AND VARIED COURSE SELECTION

The Teaching Center, based at the former Pasteur hospital, offers some thirty courses each year, running from one to twelve weeks. The courses cover a wide range of subjects in the areas of microbiology, genomics, immunology, vaccinology, neuroscience, cell biology, and



500 STUDENTS

60 NATIONALITIES REPRESENTED

220 PHD STUDENTS

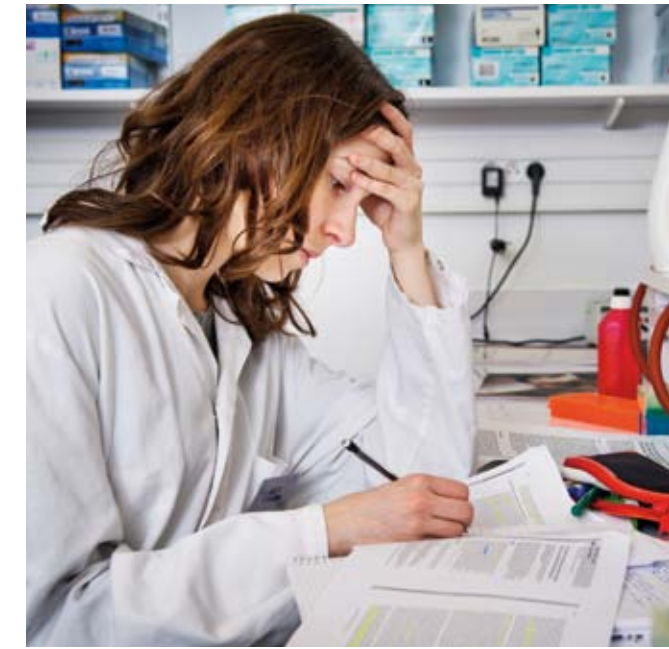
the various disciplines within the broad field of epidemiology. They are aimed at current students and graduates from French and foreign universities, university teaching hospitals, and French *grandes écoles*, as well as working professionals – scientists, doctors, and veterinarians – wishing to top 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 et Marie Curie, Paris Diderot, and Paris-Sud 11 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.

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 students from around 60 different countries come to take courses at the Institut Pasteur. With the growing number of foreign students and lecturers, an increasing number of courses are taught in English.

2012 also welcomed the fourth class of doctoral students for the Pasteur-Paris University International Doctoral Program. The program, which involves agreements with Paris Descartes, Pierre et Marie Curie, and Paris Diderot universities, is open to students who have completed courses at a foreign university. It is a three-year pro-



gram leading to a PhD. The "André Lwoff" class of 2012 included nine students from South Africa, Germany, Austria, Australia, Chile, Spain, Greece, Italy, and Tunisia.

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. After 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.



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



Global reach

The Institut Pasteur is at the heart of a unique international network that focuses on public health, teaching, and research, with 32 institutes worldwide.

A NETWORK AT THE HEART OF GLOBAL CHALLENGES

The Institut Pasteur International Network, a direct reflection of Louis Pasteur's vision, has become 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 Institut Pasteur in Paris provides scientific and administrative leadership for 14 of them and is in close partnership with many of the institutes.

The institutes in the International Network are key partners for health authorities, research institutions, and international organizations. In 2012, the Institut Pasteur and the International Cooperation Center of Agricultural Research for Development (CIRAD) signed an agreement to strengthen their scientific cooperation at international level. The International Network is also a major partner of the World Health Organization (WHO). The Institut Pasteur signed a cooperation agreement with WHO in 2012 with the aim of helping countries manage epidemic risks by applying WHO's International Health Regulations to step up their surveillance and detection capabilities.

80 GRANTS FUNDED BY THE INSTITUT PASTEUR INTERNATIONAL DIVISION, including **35** study grants
35 traineeship grants (3 PhD grants and 1 postdoctoral grant)
10 conference grants

16 GRANTS COFUNDED BY THE INTERNATIONAL DIVISION AND PARTNERS, including **10** grants from the Pierre Ledoux Jeunesse Internationale Foundation
5 grants from the Prince Albert II de Monaco Foundation
1 PhD grant from the Total Foundation

AN ACTIVE REGIONAL STRATEGY

Three regional meetings were held in 2012, in Yaoundé (Cameroon), Rome (Italy), and Montevideo (Uruguay), giving scientists from the institutes in these regions an opportunity to share their knowledge and develop new joint programs on:

- tuberculosis, malaria, emerging infectious diseases in Africa;
- infectious agents and cancer, central nervous system involvement in the Euro-Mediterranean;
- molecular research into infectious diseases in the Americas.

In Asia, the International Network is playing an active role in two ambitious new programs:

- The ECOMORE project (ECONomic Development, ECOSystem Modifications and Emerging Infectious Diseases Risk Evaluation) to study the complex relationship between economic growth, changing ecosystems, and the consequences of the emergence or re-emergence of infectious diseases for the health of local populations. The project is being conducted in Laos, Cambodia, Vietnam and Myanmar, with the support of the French Development Agency.
- The SEAE research project (South-East Asia Encephalitis Project) focuses on encephalitis in Cambodia, Vietnam, Laos, and Thailand. A regional platform for infectious disease research was set up to pool expertise from different French and international partners across the area. The project is being run in partnership with the Aviesan alliance (composed of major French stakeholders in life sciences and health) and the Mérieux Foundation.

EVENTS IN 2012

INAUGURATIONS

- The new Institut Pasteur in Laos was inaugurated in Vientiane in January 2012. This center will particularly focus on vector-borne diseases. It already hosts research teams from Laos, France, Japan, and Luxembourg. In November 2012, French President François Hollande made an official visit to the new center.
- The Pierre and Anne-Marie Moussa Training Center in Cermes, Niger, was officially opened on February 15, 2012. This unique facility will help support the development of research and teaching in Africa.
- In New Caledonia, the Institut Pasteur opened its first Biosafety Level 2 (BSL-2) laboratory in February 2012.

ANNIVERSARIES

In 2012, the Institut Pasteur in Côte d'Ivoire celebrated its 40th anniversary. The Pasteur Center in Cameroon also celebrated 20 years of International Network membership.

A POLICY TO ATTRACT YOUNG SCIENTISTS

NEW 4-YEAR GROUP PROGRAM

In 2012, two 4-year groups were selected to allow young postdoctoral fellows from the southern hemisphere to develop research programs within the International Network. One group is based at the Pasteur Center in Cameroon and the other at the Institut Pasteur in Bangui (Central African Republic).

TRAINING PROGRAMS AND FELLOWSHIPS

The aim of these programs is to develop human resources in public health and research in countries with limited resources, by offering grants for continuing training and traineeships, and international PhD and postdoctoral programs.

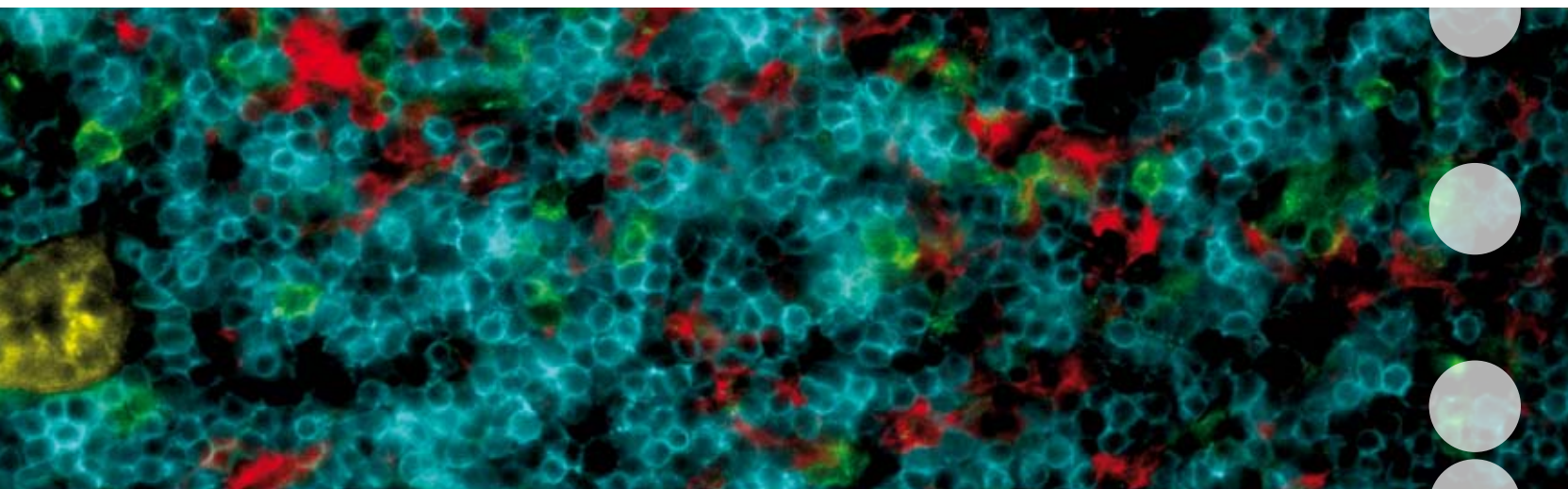
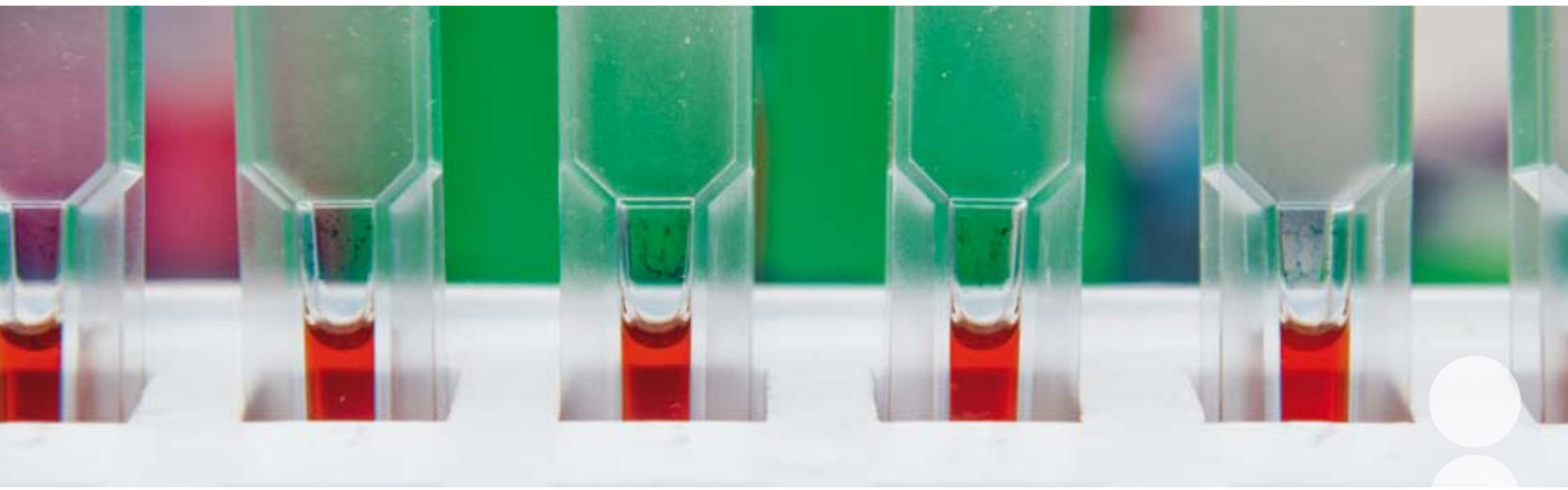
TO FIND OUT MORE

The 2012 edition of the Institut Pasteur International Network Report is available online at www.pasteur-international.org/. The open access archive HAL-RIIP allows scientists to submit and consult scientific publications from the Institut Pasteur International Network: hal-riip.archives-ouvertes.fr/.

International teaching and training

In 2012, more than 100 scientists from the Institut Pasteur International Network topped up their training with courses or internships at the Institut Pasteur in Paris. Teaching and training activities are organized each year within the 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 knowledge in national or regional structures. In 2012, 15 courses and workshops funded by the International Network were run in eight countries, including four in Africa, one in Asia, one in Latin America, and two in North Africa.

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 model and financial equilibrium, the Institut Pasteur is able to maintain its independence and freedom of research, and to provide a fast response when called upon in an emergency.

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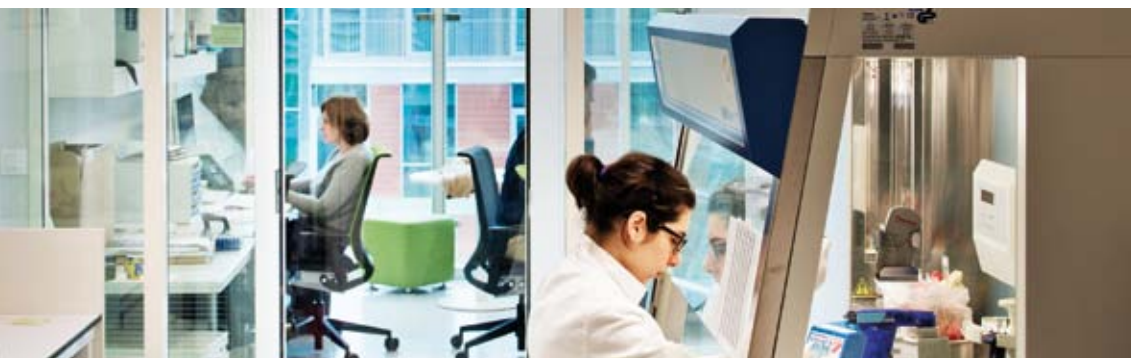
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and legacies

The HR policy in 2012 focused on organizational development and change management, employment of older workers, and professional equality.

Human resources



LABOR RELATIONS

Two major labor agreements were signed in 2012.

The agreement on employing older workers, which was due to expire, was extended. The aim of this agreement is to ensure that the proportion of the workforce aged 55 or over stays at 20% or more for the next three years. The agreement sets out four specific priority areas: anticipating career development, developing training for older workers, anticipating the high number of staff taking retirement over the next few years and implementing measures to help staff approaching retirement age, and transferring knowledge and skills. In response to the legislation, discussions will also be held on the "generation contract" designed to promote youth employment.

An agreement on professional equality between men and women was also signed. This agreement, signed by unions and management, fulfills the Institut Pasteur's legal obligation to hold talks on this subject. It was also an opportunity to demonstrate the Institut Pasteur's good record in this area and its positive results in terms of gender distribution in the workforce, equal treatment, access to training, and welfare benefits that can improve work-life balance.

The agreement focuses on three areas in particular:

- employment, to improve gender parity in some highly specific occupations or professions;
- promotion, to ensure that promotion requests are in line with the number of staff required at each qualification level;
- work/life balance, to further develop measures for working parents, an area the Institut Pasteur has been committed to for many years.

CHANGES TO THE HUMAN RESOURCES DEPARTMENT

Over the past year, changes have been made to the way the Human Resources Department is organized. The new Vice-President for Human Resources has focused on establishing a closer working relationship between HR teams and Institut Pasteur staff based on service, advice, and support.

The new organizational structure involves three main roles. Firstly, four pairs of HR employees will be assigned to a series of research and non-research departments, with the aim of developing closer links with Institut Pasteur staff. These HR pairs will act as contact people for Institut Pasteur scientists and other staff members, offering support for all their HR needs. Secondly, HR staff will offer expert guidance in a comprehensive range of HR matters including human resources management, social control, legal issues, training and recruitment processes, communications and labor relations. The third role involves monitoring, administration, payroll, management, and medical care services for Institut Pasteur employees. This new structure has been developed in close cooperation with all the teams. It will gradually be implemented from the beginning of 2013.

ORGANIZATION AND DEVELOPMENT

The opening of the new François Jacob building in 2012 was an ideal opportunity to test out the work of our preparation laboratories (cleaning surfaces, washing laboratory glassware, removing waste,



Establishing a closer working relationship between HR teams and Institut Pasteur staff based on service, advice, and support.

and generally preparing media), after discussions were held on how to optimize the activities of these laboratories. A new organizational set-up has been developed, involving the creation of specialized platforms that each focus on a specific activity. The aim is to maximize quality, modernize facilities, and offer a professional framework for the various roles, while rationalizing resources. A specialist company was commissioned to clean the new building (communal areas and laboratories).

A specific change management program was devised to ensure a smooth transition to this new organizational structure. The success of this "trial" scheme will be assessed to see whether it should be implemented in other buildings on the campus.



2,404

STAFF

(WORKFORCE AS OF DECEMBER 31, 2012)

1,877 Institut Pasteur employees (76% on permanent contracts)

464 employees from external research and higher education organizations

63 trainees

59%

WOMEN

52.4%

OF MANAGERIAL POSTS HELD BY WOMEN

41.7

AVERAGE AGE

In 2012, “Green Campus” activities gathered momentum at the Institut Pasteur in a bid to develop awareness about environmental issues. The Institut Pasteur also confirmed its membership of the United Nations Global Compact, stepping up its commitment with its “Responsible Campus” program which encompasses the broader economic, social, and environmental aspects of sustainable development.

Sustainable development



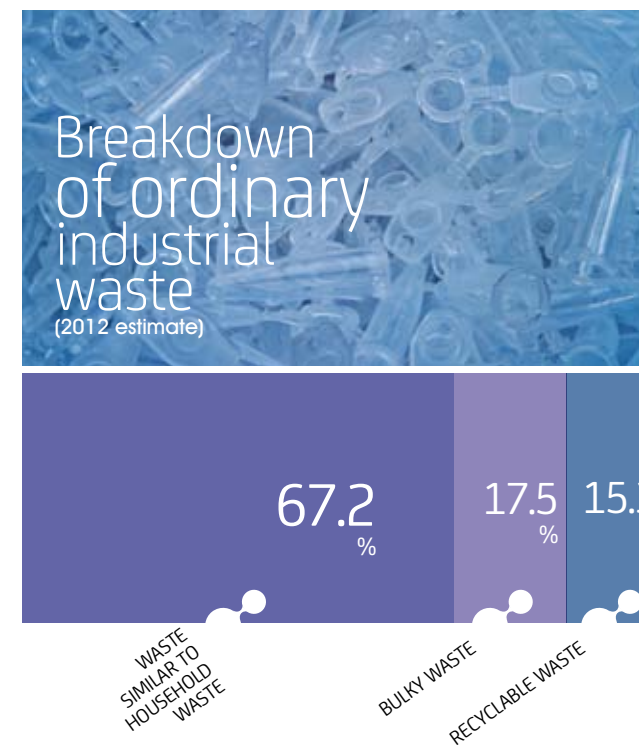
The Institut Pasteur’s sustainable development initiatives are part of its ongoing efforts for improvement in this area. Aims are set and reviewed on an annual basis by a steering committee. An action plan is then developed and implemented by the various departments concerned.



MEMBERSHIP OF THE UNITED NATIONS GLOBAL COMPACT AND PROGRESS REPORTS

The Institut Pasteur has been a member of the United Nations Global Compact since 2010. This is the world’s largest corporate citizenship initiative, seeking to promote social legitimacy in companies and organizations. Members undertake to adopt various principles in the areas of human rights, labor rights, environmental protection, and the fight against corruption, and to support and promote these principles in their spheres of influence.

Membership of the Global Compact has encouraged the Institut Pasteur to pursue and report on its environmental and social policies and practices. It also stimulates ongoing reflection on potential developments. For the second year running, the Institut Pasteur has issued a “Communication on Progress” report, which is available online on the UN and Institut Pasteur websites. The report summarizes the improvements made over the past year.



IMPROVING RECYCLING AND RECOVERY OF ORDINARY WASTE

On average, the Institut Pasteur generates 1,350 metric tons of ordinary waste each year. Before 2011, the waste was sorted into three categories before processing: waste similar to household waste, paper and card (recyclable), and bulky waste/site waste (sorted and recovered). In 2012, a new waste category was created for recycling aluminum cans and plastic bottles. The scheme will be stepped up in 2013.

REPORT ON GREENHOUSE GAS EMISSIONS

In 2012, the Institut Pasteur published a new report on its greenhouse gas emissions as required by the Grenelle 2 law of July 12, 2010, and as part of its “Green Campus” commitments. This followed on from the first carbon footprint report that the institute chose to draw up in 2009. For this new report, the Institut Pasteur used the Bilan Carbone® V7 tool supplied by the Bilan Carbone Association and also consulted one of the guides drawn up by the National Coordination Center on Greenhouse Gas Emission Reports. The volume of greenhouse gas emissions produced by the Institut Pasteur’s activities and facilities was estimated for two categories:

- direct emissions due to operation of technical facilities (fuel used by generators and the vehicle fleet, refrigerants, and gases);
- indirect emissions due to energy use (electricity, steam for heating), which account for the bulk of greenhouse gas emissions.

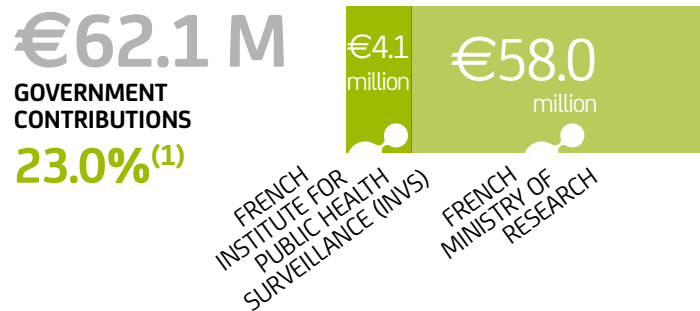
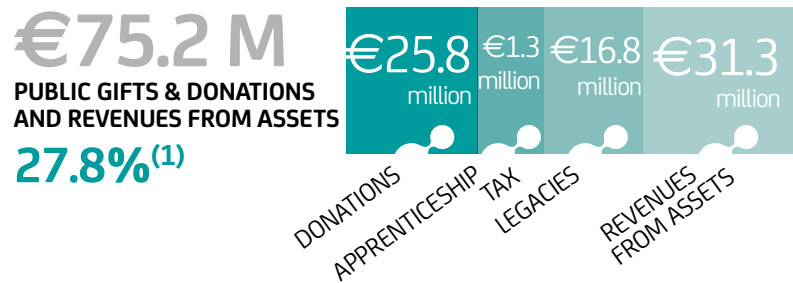
The Institut Pasteur has drawn up an action plan, which was partly implemented in 2012 and will be continued in 2013-2014, to reduce and contain these emissions as far as possible given the ongoing developments on the campus. This action plan includes:

- replacing several refrigeration plants by a single, more efficient system in connection with the François Jacob building project;
- improving building insulation;
- gradually replacing the current lighting systems (low-energy light bulbs) with a more energy-efficient LED system;
- replacing pump systems for heating and cold water by flow-control systems that can be adjusted to meet actual needs, avoiding unnecessary greenhouse gas emissions;
- incorporating sustainable development criteria into purchasing policies;
- planning an energy audit, scheduled for 2013 for the entire Institut Pasteur, to identify areas for improvement for the coming years.

The emissions report and action plan are available online on the Institut Pasteur website.

Financing structure

Current income



REVENUE FROM OWN ACTIVITIES
Research contracts and agreements (€76.9 M accounting for 28.4% of the current 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 €7.7 M and rose by €2.2 M in 2012 with the signing of new framework agreements for therapeutic research. Lastly, 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 recherche médicale [Medical Research Foundation], etc.) – amounted to €6 M, up €0.3 M compared with 2011. **Industrial royalties** (€36.2 M accounting for 13.4% of the current income) are essential for the Institut Pasteur. They are a direct result of the research carried out on campus. In 2012 the figures remained stable compared with 2011. **External services** (€15.6 M accounting for 5.8% of the current 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 showed a slight decrease in 2012 due to the sale of the medical test laboratory in November 2011.

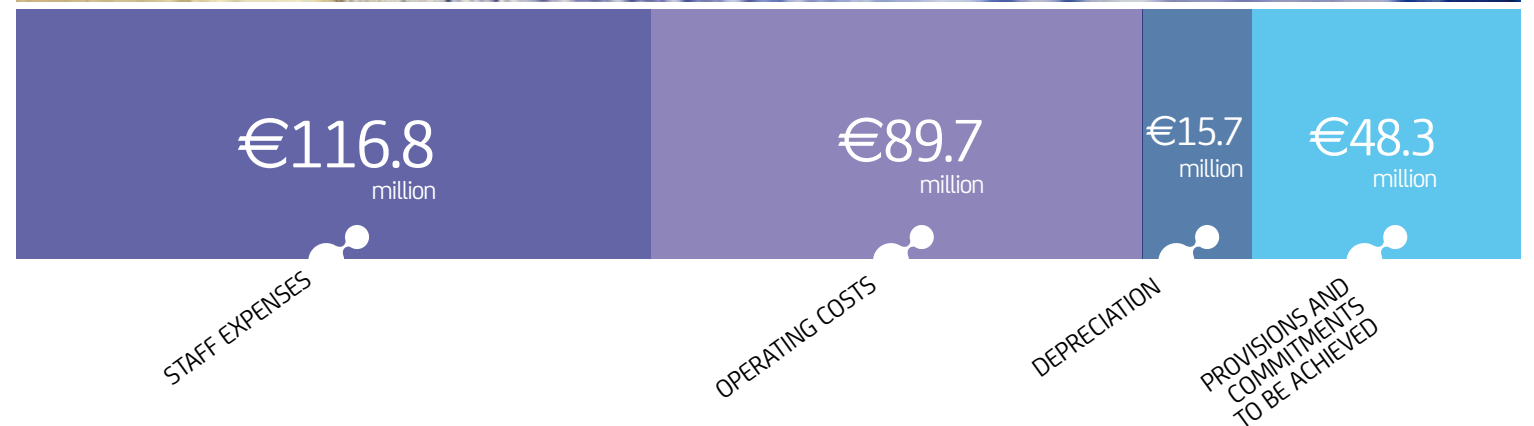
PUBLIC GIFTS & DONATIONS AND REVENUES FROM ASSETS
Revenues from assets (€31.3 M) include current financial revenue, rent from rental properties and agricultural revenue from estates registered among the Institut Pasteur's assets. **Public gifts & donations** (€43.9 M) include all donations and legacies, and apprenticeship tax. The overall fundraising figures are €20.4 M in 2012, slightly down on the previous year due to a sponsorship agreement begun in 2011, suspended in 2012, and subsequently resumed in 2013. Legacies, as regards the share allocated to current revenue (€16.8 M), rose compared with 2011. 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 (39%) of the cost 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



The structure of research spending shows that over 78% of our budget is earmarked for infectious diseases (viral, bacterial and parasitic diseases).

In 2012, the operating deficit amounted to -€23.2 M. This was due to the significant impact of high non-recurring operating costs. The financial result (€23.2 M), comprising income from investments, enabled us to balance the current result for the financial year. Exceptional items bring the Institut Pasteur's net result to €71.5 M.

Financial statements



CURRENT OPERATIONS

Current revenue (see page 50) increased by 10.9% compared with 2011. The highest rises were recorded on research agreements and contracts, (mainly financial) revenues from assets and financial support from our donors. Financial support from public authorities, particularly the French Ministry of Research, was stable and remains key to balancing the Institut Pasteur's current result.

Current expenditure (see page 51) rose by 11.6% compared with 2011 and was significantly affected by the opening of the new François Jacob building and the contribution to provisions for pension liabilities. The operating deficit, as restated according to these non-recurring charges, was stable compared with the previous year. 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.

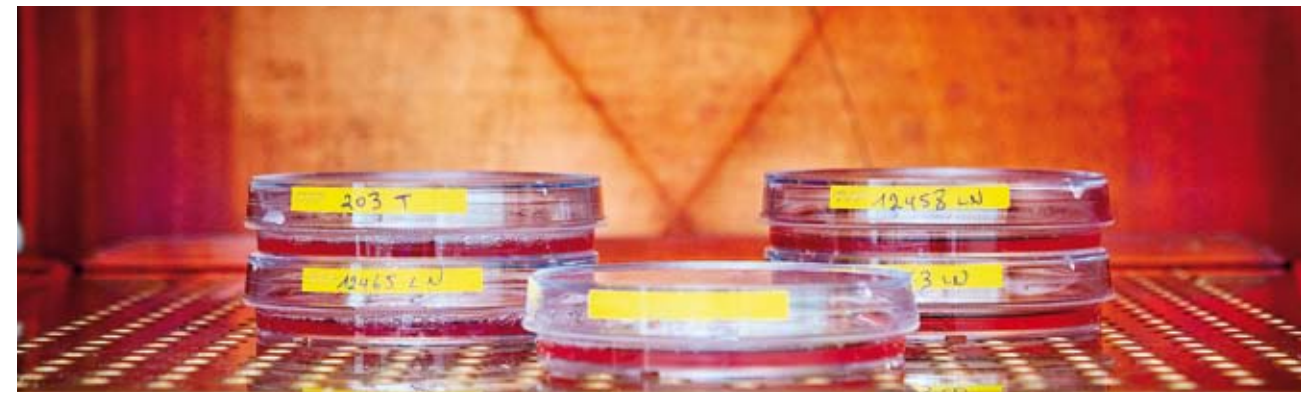
EXCEPTIONAL ITEMS

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 2012, the donations and legacies recorded as exceptional income amounted to €13.8 M, slightly down (-€1.9 M) in relation to 2011. On the other hand, the financial component (€26.1 M) rose sharply.

This year exceptional items also included capital gains of €31.7 M achieved from the sale of four rental properties and the Combray estate.

Due to these exceptional items, the Institut Pasteur recorded a net result of €71.5 M.



Communications and fundraising

2012 was a particularly eventful year for the Institut Pasteur, the highlight being the inauguration of the new François Jacob building. Throughout the year, the Department of Communications and Fundraising also worked hard to promote the Institut Pasteur's achievements and successes, improve its visibility and develop fundraising.

In 2012, the Department of Communications and Fundraising focused its efforts on three major events that took place in the second half of the year. Firstly it developed the communications campaign to promote the inauguration of the Institut Pasteur's new

François Jacob building for research on emerging diseases. The department remained in close contact with the media to ensure extensive press coverage of the event.

The department was also involved in the documentary *Les Héritiers Pasteur* ('The Pasteur Heirs'), broadcast in prime time on TV channel France 5 on November 13, 2012, and funded in cooperation with the Total Foundation. The new François Jacob building was officially opened the following day, on November 14, 2012, exactly 124 years to the day after the opening of the Institut Pasteur itself. More than 700 people attended the inauguration ceremony, including French President François Hollande and Prof. François Jacob, an eminent Institut Pasteur scientist whose remarkable career earned him the Nobel Prize in Medicine in 1965.

On October 2, at a ceremony attended by 500 people, the huge fresco designed by artist Fabrice Hyber for the new building was officially unveiled.



Finally, four internationally renowned scientists were honored at the prize-giving ceremony for the first edition of the Sanofi-Institut Pasteur Awards, held at Sanofi headquarters on November 13. The second edition of the awards will take place in 2013 with the renewed support of Sanofi.

Throughout the year, the department also continued its efforts to raise awareness of the Institut Pasteur's activities, values, and achievements. Of the 27 press releases published in 2012, around 20 presented advances in research.

A new graphic standard was also developed, establishing best practices for using the Institut Pasteur's visual identity. The department has also stepped up its digital strategy, particularly focusing on social networks in a bid to reach a wider audience.

Finally, it was a busy year for internal communications, with Pasteurdon and also the presentation of the new building to 2,400 staff members on June 11, giving them the chance to find out more about what has been going on behind the scenes at the top-ranking research center.

PASTEURDON CONTINUES TO GATHER MOMENTUM

Pasteurdon, the Institut Pasteur's annual fundraising event, supported by major French companies and organized in partnership with 13 French digital terrestrial network channels, made a major media splash in 2012. In addition to the short programs broadcast free of charge by partner channels, a specific campaign was developed for this sixth edition, with the slogan "Give'em all you got!".

This was a great opportunity to raise public awareness of science and biomedical research, and to emphasize the importance of donations for the Institut Pasteur's public health activities. Pasteurdon 2012 ran from October 12 to 14, with pledges reaching a grand total of €1.2 million. For the second year running, actress Alexandra Lamy was the Pasteurdon patron.

ACTIVE SPONSORS

Despite the ongoing economic crisis, many partner companies and corporate donors are continuing to support the Institut Pasteur, a recognized leader in its field. Alongside loyal partners such as the Total Foundation, Sanofi, the Areva Foundation, and the Le Roch-Les Mousquetaires Foundation, new sponsors have rallied to the Institut Pasteur's cause, including the AG2R La Mondiale group, which launched the "Roulons solidaires" campaign during 2012's Tour de France.

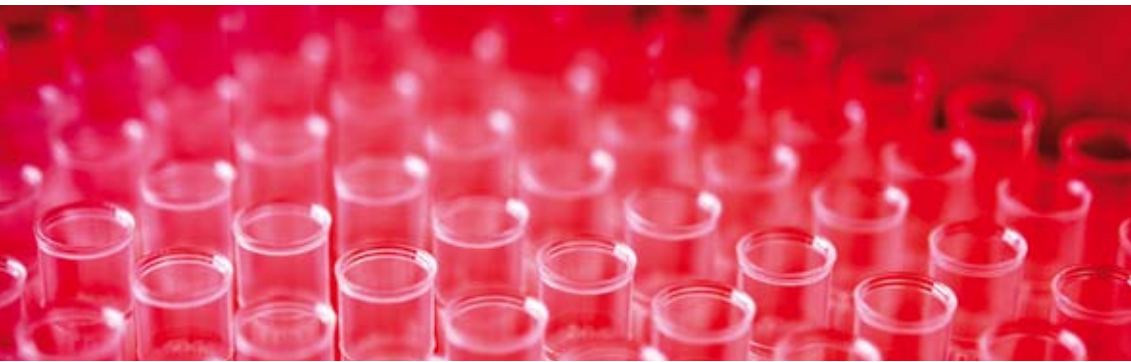
MR. PASTEUR'S WAY

The Pasteur Museum is continuing its efforts to improve the visibility of the Institut Pasteur's historical and cultural heritage. The "Mr. Pasteur's Way" lectures were attended by 428 people in 2012, a huge increase from the previous year's figure of 147. In March 2012, the museum received official accreditation under the French Ministry of Culture and Communication's "Maisons des Illustres" scheme, set up in 2011 to recognize houses that aim to perpetuate the memory of their eminent occupants.



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 and legacies – generous giving to support research



DONATIONS

A SUCCESSFUL YEAR DESPITE A DIFFICULT ECONOMIC CLIMATE

In 2012, for the seventh year in a row, donations continued to pour in, reaching a total of €21.7 million. Results are slightly down on 2011 due to an exceptionally large donation being made that year. This continued generosity has helped fund Institut Pasteur research in all fields. Donations from individuals rose by 5% in 2012 – despite the tough economic climate and the changing tax environment in this election year (which often tends to lead to a fall in donations), donors from France and abroad continued to support the Institut Pasteur's scientists with regular or one-off gifts. We are also continuing to see high numbers of new donors. Donations from companies remained at a good level, reaching €6.3 million this year. The Institut Pasteur was delighted to welcome new sponsors on board alongside its long-standing partners, who played a particularly active role in Pasteurdon 2012. The Institut Pasteur's annual fundraising campaign again helped raise awareness among the general public of the need to raise funds for research. Apprenticeship tax, which goes to the Institut Pasteur's Teaching Center, remained constant, totaling €1.3 million in 2012.

The Institut Pasteur's management practices are monitored by the "Comité de la Charte", an independent supervisory body of which it is a founder member. The accounts are certified by statutory auditors and are sent to all donors.

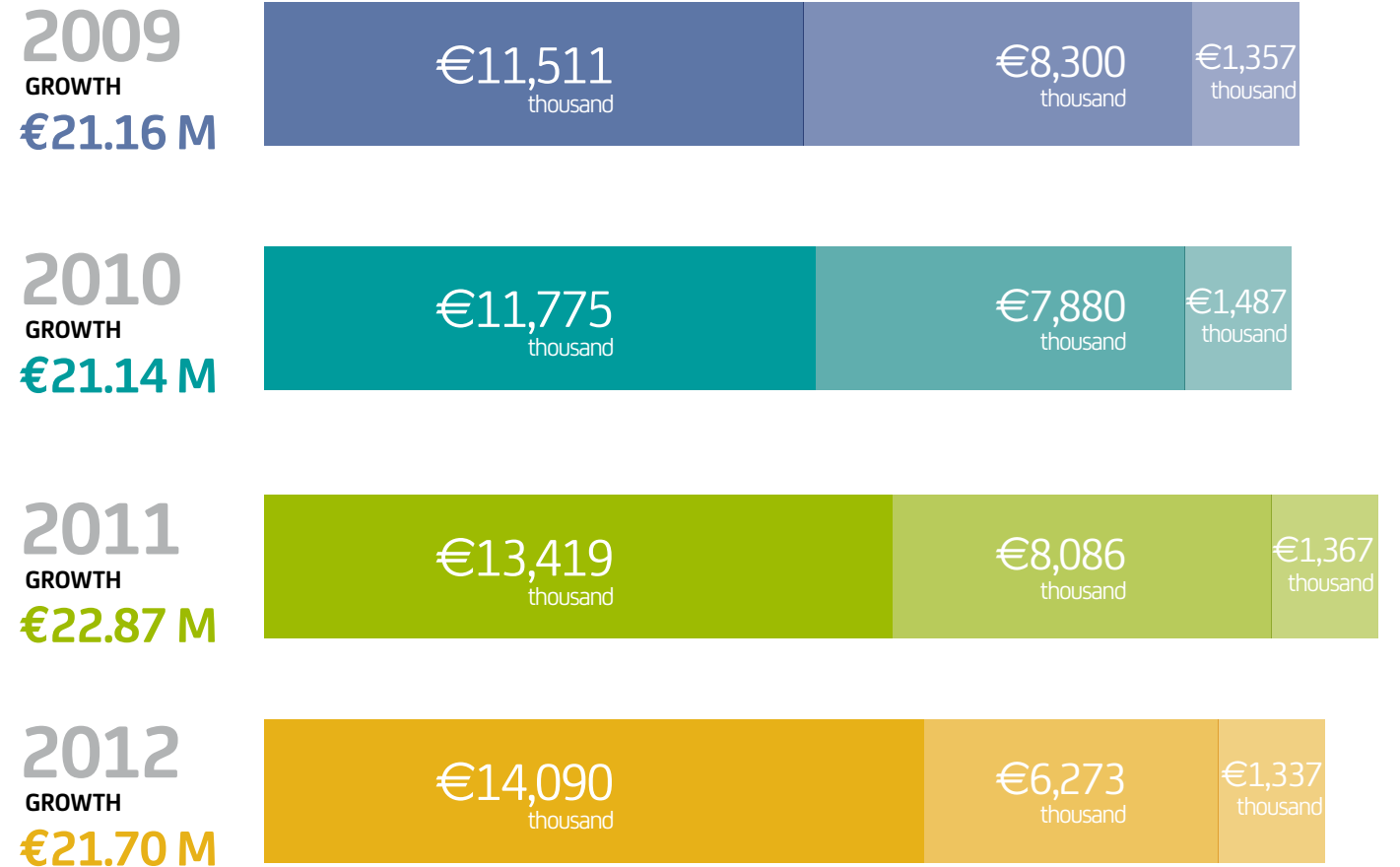
LEGACIES

TRUST IN PHILANTHROPY

In 2012, the Institut Pasteur received more than €30.5 million in legacies (general legacies, legacies by general title, and specific legacies). Of this total, €16.8 million was allocated to the budget, and around €13.8 million was recorded as extraordinary income. Although slightly lower than 2011, this figure remains remarkably high. The proportion of life insurance policies also remained high, with more than €8.8 million collected. The Legacies and Real Estate Assets Management Office stepped up its efforts to meet the needs of potential donors and legators with the recruitment of a new staff member to deal specifically with relations with legators. This new team member provides friendly, helpful advice for those considering bequeathing or

GROWTH IN FUNDRAISING

(from left to right: individuals, businesses, apprenticeship tax)

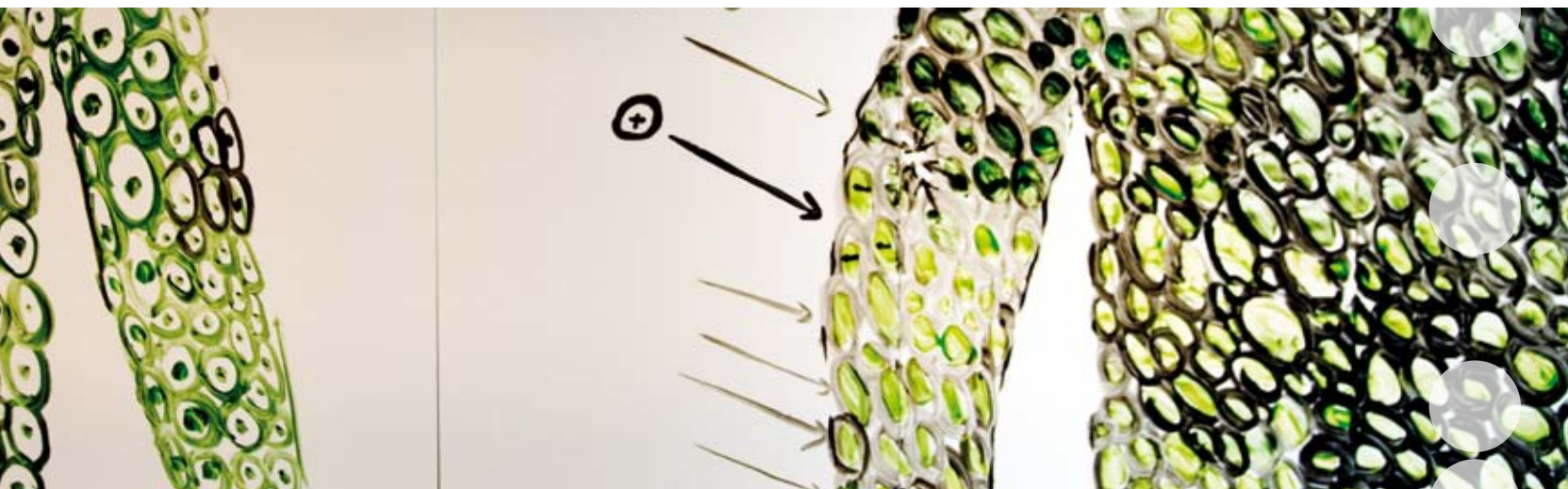


donating to the Institut Pasteur. Fostering a relationship of trust between the Institut Pasteur and its legators is vital to encourage philanthropy. After receiving certification by AFNOR for its advice and management concerning gifts and its real estate assets management in 2011, the legacies office pursued its quality policy in 2012 for the management of legacies, donations, and real estate. The Institut Pasteur is currently the only state-approved organization in France to have received AFNOR certification in this area. This is the culmination of several years of efforts to implement a structured working method and framework that satisfy the needs of all its partners, including individuals looking for information about legacies and donations, and notaries, who have an important role to play in this quality policy.

Philanthropy think tank

The think tank on philanthropic trusts set up by the Institut Pasteur following the first conference on the subject in 2009 currently has over 300 members, who meet to discuss the issues surrounding philanthropy. A committee of experts composed of eminent professionals (lawyers, notaries, and academics) and those working in this field has issued a series of technical opinions on the legal and fiscal provisions that encourage philanthropy. This open platform for discussion is the only one of its kind.

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 policy and the smooth running of the institute. The Board of Directors makes decisions on all Institut Pasteur matters and gives its opinion on the strategic policies set out by the President. It votes on budgets and approves the accounts. The General Meeting approves the Board of Directors' Annual Report and elects 16 members to the Board.

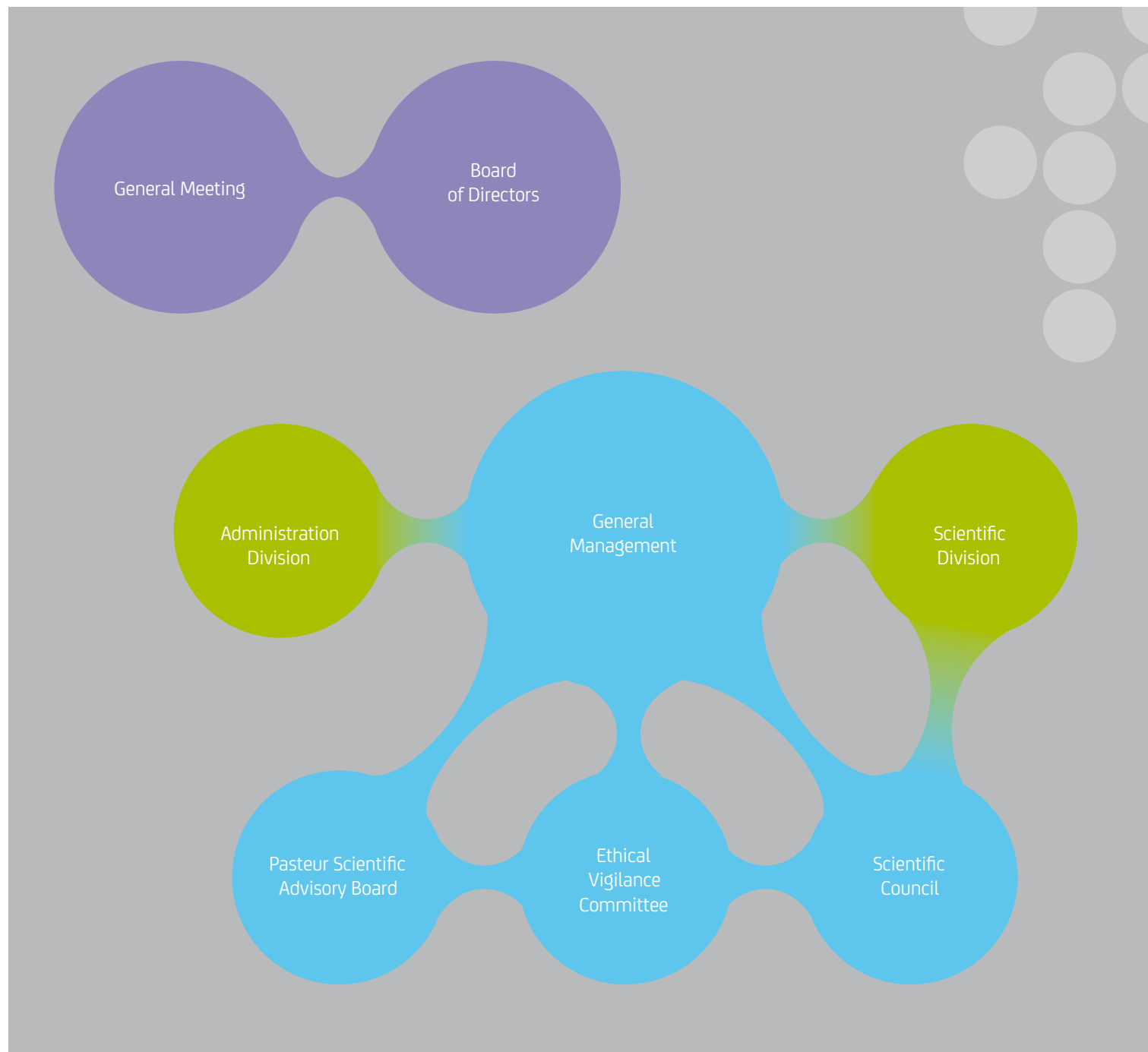
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Board

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Council

General organization



Board of Directors

BOARD OF DIRECTORS BUREAU

CHAIRMAN

JEAN-PIERRE JOUYET⁽¹⁾

Chief Executive Officer of the Caisse des dépôts, President of the Banque publique d'investissement

VICE-CHAIRMAN

DANIEL LOUVARD

Director of the Institut Curie Research Division

VICE-CHAIRMAN

BERNARD GUIRKINGER

Senior Executive Vice-President, Suez Environnement

TREASURER

GUILLAUME GAUBERT

Head of Department in the Budget Division of the French Ministry of the Economy and Finance

SECRETARY

ALAIN JACQUIER

Head of the Macromolecular Interaction Genetics Unit, Institut Pasteur

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Director of the French Institute for Higher Scientific Studies (IHEC)

JEAN-FRANÇOIS DELFRAISSY

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

DOMINIQUE DEVILLE DE PERRIÈRE

SPFCO – B4, Directorate-General of Research and Innovation, French Ministry of Higher Education and Research

YVES FARGE

Chairman of the Works Committee, Académie des technologies (French Academy of Technologies)

ALAIN FUCHS

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

JEAN-YVES GRALL

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

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 Unit, Institut Pasteur

ARMELLE PHALIPON

Molecular Microbial Pathogenesis Unit, Institut Pasteur

THIERRY PLANCHENAUT

Molecular Microbial Pathogenesis Unit, Bacteria-Cell Interactions Unit, Institut Pasteur

BRUNO RÉMOND

Chief Adviser to the French Government's Accounting Office

ANDRÉ SYROTA

Chief Executive Officer, Inserm (French National Institute for Health and Medical Research)

ROSE-MARIE VAN LERBERGHE⁽¹⁾

Member of the High Council of the Judiciary

LIONEL ZINSOU

Chairman and Chief Executive Officer, PAI Partners

(1) Jean-Pierre Jouyet resigned as Chairman of the Board of Directors but remains a member of the Board. Rose-Marie Van Lerberghe took over as Chairman May 1, 2013.

Executive Board

**ALICE DAUTRY**

President
(until September 30, 2013)

CHRISTOPHE MAURIET

Senior Vice-President
responsible for
Administration

MURIEL DELEPIERRE

Vice-President
Assessment and
Development
for Researchers

CORINNE FORTIN

Vice-President
Financial Affairs

OLIVIER GRAMAIL

Vice-President
Human Resources

ANTHONY PUGSLEY

Senior Vice-President
responsible for Scientific
Affairs

SYLVAIN COUDON

Vice-President
Communications
and Fundraising

JEAN DERÉGNAUCOURT

Vice-President Research
Applications and Industrial
Relations

ALAIN ISRAËL

Vice-President
Scientific
Assessment

MARIE GLOMET

Vice-President
Legal Affairs

MURIEL ELIASZEWICZ

Vice-President
Medical Affairs
(until April 10, 2013)

Scientific Council

June 2013

Institut Pasteur
Members, Elected
Heads of Unit

ANDRÉS ALCOVER

Professor at the Institut Pasteur
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