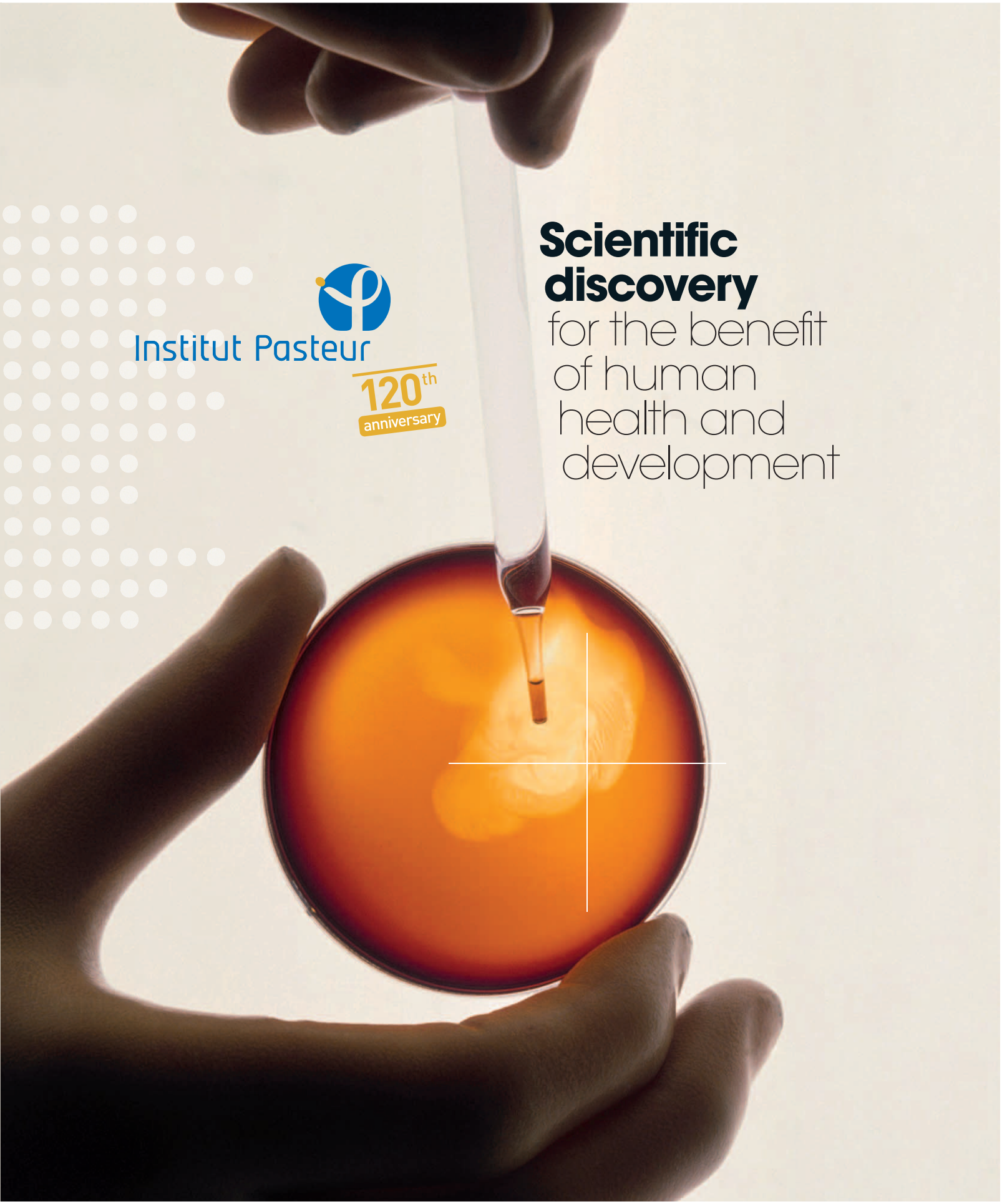

Institut Pasteur
120th anniversary
Scientific discovery
for the benefit of human health and development

The global **public health challenge**

The Institut Pasteur is an outward-looking **integrated research and teaching campus** with international appeal, focusing on a broad spectrum of scientific disciplines at the cutting edge of biological research. It is also a major stakeholder in public health thanks to its involvement in national, European and international research, monitoring, expert analysis and training initiatives for infectious diseases.

Contents

Interview with
François Ailleret, Chairman of the Board of Directors

How do you view last year?

F.A. > Well, like every year there is obviously a lot to say as the Institut Pasteur is a real hive of activity and there is always something going on… But to avoid trying to cover everything at once, I'd like to focus on two themes that the Board of Directors has particularly concentrated on — future strategy and the financial situation. I'd also like to mention a few events that have marked or illustrate life at the Institut Pasteur.

2008 was punctuated by important events, notably with the 120th anniversary of the Institut Pasteur. What would you like to highlight in particular?

F.A. > Well, firstly, the Nobel Prize was awarded to two Pasteurians, Professors Françoise Barré-Sinoussi and Luc Montagnier. It is a great recognition of the high-quality research conducted at the Institut Pasteur.

But it is more than that, as Françoise Barré-Sinoussi has worked tirelessly at the Institut Pasteur for 30 years and has always been true to the Pasteurian spirit, which associates research, public health, higher education and concern for the sick wherever they are in the world.

Pasteurian researchers were also recognized nationwide for their excellence through the appointment of Philippe Sansonetti, head of the Molecular Microbial Pathogenesis Unit, to the *Collège de France,* a higher education and research institution. As professor of the Microbiology and Infectious Diseases Chair, his course is entitled "Microbes and humankind: War and peace on mucosal surfaces."

The Institut Pasteur therefore celebrated its 120th anniversary in good health, which is fairly rare for a human institution.

> I believe that the Institut Pasteur will be able to get through this difficult period without compromising its ambition for research, public health, higher education and international cooperation.

And the Institut Pasteur was also able to promote its work, particularly among young people, and demonstrate just how relevant Louis Pasteur's founding principles still are in the early 21st century.

Finally, to show that the Institut Pasteur is continually evolving and adapting, its new articles of association came into force in 2008, and the Board of Directors welcomed Claude Leclerc, Isabelle Pelletier-Doucement, Vincent Berjot, Yves Farge, Bernard Guirkinger and Bruno Latour. I'd like to take this opportunity to thank Agnès Labigne, Rose-Marie Van Lerberghe, Hugues Bied-Charreton, Renaud Denoix de Saint Marc, Jean-Yves Fleurance and Jean-Pierre Jouyet, who left the Board half way through last year, for all their work.

In light of the current global financial crisis, where does the Institut Pasteur stand financially?

F.A. > The 2008 fiscal year recorded a positive operating surplus of approximately €2 M, and the investment program amounted to €25 M. There was a major increase in public donations (+30% in two years) thanks to improved communications initiatives. This is reassuring and encourages us to continue, not just for donations but also for legacies and sponsorship. Funding from the French government amounted to €57 M and given the difficult financial situation, this amounts to a sizable sum for research and the Institut Pasteur International Network. I should remind you that this International Network currently comprises 30 institutes worldwide, all of which are united by the same Pasteurian values regarding research and the fight against infectious diseases. And the 31st institute in Laos should soon be up and running.

Given this particular situation, how do you foresee 2009?

F.A. > The Institut Pasteur is healthy but it is obviously not immune to the serious global crisis and must therefore prepare for difficult times ahead, perhaps lasting several years. It boasts indisputable advantages: the work, expertise and determination of its staff; the support of the public; increased partnerships with companies and the worlds of research and public health; and also the French government's forward-thinking policy for research. And I believe that the Institut Pasteur will be able to get through this difficult period without compromising its ambition for research, public health, higher education and international cooperation.

And in the longer term, how is the Institut Pasteur preparing for the major challenges of tomorrow?

F.A. > A 20-year prospective study and its continuation as a strategic vision have highlighted the Institute's strengths and weaknesses, as well as the threats and opportunities that it must prepare for, particularly through action plans currently being drawn up. To single out one line of action in particular, the Institute needs to strike a balance and give equal weight to fundamental research and health applications. This is one of the essential cornerstones of the Institut Pasteur, which at the grand old age of 120 has a bright future ahead of it…

Interview with
Alice Dautry, President

What were the significant events of 2008 in your opinion?

A.D. > 2008 was an outstanding year for the Institut Pasteur. During the celebrations marking 120 years since its inauguration, our campus was delighted to welcome numerous French politicians, including François Fillon, Valérie Pécresse, Roselyne Bachelot and Bertrand Delanoë, as well as leading names in the pharmaceutical and food industries, such as Jean-François Dehecq, CEO of Sanofi-Aventis, and Daniel Vasella, CEO of Novartis. The French Prime Minister also commemorated this anniversary by awarding the Institut Pasteur the title of "major national cause." Finally, what gift could be better than the Nobel Prize for Medicine, awarded to Françoise Barré-Sinoussi and Luc Montagnier on December 10th? This prize came in addition to many other renowned international awards received by Pasteurians in 2008. We also organized many international conferences to mark the 25 years since the discovery of the AIDS virus and the 120 years of the Institut Pasteur.

What are the main achievements of the scientific policy adopted?

A.D. > Scientific strategy is based on three guiding principles that were set out three years ago — development of new research themes, an increase in multidisciplinary initiatives and consolidation of "translational research." We set up eight new five-year groups, constituted following international calls for tenders, and they have already achieved outstanding results. This recruitment drive drew in promising young international and multidisciplinary researchers, thus demonstrating the growing appeal of the Institut Pasteur. And research activities have been measured by publications in leading

> Scientific strategy is based on the development of new themes, an increase in multidisciplinary initiatives and the consolidation of "translational research."

international journals. Two of our researchers were awarded Advanced Grants from the European Research Council and another two received Starting Grants. I'd like to take this opportunity to thank our researchers for all their efforts in obtaining grants.
As regards public health, I should mention the creation of a National Reference Center for Human Papillomaviruses, the 21st such center to be housed at the Institut Pasteur. In addition, the new Clinical Research Center enables the Institut Pasteur to more effectively combine exploratory and clinical research.

Teaching is the third mission assigned to the Institut Pasteur by its founder. How do you remain faithful to this teaching vocation?

A.D. > I think that we need to train the younger generations to secure the future. The Institut Pasteur has a specific role to play in this area through its highly specialized international courses. The School of Public Health, set up in partnership with the French National Conservatory of Arts and Trades (CNAM), welcomed its first year of students.
The aim is to train specialists needed by the global community to meet health challenges in the next few years. The Teaching Center has been fully refurbished and offers new courses, such as the Vaccinology course, which also hopes to produce the best specialists in this field.

In what way has the Institut Pasteur consolidated its international presence?

A.D. > We have adopted an outward-facing strategy for our international work. In fact, I am convinced that we will only be able to meet global public health challenges through a combined response, based on shared experiences and coordination between local, regional and international stakeholders. This is why we have signed collaboration agreements with the Wellcome Trust, the National Institutes of Health in the U.S., the National Institute of Infectious Diseases in Japan, and the Harvard School of Public Health. We have also invested in research resources for Network institutes with, for example, a BSL3 laboratory at the Institut Pasteur in Cambodia.

How do you foresee 2009?

A.D. > Well, the world (and France is no exception) is experiencing a serious financial crisis. There are so many new challenges to be met and we must prepare more than ever for the future. By way of example, work has begun on a new Center for Integrative Biology of Emerging Diseases.
Despite the current economic situation, our careful management — evidenced by balanced current operations — and our efforts to obtain support from companies and the public have enabled us to pursue projects that will secure the Institut Pasteur's position as a major stakeholder in research and public health. The challenges awaiting the Institut Pasteur in the future will require the involvement of all staff members. The general management, together with scientists and the entire Pasteurian community, therefore embarked on a reflection process to set out a vision for the Institut Pasteur. This work, which was subsequently approved by the Board of Directors, has led to a medium-term vision and its main lines will guide the work of the Institut Pasteur for the years to come.

120th anniversary

2008 an outstanding year

One hundred and twenty years after it was set up, the Institut Pasteur remains one of the world's leading biomedical research centers and it aims to retain its position. To underpin this commitment, 2008 was marked by celebrations for a very special anniversary.

"Major National Cause"

The "major national cause" title was awarded to the Institut Pasteur by French Prime Minister François Fillon.

In addition to recognizing its service to world health and the expertise of its researchers, this title also legitimizes its fundraising activities.

> **Finally a Nobel against AIDS.**
>
> FRENCH DAILY NEWSPAPER "LIBÉRATION", 10/07/2008

Nobel Prize for Medicine awarded to Françoise Barré-Sinoussi and Luc Montagnier

On May 20, 1983, the first description of the AIDS virus, furnished by an Institut Pasteur team, was published in the important scientific journal *Science*.

Twenty-five years later, the Nobel Prize for Medicine was awarded to Professors Françoise Barré-Sinoussi and Luc Montagnier, who were behind this research work.

It was in December 1982 that the task to isolate a then-unknown virus — one that would trigger a pandemic of devastating proportions — began at the Institut Pasteur.

Following advice from Françoise Brun-Vézinet, who worked with him at Pitié-Salpêtrière Hospital as a virologist, clinician Willy Rozenbaum contacted the Institut Pasteur's Viral Oncology Unit, specialized in cancer-causing retroviruses. The team, which was linked to that of Jean-Claude Chermann and headed up by Luc Montagnier, therefore began research and the main part of the work on the new virus was carried out by Françoise Barré-Sinoussi. Using the first ganglionic biopsy from a patient at the "pre-AIDS" stage (i.e. before the emergence of severe immunodeficiency), Françoise identified the Lymphadenopathy Associated Virus or LAV, which was later renamed HIV, or the Human Immunodeficiency Virus.

A few months later, this discovery led to molecular biologists from the Institut Pasteur describing the viral sequence, and the first screening tests were also devised. Consequently, identification of the viral replication cycle resulted in the development of several new antiviral classes.

Today, despite the incredible progress made, particularly in the field of triple therapy, AIDS remains a global threat. At the Institut Pasteur, a dozen units are conducting research into AIDS, including Françoise Barré-Sinoussi's unit. All are involved in the various aspects of the infection and the action and propagation mechanisms of HIV.

> **The first French woman scientist to receive the Nobel Prize for Medicine is a true Pasteurian who has fought tirelessly against AIDS.**
>
> FRENCH DAILY NEWSPAPER "LE MONDE", 10/08/2008

Events throughout France...

During the year, the Institut Pasteur reached out to the general public through all kinds of events. Here is an overview of these events, held throughout France.

> **... The Institut Pasteur, a leader in research, is opening its doors to the public.**
>
> FRENCH RADIO STATION FRANCE INTER 11/23/2008

In tune with music and science

On September 17th, for the 120th anniversary of the Institut Pasteur, the *Théâtre des Champs-Élysées,* which was loaned by the *Caisse des dépôts et consignations* for the occasion, welcomed the Paris Orchestral Ensemble for a fabulous classical music concert conducted by Hans Laureyn.

Works by Gabriel Fauré, Johann Sebastian Bach and Camille Saint-Saëns were performed by the soloists Ivry Gitlis, the famous Israeli violinist, Brigitte Engerer, the internationally renowned pianist, and Sébastien Van Kuijk, the talented cellist. The proceeds from the evening went to Institut Pasteur research.

A guided tour to the heart of Pasteurian research

The Institut Pasteur opened its doors to the general public for two days as part of the French national Science Festival. The operation was a success as a great number of Pasteurian teams got involved in the various activities — laboratory visits, discussions with researchers, scientific talks, introduction to the Institut Pasteur International Network, experimental workshops and career forums for young people.

Lectures throughout France

Close to 200 lectures, focusing on the Institut Pasteur's history and research activities, were organized throughout the year.

The second Pasteurdon was a great success

The second Pasteurdon — a publicity and fundraising event — raised over one million euros for Institut Pasteur research programs. From September 20 to 27, Pasteurdon, which was supported by artists, sponsored by the top French companies and promoted by the leading national radio stations, invited the public to actively support scientific research. Events were organized throughout France by town councils and associations, which also welcomed Institut Pasteur speakers.

"Live from the Institut Pasteur"

During the second Pasteurdon, France Inter and RMC were invited to the Institut Pasteur for two unique radio days. This enabled these two leading national radio stations to show their support for the operation. France Inter's *La Matinale* and *Le Sept dix* radio shows and RMC's *Le téléphone sonne* and *Les Grandes Gueules* featured Institut Pasteur researchers, and listeners were invited to phone in with their questions.

... and scientific conferences

Thanks to its 120th anniversary celebrations, the Institut Pasteur was able to look back over the major discoveries that have marked its history and assert itself as a key stakeholder in public health and today's scientific research.

25 years since the discovery of HIV

The "25 years of HIV" conference, opened by French Minister for Health Roselyne Bachelot-Narquin, focused on what is currently known about the virus and the latest developments in clinical trials. The great international specialists, including Françoise Barré-Sinoussi and Luc Montagnier, were brought together to remind us how the discovery of HIV radically changed the world of research, and also more importantly to set out the main lines of research that will enable us to continue fighting the virus.

Research into infectious diseases: a global challenge

The Institut Pasteur and the Institut Pasteur International Network organized an international scientific conference entitled "Research into infectious diseases: a global challenge." 330 scientists attended this conference which concentrated on the molecular mechanisms of disease, advances in the control of these diseases and the problems of field research.

> A three-day conference organized in Paris will focus on the main developments in the fight against disease.
>
> FRENCH DAILY CATHOLIC NEWSPAPER, LA CROIX, 05/20/2008

The international conference on infectious diseases

The 7th Louis Pasteur conference on infectious diseases brought together over 460 delegates, including the world's leading experts in epidemiology, public health, microbiology and immunology. The latest concepts and methodologies for research into infectious diseases were presented and debates centered on monitoring the emergence of new infectious diseases, understanding their pathogenesis, modeling and controlling epidemics, and the discovery of new treatments and vaccines.

Celebrating the centenary of Élie Metchnikoff's Nobel Prize

In 1908, Élie Metchnikoff won the Nobel Prize for Physiology and Medicine for his work on phagocytes. His research paved the way for the field of immunology. The Institut Pasteur paid homage to this great researcher by bringing together over 300 participants for a conference entitled "Metchnikoff's heritage in 2008."
Internationally renowned researchers demonstrated how Metchnikoff's heritage remains relevant 100 years on. They included Sidney Brenner from the Salk Institute for Biological Studies in the U.S., who won the 2002 Nobel Prize for Physiology and Medicine.

> **Pasteur is focusing on the future (…) and the new challenges to be met to improve world health.**
>
> FRENCH DAILY MEDICAL NEWSPAPER
> "LE QUOTIDIEN DU MÉDECIN"
> 11/18/2008

120th anniversary

The world health challenge closes the 120th anniversary celebrations

The "Health: a major challenge for sustainable development in the world" conference was organized on November 14th, 120 years to the day since the Institut Pasteur was opened. This event received outstanding support from Sanofi-Aventis and included debates on the acute public health problems affecting modern societies in industrialized and developing countries. Following the opening of the conference by French Prime Minister François Fillon, two sessions brought together leading manufacturers and scientists, who discussed organization, funding and partnerships for public health, and the strategic theme of North/South cooperation in this field. Short speeches from Safiatou Thiam, the Senegalese Minister for Health and Prevention, Roselyne Bachelot-Narquin, the French Minister for Health, and Valérie Pécresse, the French Minister for Higher Education and Research, brought the morning to a close.

Top row from left to right: Federico Mayor, President of the Fondation Culture de la Paix, Elias A. Zerhouni, former Director of the National Institutes of Health, Alice Dautry, President of the Institut Pasteur, Roselyne Bachelot-Narquin, French Minister for Health, François Ailleret, Chairman of the Board of Directors of the Institut Pasteur, Mark Walport, Director of Wellcome Trust, and Safiatou Thiam, Senegalese Minister for Health and Prevention. **Middle row:** François Fillon, French Prime Minister, Valérie Pécresse, French Minister for Higher Education and Research, and Androulla Vassiliou, European Commissioner for Health. **Bottom row:** Elias A. Zerhouni, Robert Sebbag, Vice President, Access to Medicines at Sanofi-Aventis, and Daniel Vasella, Chairman and CEO of Novartis SA.

Laying the first stone of the Integrative Biology of Emerging Diseases Center

> **Pasteur treats emerging diseases.**
>
> FRENCH WEEKLY MAGAZINE "L'USINE NOUVELLE" 04/10/2008

The purpose of the forthcoming Integrative Biology of Emerging Diseases Center is to reinforce the Institut Pasteur's response to new diseases threatening world health with high-tech facilities.

This project particularly aims to address issues such as the risk of propagation of viral or bacterial diseases (avian influenza, chikungunya, SARS, cancers of infectious origin, etc.), the emergence of drug resistance, and the problems posed by the emergence of new pathologies and the increase in diseases linked to population aging.
The new center, which will open its doors in 2011/2012, will welcome multidisciplinary teams equipped with the latest in high-tech equipment. Eventually, the 16,000 sq. m. building will house 350 scientists, engineers and technicians within newly created research units staffed through internal mobility.

60 million euros for a new Institut Pasteur research center.

FRENCH DAILY FINANCIAL NEWSPAPER "LES ECHOS" 10/24/2008

The first stone of the forthcoming Integrative Biology of Emerging Diseases Center was laid on October 23.

The event was attended by Valérie Pécresse, French Minister for Higher Education and Research, Bertrand Delanoë, Mayor of Paris, and Marc Lipinski, Vice President of the Greater Paris Regional Council, responsible for Higher Education, Research and Scientific and Technical Innovation. The ceremony included councilors, Institut Pasteur donors and researchers and provided the perfect opportunity for thanking each contributor for their support. An investment of €60 M (excl. VAT) is in fact required to build the center and purchase the high-tech equipment. The French government (€10 M), Greater Paris Region (€10 M) and City of Paris (€3 M) have lent their support, thus demonstrating the priority given to this high-profile project. The Institut Pasteur is to contribute a third of the cost, that is €20 M, from its own resources and the remaining €17 M is being sought from private sponsors, the general public, companies and foundations that are willing to support such an undertaking.

01

Scientific discovery for sustainable health

The Institut Pasteur is at the forefront of high-quality research and its applications in society, working daily to combat the most widespread infectious diseases, including AIDS, tuberculosis and malaria, emerging diseases such as chikungunya, dengue and avian influenza, and "neglected" diseases such as sleeping sickness, Chagas disease and leishmaniasis.
The Institut Pasteur's work also concerns a number of genetic diseases and nervous system disorders, sensory disabilities, metabolic diseases, psychiatric disorders, drug addiction and aging.
Laboratories carry out research into the "upstream" causes of diseases, furthering our knowledge of living organisms by studying embryonic development, the immune system, the structure of molecules and certain functions of the brain.


Effective
multidisciplinary
research

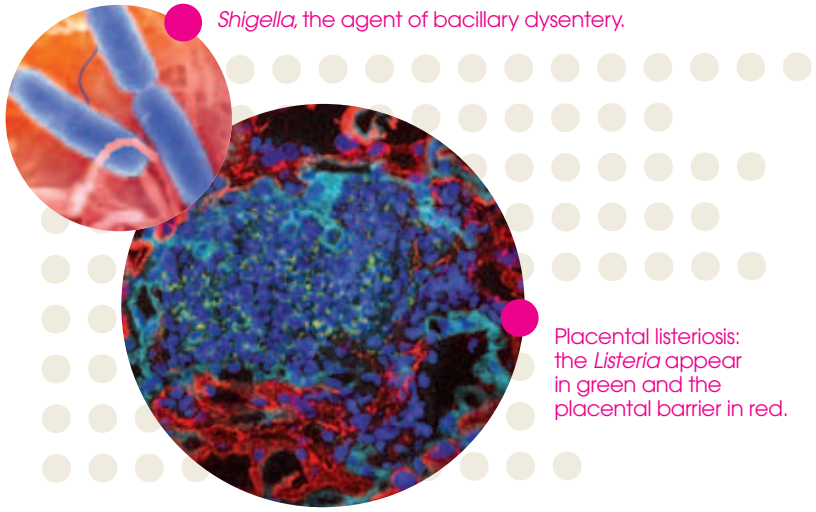
In its efforts to develop multidisciplinary, innovative and effective research while ensuring that the results of this research find applications for public health, the Institut Pasteur has developed a flexible strategy to encourage synergy between its various laboratories and to increase the number of partnerships.

The Institut Pasteur boasts 10 scientific departments housing 130 units and laboratories according to their research theme.

- Cell Biology and Infection
- Developmental Biology
- Structural Biology and Chemistry
- Genomes and Genetics
- Immunology
- Infection and Epidemiology
- Microbiology
- Neuroscience
- Parasitology and Mycology
- Virology

The department analyzes the interactions between infectious agents and their targets — cells and tissues — at all stages of infection. Several teams carry out research on one single infectious agent. Others work towards in-depth knowledge of the cell, in a non-infectious context. The department's research activities involve the development of new techniques, including imaging and image analysis or post-genomics.

Cell Biology and Infection



Shigella, the agent of bacillary dysentery.

Placental listeriosis: the *Listeria* appear in green and the placental barrier in red.

When a pathogen comes into contact with a cell, the cell is often unable to prevent the onset of infection: the pathogen adheres to its surface and may enter. A programmed fight then begins against the invader. The department analyzes this conflict using a variety of spatio-temporal approaches, with the support of the Dynamic Imaging and Electron Microscopy platforms.

Bacterial models

Some bacteria are easier to study than others and can be used as models to help understand basic phenomena. *Listeria monocytogenes* and *Shigella flexneri* are models of intracellular bacteria that are responsible for intestinal diseases.

••• *Shigella*: a bacterium that neutralizes immune defenses

Shigella, responsible for bacillary dysentery, is particularly harmful for young children, especially in tropical countries. The disease begins with the invasion of intestinal cells.

The Molecular Microbial Pathogenesis Unit is looking into various aspects of the infection and has particularly studied how cells sense the arrival of this bacterium and send out alarm signals, causing the rupture or even destruction of the intestinal epithelial barrier. It has also shown how the bacterium modulates the inflammatory response to ensure its survival. This research has led to the development of a vaccine candidate for *Shigella* and clinical trials are on-going.

Highlights

SHIGELLA MODULATES THE INNATE IMMUNE RESPONSE

The Molecular Microbial Pathogenesis Unit has discovered how *Shigella,* the bacterium responsible for an acute inflammatory disease of the intestine, succeeds in regulating the first immune defenses so that it can survive and then invade the mucosa. Understanding such mechanisms opens up interesting therapeutic prospects, not only for the treatment of shigellosis but also for that of other infectious intestinal diseases.

MAPPING GENE TERRITORIES IN YEAST

The Imaging and Modeling five-year group has developed and validated a computer technique that automatically analyzes the images of thousands of cells and generates

••• Listeriosis, a disease on the rise in developed countries

Listeria is a severe food-borne infection which leads not only to intestinal infections but also to meningitis and abortion (the death rate is 30%). *Listeria* contaminates foodstuffs relatively easily and is capable of multiplying at low temperatures (4°C, the temperature of refrigerators). The Bacteria-Cell Interactions Unit is working to understand the various stages of the infection by analyzing the bacterium's components and specific properties, its interactions with cells, and host cell signaling and responses. Some concepts are then generalized to other pathogens. The results obtained at the cell level are then validated in relevant animal models, which recently helped scientists to understand how the bacteria cross the intestinal barrier and the maternal-fetal barrier.

Almost 165 people

8 units, 3 five-year groups

2 platforms, 1 associated laboratory

6 attached entities

Other infectious agents

••• *Chlamydia*

The Biology of Cell Interactions Unit is carrying out research on infection by *Chlamydia*. These bacteria are responsible for pulmonary infections, sexually transmitted diseases and blindness, and may be involved in atherosclerosis. They cannot easily be studied because they develop exclusively inside eukaryotic cells. Research on these bacteria therefore uses the work carried out, and concepts established, using other bacterial models. The unit is studying their entry pathway and their interactions with host cells, and is particularly focusing on the role of proteins secreted in host cells.

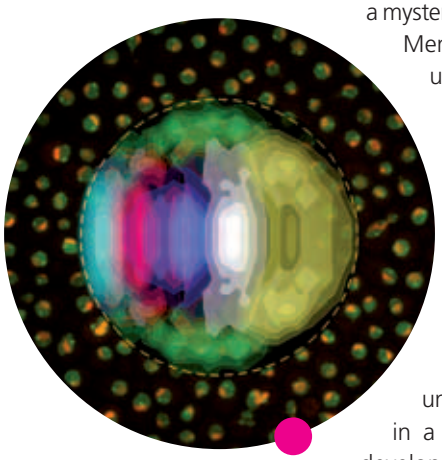
••• Amebae

Amebae are parasites responsible for very serious infections in tropical countries. They are highly mobile organisms that destroy the intestinal mucosa and spread to the liver. The Cell Biology of Parasitism Unit is looking into the motility of this parasite and its role in infection, to be able to diagnose the infection easily and treat it. The unit is also studying chemotaxis, the attraction of amebae to a chemical compound that may be linked to the immune response. Finally, the unit is conducting research into the inflammation produced during amebiasis, mainly using *ex vivo* models.

high-resolution maps of gene territories in yeast. It has discovered that the territorial organization of genes is far more developed than previously thought.
These results have significant implications for understanding gene expression.

MOTHER TO CHILD TRANSMISSION OF *LISTERIA*

In 2008, the Bacteria-Cell Interactions Unit, in cooperation with the Microbes and Host Barriers five-year group, discovered how the bacterium responsible for listeriosis is able to cross the placenta of pregnant women and cause severe, sometimes fatal, fetal infections, premature birth and infections in newborn babies. This is the first time that a molecular mechanism that enables a pathogenic bacterium to cross the placenta in vivo has been identified.



High-resolution map of gene territories. The background shows the nuclei of yeast observed under a fluorescence microscope; the bright green dot indicates the position of the gene; and the red structure that of the nucleolus, a nuclear subcompartment. In the center, the circle symbolizes a yeast nucleus and shows the probability of several genes being present (represented by different colors), calculated automatically using images of several thousand cells. This representation reveals a previously unsuspected level of spatial organization. *Ref.: Berger et al., Nature Methods 2008.*

••• Prions

Prions are responsible for Transmissible Spongiform Encephalopathies (TSEs), including mad cow disease, sheep scrapie and Creutzfeldt-Jakob disease in humans. They are the pathological form of a normal prion protein whose function remains a mystery. One of the major research themes of the Membrane Traffic and Pathogenesis Unit is understanding the role of the normal protein and its transformation into an infectious prion, the site of this transformation and the propagation of the cells in the brain.

The cell — the focus of research

Understanding an infectious disease means understanding the routine events that occur in a cell at all stages of life, from embryo development to death. Several fundamental phenomena are being investigated.

••• Cell signaling

An organism's cells constantly receive external signals that cause them to proliferate or not, to differentiate into other cell types, or to die. When a cell stops obeying these signals, it can be transformed into a cancerous cell. The Cell Signaling and Activation Laboratory is carrying out research into two signaling pathways: NF-kB, which is involved in the immune response to infection by various pathogens, and the Notch pathway, which plays an important role in the development of the egg through to adulthood. The laboratory is attempting to understand how the signals received by the cell outer membrane are transmitted to the nucleus.

••• Cell migration

Cell migration enables the formation of tissues and organs, the transportation of immune cells to infection sites, the healing of damaged tissues and the dissemination of tumor cells during metastasis. The cell machinery determines a front-rear polarity axis in the direction of migration. Extracellular factors, involved in establishing and regulating this axis, play a major role in initiating and controlling the migration. The aim of the work carried out by the Cell Polarity and Migration five-year group is to determine the molecular mechanisms that accompany cell polarization and migration, to identify new therapeutic targets. The researchers are particularly focusing on cell migration within the central nervous system (brain and spinal cord).

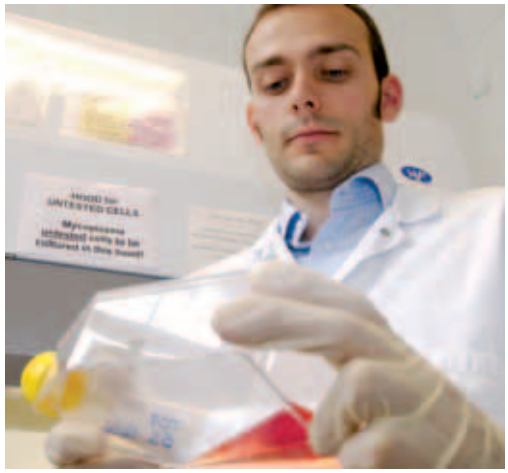
The Nuclear Organization and Oncogenesis Unit is researching the molecular and cell mechanisms involved in oncogenesis, in particular the SUMO signaling pathway, which leads to protein modifications in the nucleus.

Quantitative imaging for research

The Quantitative Image Analysis Unit is developing methods and programs for image processing and analysis, to extract, quantify and model information contained in images obtained from biological research. It is helping to decipher the complex spatio-temporal relations that govern biological phenomena.

As its name suggests, the Imaging and Modeling five-year group is also trying to exploit imaging data to its full potential in order to improve understanding of fundamental events, such as transcription.

The Dynamics of Host-Pathogen Interactions five-year group is studying cell signaling pathways from the moment a bacterium enters the cell to the moment the cell begins to react, quantifying the time, intensity and duration of the signals.



Put simply, the department's mission is to understand how a highly integrated and sophisticated multicellular organism, such as a human, can develop from a fertilized egg. How is the genetic information interpreted during differentiation to allow cells to emerge with distinct identities and roles? What types of communication guarantee their perfect coordination? How are stem cells regulated to accurately replace defective or aging cells?

Developmental Biology

Zebra danio bred in the Macrophages and Development of Immunity Unit.

Whilst fundamental research is central to all that the Developmental Biology Department does, our research covers fields that are closely linked to public health concerns through topics such as stem cells and their possible applications to cell therapy: epigenetics to cancer, and development to congenital disorders.

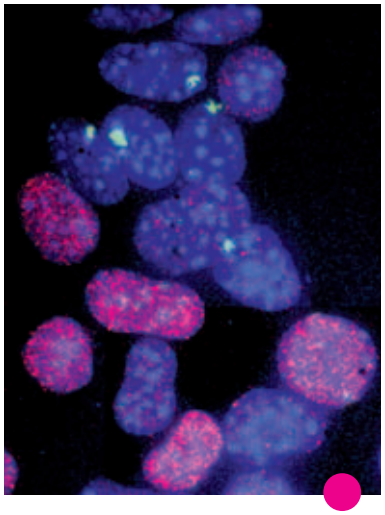
The research areas of the seven units, two provisional units and five-year group focus on four central issues:

- How are tissues and organs formed? Which cells contribute to the process, and which cell movements and migrations are required? How do cells communicate with each other? What type of "signaling" enables cells to find each other during the process of organ formation?
- How is cell identity established and maintained via specific programming mechanisms, such as epigenetics? What contributions to this programming are made by the various epigenetic mechanisms, such as non-coding RNA, microRNA, alternative splicing and chromatin modifications?
- What defines and sets apart stem cells and tissue-specific stem cells? What is their role and what are the regulating mechanisms involved during embryogenesis, and in adults? How do they carry out tissue formation, and how do they contribute to maintaining these tissues and organs in adults?
- In the phenotype developed by the individual, what are the respective roles of innate and non-genetic factors? What are the genetic and non-genetic factors in host resistance to infectious diseases and/or congenital and metabolic disorders?

Highlights

OVARIAN FAILURE: A GENETIC CAUSE IDENTIFIED

The Human Developmental Genetics Unit is conducting research into the genetic and developmental circuits involved in sex determination. It recently identified and explained a major genetic cause of some cases of ovarian failure. By analyzing families affected by testicular developmental disorders, researchers pinpointed various problems in the development and functioning of ovaries in some women from the same family.
A genetic study identified various mutations in a specific gene called NR5A1, which plays a key role in sexual development in these women. This gene not only controls testicle and ovary formation, but is also involved in regulating the biosynthesis of hormones produced by these gonads. Mutations of this gene were also observed in around 10% of the sporadic cases of ovarian failure investigated, a significant proportion given that ovarian failure concerns a minimum 1% of the female population.



Female embryonic stem cells during differentiation. The inactivation of the X chromosome, identified by the accumulation of Xist RNAs (in green) on the inactive X chromosome, is only induced in cells that have lost the pluripotency factor (in red).

A range of models

While the mouse, the most widely used mammal experimentation system, remains the model organism used by the majority of the department's laboratories, there have been changes in recent years and several groups now carry out experiments using *Drosophila,* a fly with significant genetic capabilities for which development data is easily available. A number of groups are also working with a small fish, the zebra danio, which is easy to work with and whose transparency enables the early stages of embryogenesis to be observed.

Many successful national and international partnerships

Multidisciplinarity approaches are absolutely central to our research. This explains the many scientific partnerships that have been established, both within the department and with scientific entities from other departments. By way of example: genetic resistance to infectious diseases in the host is studied with the Virology Department; the contribution of epigenetics to infection with the Cell Biology and Infection Department; and cell programming with the Genomes and Genetics Department.

The department's researchers are also very active internationally, with a number of collaborative agreements and involvement in multiple international projects (within the European Union). In recent years the department has sought to increase its involvement with the Pasteur International Network (Istituto Pasteur-Fondazione Cenci Bolognetti) and to develop contacts with research institutes in Japan, China and India (Center for Developmental Biology at the Riken Institute, in Kobe, Japan).

Research and research issues for 2009

Research into sex determination and, to a lesser extent, work on X chromosome inactivation, demonstrate how entirely fundamental aspects of developmental biology can have translational implications and even direct clinical applications. Improving scientific communication so that fundamental research in developmental biology is more readily accepted as an integral part of biomedical research (which indeed it is) remains one of the key objectives for the coming year.

At a scientific level, the department is working to integrate genomics and bioinformatics more effectively into its daily practices

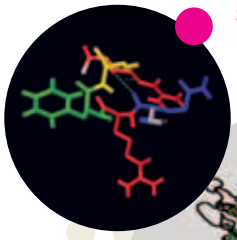
Highlights

INACTIVATION OF THE X CHROMOSOME ASSOCIATED WITH DIFFERENTIATION

In mammals, the presence of two X chromosomes in females and only one in males creates a potential imbalance in the 'dosage' of X chromosome genes. This difference is compensated for by inactivation of one of the two X chromosomes and this occurs during early female embryonic development. Inactivation is a complex process involving a number of factors. The work carried out by the Mouse Molecular Genetics Unit demonstrates how this inactivation is regulated by pluripotency factors, which are capable of maintaining a cell in its undifferentiated state. This research shows that undifferentiated state master genes directly regulate inactivation. It opens up new possibilities for research into the epigenetic reprogramming mechanisms involved in embryogenesis, and for reprogramming adult cells for cell therapy through the derivation of iPS cells (Induced Pluripotential Stem Cells).

The department's researchers study the 3D structure of molecules (such as proteins, nucleic acids, and carbohydrates) to understand their function and their role in cellular processes and pathologies. This leads to a more profound, molecular understanding of infectious diseases (such as tuberculosis, Chagas disease and malaria) and the processes associated with cancer and genetic disorders. The scientists also design chemical tools to explore these mechanisms, interfere with them and develop vaccines and therapies.

Structural Biology and Chemistry



Structure representing the Opiorphin QRFSR peptide, involved in the regulation of pain perception.

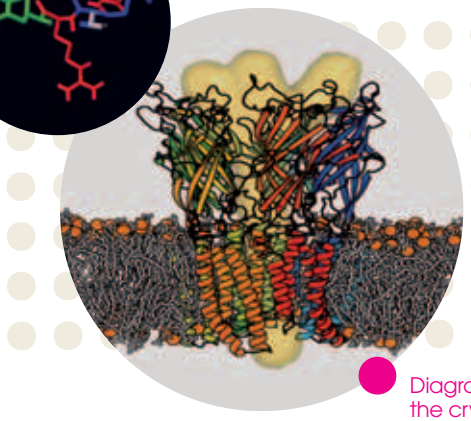


Diagram representing the crystallographic structure of the nicotine receptor bacterial analog.

Cutting-edge technology for a structural approach

The department uses cutting-edge methods, including crystallography, nuclear magnetic resonance (NMR), modeling, and biochemical and biophysical characterization, to determine the 3D structure of proteins (and other biological molecules).

Molecular modeling plays a key role in determining structures and how they are used, and the department's expertise in the use of this method is recognized at an international level. A training session on modeling is run on the campus for around twenty students from all over the world, every two years.

Crystallography, the most important structural biology methods, enables the 3D structure to be determined using high-precision, high-quality data. It is ideal for initiating drug design studies on potential targets.

NMR also provides access to the structure of molecules that are smaller in size. The molecules are studied in their natural environment. NMR supplies information about molecular motions, providing an important insight into molecular function. This technology is also a powerful tool for studying molecular interactions, particularly weak interactions.

In January 2008, the Institut Pasteur organized its eighth international conference on NMR in biology. Top international researchers met to discuss the subject. This event, which included presentations of biological projects and technological breakthroughs made possible by

Highlights

PROMISING RESULTS FOR A *SHIGELLA* VACCINE

Together with the Molecular Microbial Pathogenesis Unit, the Chemistry of Biomolecules Unit has designed a first semi-synthetic glycoconjugate vaccine capable of triggering protective immunity to endemic bacillary dysentery caused by *Shigella* bacteria. Promising results obtained *in vivo* in mice have paved the way for a proof-of-concept clinical trial in humans for this vaccine candidate. Pre-clinical trials are being carried out for this purpose.

NMR, has a considerable impact among the scientific community and confirms the Institut Pasteur's leading role in structural biology and the use of cutting-edge technology.

Research areas

••• Structures revealed

The department has resolved the 3D structures of a number of proteins that are crucial for a range of pathogens and likely to represent drug targets. The Structural Biochemistry Unit has determined the structures of proteins, such as kinases, and proteins involved in the synthesis of the cell wall of *Mycobacterium tuberculosis,* the infectious agent responsible for tuberculosis. Following on from this discovery, the current aim is to design inhibitors of these proteins to prevent cell wall formation and therefore pathogen propagation.

Together with the Structural Virology Unit in the Virology Department, the Cellular and Structural Biochemistry Unit determined the structure of the NEMO protein regulation domain. NEMO plays a key role in regulating the NF-kB pathway. This pathway is implicated in many cancers as it controls apoptosis (or programmed death) in certain cells. Research is under way to find inhibitors of NEMO function that could lead to the development of new cancer drugs.

••• Designing therapeutic molecules

Understanding the function of proteins and their interactions with other molecules is essential for combating certain pathogenic mechanisms and developing vaccines or therapeutic agents. When the role of a protein in the development of a disease has been clarified, it becomes a potential therapeutic target.

Once the potential target has been identified and characterized, the department is able to carry out computer screening for several hundred thousand virtual molecules (Structural Bioinformatics Unit). This virtual screening predicts the molecule's interaction with the protein. The best molecules (generally a few hundred) can be tested in the laboratory.

Experimental screening of molecules on models of infectious diseases, such as tuberculosis, malaria and chikungunya, backed by the Île-de-

9 units

6 platforms

150 people

Highlights

THE PROMISE OF A THERAPEUTIC TUMOR VACCINE

Research carried out in cooperation with the Immune Regulation and Vaccinology Unit has led to the development of MAG:Tn3, a synthetic molecule based on the Tn antigen. This vaccine candidate has the potential to target adenocarcinomas, especially breast, lung and prostate cancer. Findings obtained *in vivo,* in particular in mice, could lead to a phase I/II clinical trial for MAG: Tn3. Pre-clinical trials are being carried out for this purpose.

France regional council, is enabling biological and medicinal chemistry research projects to be carried out (work undertaken by the Organic Chemistry Unit). This research has several aims: the discovery of a selective inhibiting compound could prove to be a very useful molecular tool for research into a specific biochemical process. Furthermore, demonstrating the efficacy of such inhibitors on cell culture, or even on animal models, could lead to the development of new drugs, particularly in the field of infectiology.

The Organic Chemistry Unit is contributing to several multidisciplinary programs in this field involving the biochemical and structural characterization of proteins of therapeutic interest and the synthesis of new chemical entities derived from nucleosides. The aim of this research is to validate the targets selected to develop innovative therapeutic strategies. The Chemistry of Biomolecules provisional unit develops biologically active molecules of therapeutic or preventive interest. A tumor vaccine candidate and a synthetic *Shigella* vaccine candidate have been developed in the laboratory and are undergoing pre-clinical trials.

The molecular and functional characterization of a new peptide mediator involved in the regulation of pain perception in humans opens up molecular opportunities that may lead to innovative drug candidates to treat acute and/or chronic pain. The aim of the virtual and experimental screening approaches adopted in the department is to select functional mimetic derivatives of the natural molecule that present with more stable bioactive conformations.

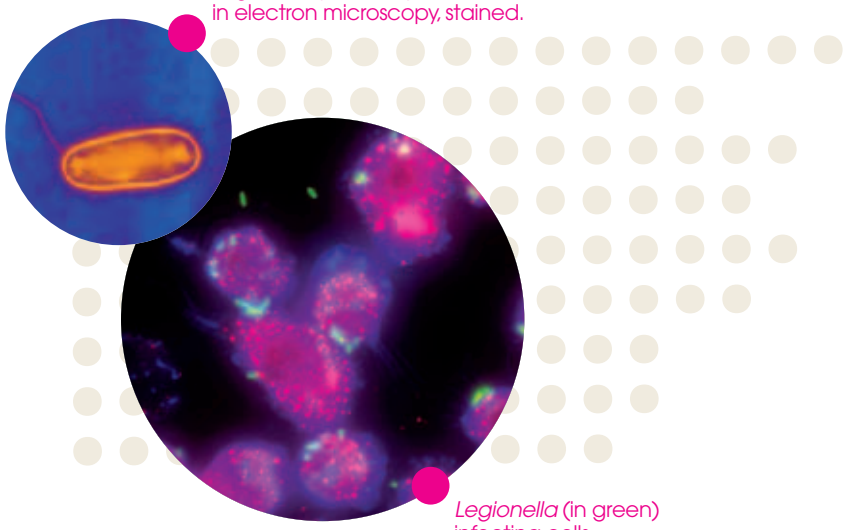
Validating the targets selected to develop innovative therapeutic strategies.

BLOCKING HIV ENTRY INTO CELLS

HIV entry into cells requires close contact between the viral envelope and the CD4 receptors and CCR5/CXCR4 cell co-receptors. Very promising glycoconjugates that simultaneously target interaction areas on the viral envelope are under development.

As new genes continue to be discovered and new biological functions are identified, genomics poses an increasing number of questions that still remain unanswered. Curiosity is the driving force of the Genomes and Genetics Department, which draws on the history of humanity to investigate susceptibility and resistance to infection.

Genomes and Genetics



Legionella pneumophila, observed in electron microscopy, stained.

Legionella (in green) infecting cells.

The department studies the genetic information of humans and microorganisms, such as bacteria and yeast. This research, initially fundamental, is aimed at understanding life itself and also, in the case of pathogenic microbes, their lifestyles and what determines their pathogenic nature. Tuberculosis, Legionnaires' disease, malaria and the pathogens that cause them are central to this research. The department is involved in international research programs, such as the Malaria Genomic Epidemiology Network. In human genetics, research focuses on populations and their susceptibility or resistance to epidemics. Five laboratories from the department use information technology as a main research tool. They analyze the interactions between complex biological networks and carry out *in silico* genome analysis, particularly to demonstrate biological properties. They also manage databases which are essential for researchers.

Human genetics

The Human Evolutionary Genetics Unit focuses on the various factors (selection, demography, genomics) involved in human genome variability and strives to piece together part of the history of humanity. They also study the diversity of the genomic regions involved in immune response and host-pathogen interactions, enabling traces of natural selection to be revealed. The unit has adopted an evolutionary approach to explore how infectious agents have exerted selective pressure on human genes, which genes have played a biological role in surviving hosts, and the role of genes in immunity.

Highlights

THE HISTORY OF CENTRAL AFRICAN PYGMIES AND BANTU FARMERS

The Human Evolutionary Genetics Unit has studied the demographic and genetic history of Pygmies and Bantu farmers of Central Africa. It appears that the two groups began to diverge from a common ancestral population less than 70,000 years ago. They remained isolated from each other before genes were once again exchanged 40,000 years ago, through marriages between Pygmy women and male farmers. These findings could serve as a basis for research into the impact of the settling process on genome evolution, especially on vulnerability or resistance to certain pathogenic agents.

Researchers have identified over 580 genes that seem likely to have contributed to the morphological diversity of populations and their differences in terms of susceptibility to disease. This work opens up considerable possibilities for research on the genes controlling predisposition to various pathologies.

Given that our genome is made up of around 20,000 genes, there are plenty of reasons to explain our uniqueness. It would be restrictive to attribute one characteristic to one gene. On the contrary, the complex network of interactions between these genes is a concept that needs to be fully understood. The Institut Pasteur therefore carries out research into human genetics from many angles — all the genetic determinants involved in a phenomenon within a natural population are studied. This is the case for research into susceptibility or resistance to malaria or tuberculosis, for example.

Genetics and bacteria

Several units are studying the genomics of model or pathogenic bacteria. The Bacterial Genome Plasticity Unit, for example, is researching the ability of bacteria to acquire and exchange genes, an astonishing method for rapid and effective development The aim of research conducted by the Mycobacterial Genetics Unit is to understand the interactions between the tuberculosis bacillus and the cells of the infected patient at molecular level, with a view to developing new means of prevention and treatment for the disease. Scientists are also attempting to understand the host factors involved in the infection; they have succeeded in identifying, for example, the major receptor of the bacillus on its target cells.

Legionella, a pathogenic bacterium, is the focus of research carried out by the Biology of Intracellular Bacteria Unit, which has compared the genomic content of dozens of strains of this bacterium responsible for Legionnaires' disease. Their work paves the way for the development of rapid diagnosis tests, something which is currently lacking for the environmental monitoring of legionellosis and therefore its effective prevention.

Highlights

CUTS: CRYPTIC UNSTABLE TRANSCRIPTS

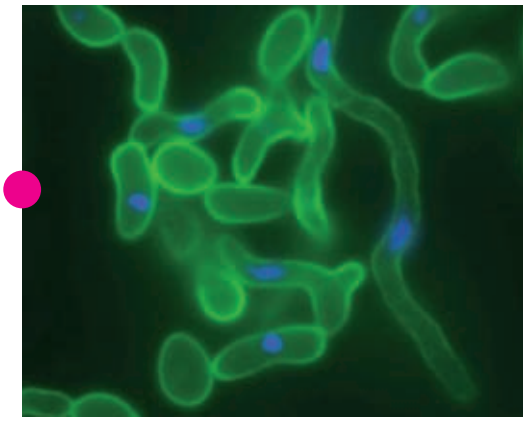
The Macromolecular Interaction Genetics Unit has made a fundamental discovery in the way in which genes are expressed in eukaryotic cells. In bacteria, gene regulation normally occurs with transcription. The team showed that in yeast, which is used as a eukaryotic cell model, the polymerase that catalyzes the transcription of genes into RNA does so randomly, and in both directions from a given point on the DNA strand. These RNAs, known as CUTs, are born and die almost instantly due to a highly effective degradation complex. They have a very short lifespan and are extremely difficult to observe. The unit created mutants, which allowed them to observe slowed down RNA degradation and characterize the phenomenon, mapping all the sites where it occurs in yeast.

Other units are using modern genomics methods to characterize bacterial strains, such as streptococci and vibrios. They are particularly studying the development of these bacteria.

Synthetic biology for cell reconstruction

Synthetic biology represents a significant development in today's biological research. It combines genetic engineering principles and methods to create informative molecules that differ from those existing in nature, with the aim of constructing new biological systems and functions (artificial genome, new amino acids, etc.). One reason for this is to be able to artificially produce genomes that are more effective than those that have been, or could be, produced naturally. Increasing complexity and introducing new amino acid functions will be major challenges for biology in the coming years.

The Systems Biology group modified *Escherichia coli,* an intestinal bacterium, in order to demonstrate the mechanism used to shift from a unicellular to a multicellular state. The bacteria produced were interdependent and unable to live without each other. Research carried out by the Genetics of Bacterial Genomes Unit has led to extension of the genetic code and consequently to the synthesis of totally new amino acids.



Cells of *Candida albicans,* a single-celled fungus responsible for candidiasis. Nuclei in blue.

Yeasts: fungi so close to humans

Yeasts are single-celled fungi that share a relatively recent evolutionary origin with animals and therefore with humans. They can be found all around us: on plants, people, in alcoholic fermentation and bread making, in the digestive tracts of insects, etc. Some of them are pathogenic for humans, such as *Candida albicans,* a yeast that can be fatal and for which there is no antibiotic. These yeasts serve as models for studying the fundamental mechanisms in eukaryotic cells, most of which can be transposed to human cells.

The Fungal Biology and Pathogenicity Unit, which studies these yeasts, is particularly working to discover how the biofilms of these fungi are formed, and to characterize the signaling pathway that leads to pathogenesis. The unit also carries out strain typing. This unit has characterized a new mechanism, loss of heterozygosity, which sustains the genome evolution in this yeast.

The genomes' instability and their consequences for both evolution and genetic pathologies in humans is the focus of research in the Yeast Molecular Genetics Unit.

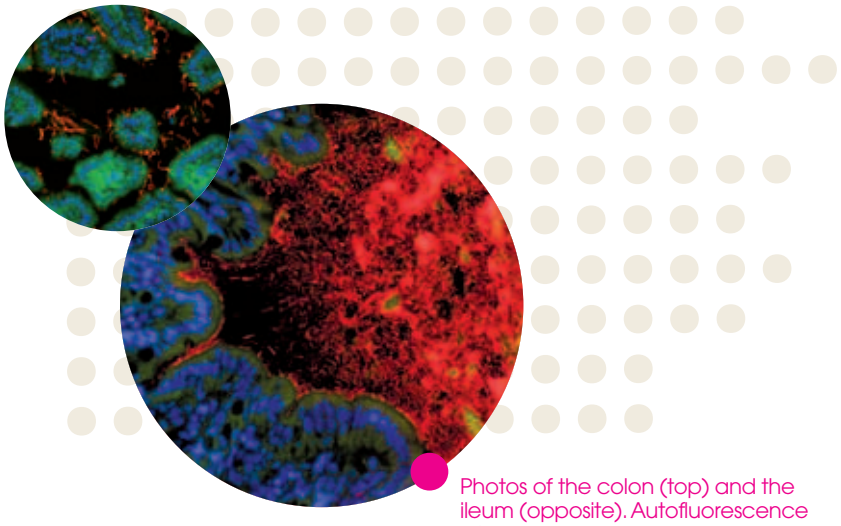
Scientists have discovered a new molecular mechanism responsible for the frequent, random duplication of large pieces of chromosomes leading to an imbalance in the number of genes and to genomic instabilities.

Sequencing and genotyping

The department has the privilege to host a new cutting-edge high-throughput sequencing facility, a real asset for the Institut Pasteur. This equipment has revolutionized research into populations of pathogenic microorganisms, gene expression and especially genome modification and epigenesis. The Genotyping Platform carries out the typing of pathogenic organisms and studies population genetics. Finally, the Genome Analysis and Integration team uses IT methods to analyze and manage genomic and post-genomic data, using a range of algorithms to facilitate their analysis.

The department has eleven research units, three five-year groups, a laboratory and two platforms. Almost 200 people work in the department, which also has links with two teams from the Infection and Epidemiology Department, one team from the Developmental Biology Department, and one team from the Institut Pasteur International Network. The research carried out ranges from purely fundamental work to clinical trials, and includes the construction of murine models for the *in vivo* analysis of mechanisms responsible for human diseases.

Immunology



Photos of the colon (top) and the ileum (opposite). Autofluorescence of the tissues in green, commensal bacteria in red, cell nuclei in blue.

Innate and acquired immunity

We now know that we have "two immune systems": an ancient immune system and a modern immune system. The ancient system confers an "innate" immunity. It is composed of mostly myeloid cells, which possess receptors for a limited number of molecular "motifs" that are conserved by numerous microorganisms. They can therefore interact with microbes and destroy pathogens. Given the number of these cells and their instant action, innate immune responses are immediate.

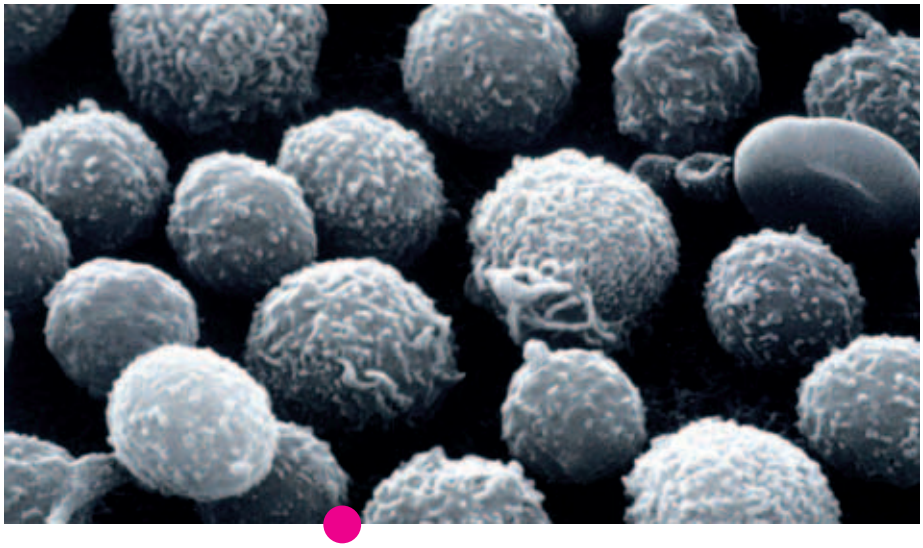
The modern immune system confers an "acquired", adaptive, immunity. It is composed of lymphocytes with receptors that are able to specifically "recognize" numerous molecules (the antigens). Because each lymphocyte expresses one such receptor only, because there is a finite number of lymphocytes and because the immune system repertoire is immense, few lymphocytes only can recognize a given antigen. They must first multiply and differentiate into effector cells (antibody-producing cells or cytotoxic cells, for example), to act on this antigen. Acquired immune responses take several days to develop.

The modern immune system has not replaced the old system; the two work together. Cells of the innate immune system, such as dendritic cells, capture and degrade the antigen, the resulting fragments of which they associate with their histocompatibility molecules to "present" them to T lymphocytes. This cooperation is necessary for the development of acquired

Highlights

AN ESSENTIAL BALANCE BETWEEN BACTERIA AND THE IMMUNE SYSTEM

The five-year group *Development of Lymphoid Tissue* studies the interactions between the commensal flora and the immune system. Deciphering this dialog has revealed how intestinal homeostasis is established and maintained. The recognition of intestinal bacteria by innate immunity receptors leads to the formation and the maturation of lymphoid tissues involved in adaptive immunity which, in return, regulates the commensal flora.



Lymphocytes and erythrocyte (smooth membrane) as seen by scanning electron microscopy.

immunity. When antibodies have been produced, they bind to receptors for antibodies, which are expressed by numerous myeloid cells, and they provide these cells with *bona fide* antigen receptors. Antibodies thus "enroll" cells of the innate immune system in acquired immunity.

The Immunology Department is studying cell differentiation in the two immune systems and their organization into lymphoid tissues, how innate and acquired immune responses are triggered and what their biological effects (protective and/or pathogenic) are, the regulatory mechanisms that control them and the dysfunctions of these mechanisms.

Development and homeostasis of the immune system

Several teams are studying the formation of the immune system, from the very first hematopoietic precursors that appear in the yolk sac in the mouse embryo, and their organization into lymphoid tissues. One team is exploring the mechanisms that bring about the somatic mutations that regulate antibody affinity. Others are looking into the homeostasis that maintains the balance of the various lymphoid populations after they have multiplied during the immune response, and how cell death mechanisms are programmed which can eliminate autoreactive and transformed cells.

Immune responses and diseases

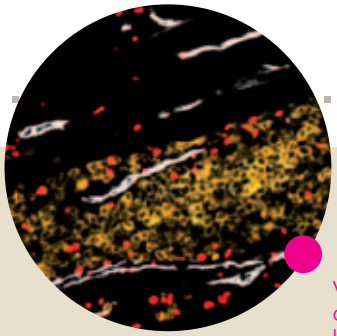
Immune responses provide protection against infection, and also against some cancers. Teams are studying the protective mechanisms involved in immunity to infection and cancer. Others are developing new vaccinal strategies and immunotherapy protocols to make these mechanisms more effective.

Immune responses, however, can themselves be pathogenic. Mechanisms that can kill are indeed potentially harmful. This is the case when they are directed against self molecules, as with autoimmune diseases, or when their intensity is

Highlights

CONSEQUENCES OF THE SLOW IMMUNE SYSTEM

The five-year group *Dynamics of Immune Responses* has used two-photon microscopy to view *in vivo* interactions in real time between CD8 cytotoxic T cells and tumor cells, in a cell therapy model. The findings revealed that the T cells kill the tumor cells individually through a process that lasts an average of six hours. This slow process may partly explain the ineffectiveness of the immune system in eliminating cancer cells.



Visualization of cytotoxic T lymphocytes (red) entering a tumor (yellow).

exaggerated, as with inflammatory or allergic diseases. Immune responses must therefore be tightly controlled. Several teams are studying these regulatory mechanisms, their dysfunctions and their potential therapeutic use.

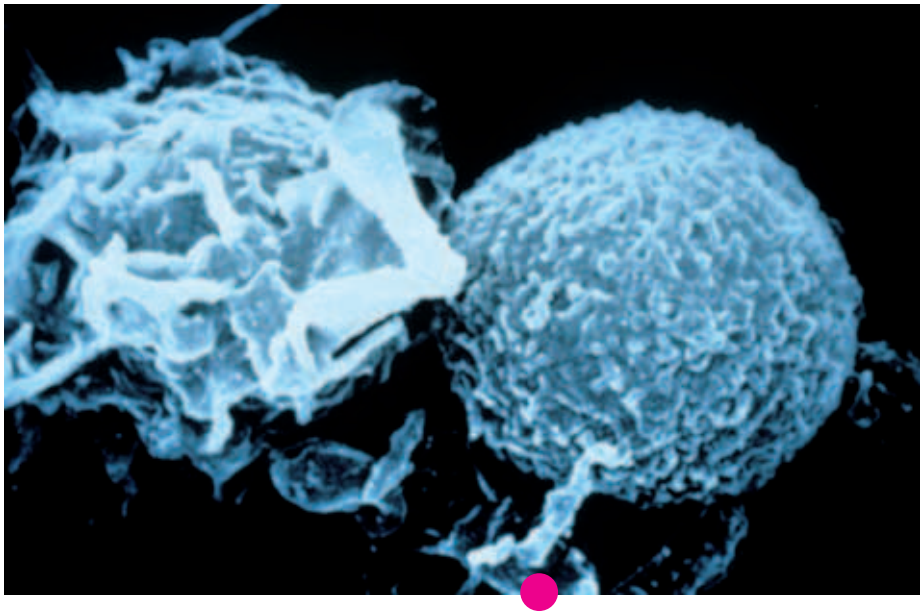
Of mice and men…

Genetic recombination and transgenesis techniques have been used to produce genetically modified mice, which provide powerful analytical tools for determining the biological roles of immune molecules. However, mice are not humans. The department is therefore involved in creating and studying "humanized" mice in which key immune system molecules, or even immune cells, have been replaced by their human counterparts.

Mice whose major histocompatibility complex molecules have been replaced by their human counterparts are thus capable of presenting antigens in the same way as humans. These mice can be used for research into antiviral immunity; they enable the identification of peptides that are immunogenic in humans and can be used to produce vaccines.

Similarly, mice whose antibody receptors have been replaced by their human counterparts can be used to investigate inflammatory diseases induced by antibodies, such as allergies or some autoimmune diseases. They can also be used to assess the efficacy and toxicity of therapeutic antibodies and to optimize them.

Finally, mice with no immune system — due to inactivation of the genes that must be expressed in order for immune cells to develop — can be "reconstituted" with human lymphoid cells and acquire a human immune system. Human immune responses can therefore be studied, in mice. These mice can also accept human tissues, such as hepatic cells, and be infected by viruses responsible for human diseases, such as hepatitis C. The immune responses of human cells can therefore be studied *in vivo.*



Contact between macrophage (left) and lymphocyte as seen by scanning electron microscopy.

The relationship between fundamental and clinical immunology

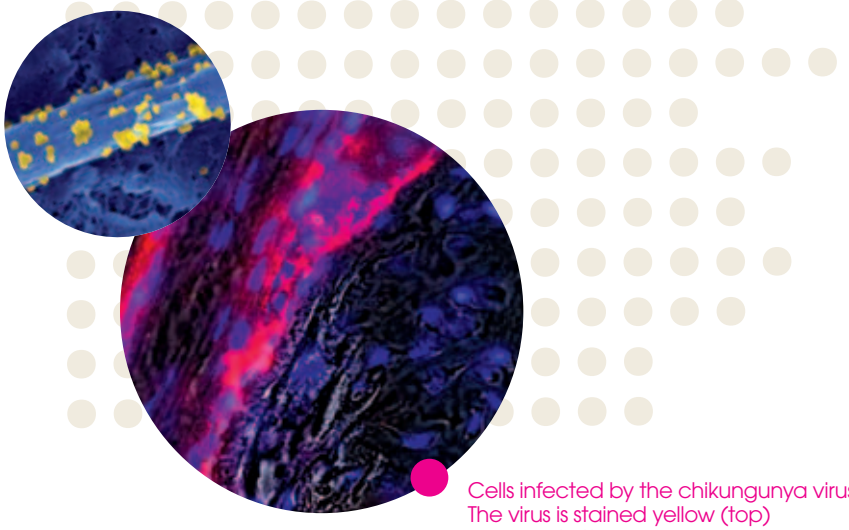
The department is committed to research into human immunology. It is important to compare the results of fundamental research observed in animal models, *in vitro* or *in vivo,* with the reality of human physiology and pathology.

A *Center for Human Immunology* (CIH) was set up for this purpose in 2008 so that researchers and clinicians can meet and work together. The center not only aims to develop "translational" research, enabling concepts developed in experimental models to be applied to clinical situations but it also, and perhaps especially, seeks to develop experimental models to answer the questions raised by human pathologies. Pathologies often reveal a great deal about physiology. The center is affiliated to the Immunology Department and the Imagopole and is open to researchers from the entire campus and to any interested clinicians. It was recognized as a *FOCIS Center of Excellence.*

A *Center for Human Immunology* (CIH) was set up in 2008 so that researchers and clinicians can meet and work together.

This multidisciplinary department uses immunology, epidemiology, bacteriology and virology to study infectious diseases from every angle: the reservoirs and transmission mechanisms of pathogenic agents, the virulence factors of pathogens, the pathophysiological processes of the host, the innate immune response and the role of vaccines.

Infection and Epidemiology



Cells infected by the chikungunya virus. The virus is stained yellow (top) and red (left).

The infections studied include nosocomial, pulmonary, fungal and enteric infections, listeriosis, meningitis, whooping cough, antibiotic resistance, sepsis, AIDS, rabies, chikungunya, viral hepatitis and emerging viral infections — invariably serious diseases and major public health concerns.

Responsiveness to emerging diseases

Emerging infectious diseases are a major threat to human health, and the fight against these new pathogenic agents is one of the Institut Pasteur's priorities. The department includes the Laboratory for Urgent Response to Biological Threats (CIBU), which is available 24/7 and intervenes in epidemic situations. Much of its work focuses on avian influenza. It also looks into factors associated with emergence in the environmental reservoir, such as those likely to aid the spread of avian influenza among humans. The CIBU relies on the work of reference centers. It is particularly responsible for assisting with the diagnosis of biological agents or confirming diagnosis. The CIBU provides the Institut Pasteur with a highly responsive intervention service.

Areas of research

Researchers in the Microbes and Host Barriers five-year group have discovered the molecular mechanism that enables *Listeria monocytogenes,* the bacterium responsible for listeriosis, to cross the placental barrier in pregnant women.

Highlights

INFECTIOUS DIAGNOSIS FOR HIDRADENITIS SUPPURATIVA

Through successful cooperation between scientists and clinicians, the Institut Pasteur Medical Center team has discovered that Hidradenitis suppurativa, a chronic cutaneous condition often treated with corticosteroids, might be an infectious disease.

Treatment with antibiotherapy has proved very effective. These observations open up extremely promising possibilities for further research.

The Enteric Bacterial Pathogens Laboratory, which includes the National Reference Center (CNR-Salm) and the WHO Collaborating Center for *Salmonella,* was involved in the sequencing of 19 strains representative of the biodiversity of *Salmonella enterica,* 11 of which came from the CNR salmonella collection. After analysis, it appears that the genomes' development is characterized by a continual loss of genes and adaptive selection of mutations, making the Asian strains resistant to antibiotics.

The Antiviral Immunity, Biotherapy and Vaccines Unit was responsible for monitoring immunological responses during a clinical trial to assess the efficacy of an oral vaccine against *Shigella,* the bacterium responsible for the epidemic form of shigellosis, a severe and often fatal diarrheal disease. This vaccine proved to be well tolerated and generated a level of immune response which suggests that satisfactory protection is provided after a single dose. Researchers now hope to develop a vaccine that is effective and easy to administer.

Several clinical trials are carried out with clinicians and partner hospitals.

Biomedical research and public health

A multicenter study carried out by the Epidemiology of Emerging Diseases Unit and International Network institutes demonstrated the significant incidence of pneumocystic pneumonia among opportunistic pulmonary infections in HIV patients in Asia, compared with Africa. A diagnostic algorithm of pneumocystic pneumonia based on simple clinical, radiological and biological criteria has been developed for Asian countries.

In connection with its work on cryptococcosis, an opportunistic disease that particularly affects HIV patients, the Molecular Mycology Unit set biomarkers justifying the use of neuroimaging techniques, regardless of whether neurological disorders exist, on diagnosis. Research findings were then confirmed by an observational study to decide on the best therapeutic protocol to implement.

10 units
2 provisional units
1 five-year group
2 laboratories
1 platform: genotyping of pathogens

Highlights

NEW FINDINGS FOR CHIKUNGUNYA

Researchers from the Microbes and Host Barriers five-year group have developed the first animal model able to mimic severe and benign forms of the disease caused by the chikungunya virus. This work has led to identification of the virus's main tissue and cellular targets. Moreover, a vast prospective study conducted among more than 7,500 pregnant women demonstrated the mother-to-child transmission of this virus. An increased risk of transmission during labor was also highlighted.

Vaccine-preventable diseases and the result of widespread vaccination on disease transmission, evolution of the targeted germ and population immunity are the focus of research conducted by the Molecular Prevention and Therapy of Human Diseases Unit. In 2008, this unit demonstrated that vaccination against whooping cough using inactivated whole-cell bacteria is successful if vaccination coverage is high. But this immunity remains limited in time and only controls germs identical to the vaccine strains. Germs that are slightly different but just as virulent continue to circulate. These germs are the target of subunit vaccines that can control all virulent isolates, as is the case for diphtheria. This research resulted in changes to this year's French vaccine plan, which extends vaccination coverage to all healthcare workers and adults who have not been vaccinated in the past ten years.

From the bedside to the bench

The department is closely involved in public health activities — it has many units specializing in epidemiological risks and houses National Reference Centers, the Medical Center, and the Vaccine and Biomedical Research Center. To apply this research successfully to human patients, several clinical and epidemiological trials are carried out with clinicians and partner hospitals.

The aim of the Cytokines and Inflammation Unit, for example, is to identify the molecular mechanisms responsible for the deterioration of patients' immunological status in intensive care, making them particularly susceptible to nosocomial infections. The unit is also carrying out research to define the ideal combination of biomarkers that would enable early, reliable identification of infection.

The department's units also work with International Network institutes and 40 International Network researchers have links with the department. The department's teams are responsible for a third of the Institut Pasteur's clinical research. They apply the principles of translational research — from the bedside to the bench and from the bench to the bedside — enabling the medical application of fundamental research findings, and vice versa.

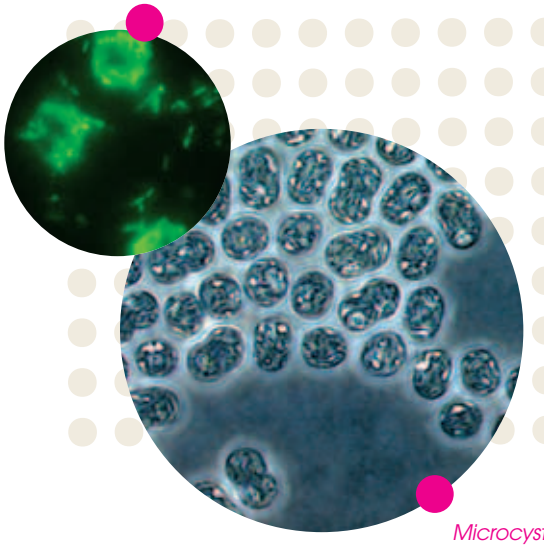
Unique teaching on infectious risks

The Public Health Masters, recently set up at the Pasteur/CNAM School of Public Health, is an important means of consolidating the Institut Pasteur's public health research. Monitoring, clinical trials, vaccinology, entomology and medical microbiology are some of the possible options of the "infectious risk" specialization available on the Masters program, with 11 courses set up in the past five years. This Masters degree helps to increase cooperation with International Network researchers who are involved in the lectures.

The Microbiology Department carries out research into the bacteria responsible for infectious diseases including meningitis, plague, anthrax and nosocomial diseases. But over and above these specific pathologies, it is the secret microbial world itself that interests the department's researchers.

Microbiology

Research into biofilm development: adhesion of bacteria (green rods) to micrometric particles.



Microcystis aeruginosa, freshwater cyanobacterium.

Scientists in the Microbiology Department work on various microorganisms (bacteria, archaea, parasites) and their viruses. They firstly explore their unique way of life and interactions with the environment, independently of any pathogenic action. They also study the pathogenic principles of these model systems to find new treatments for bacterial infections. Over the past ten years there has been renewed interest in microbiology as a result of the spectacular progress made in genomics, cell imaging and molecular ecology — all of which are methods and approaches used by the department's researchers. The department also houses the Institut Pasteur's collections, including the fungi and bacterial collection, and the best worldwide collection of cyanobacteria.

Pathogenic microorganisms

Several units in the department focus on the pathogenic microorganisms that cause severe, often fatal diseases, including plague, anthrax, nosocomial diseases, ulcers and gastric cancer caused by the *Helicobacter pylori* bacterium, and botulism. The main activities of the *Yersinia* Unit (*Yersinia* is the bacterium responsible for plague) involve analyzing horizontal gene transfers, bacterial development, the molecular bases of pathogenesis, host immune, patho-physiological and genetic response to infection, and the resistance of pathogenic species to antibiotics.

Gram-positive pathogenic bacteria (enterococci, streptococci and staphylococci) are responsible for

Highlights

STABLE VIRUSES FOR NANOTECHNOLOGY APPLICATIONS

The Molecular Biology of the Gene in Extremophiles Unit is working on archaea — microorganisms that are found in hot springs — and the viruses which infect them. These viruses with their characteristic shapes have very stable proteins at high temperatures and can prove useful in biotechnology applications. Scientists have demonstrated the possibility of grafting reactive molecules to viral particles, enabling other structures to be assembled. These structures can then be used to construct new, more complex materials, for use in nanotechnology, for example.

at least a third of bacterial infections in humans, including throat infections, meningitis, pneumonia, food poisoning, skin diseases and toxic shock syndrome. The Biology of Gram-Positive Pathogens Unit aims to identify the molecular aspects of bacterial virulence to improve understanding of the pathophysiological scenario of the infectious process and contribute to the development of new therapies or tools.

Research is also carried out into spirochetes, the bacteria that cause syphilis, Lyme disease and leptospirosis. The Biology of Spirochetes Unit is studying virulence factors in pathogenic *Leptospira.* This year it developed the first genetic tools capable of inactivating the genes of these bacteria — an important technique for determining their function.

Life closely monitored

In most environments, bacteria develop on surfaces and form populations that are encased in a self-generated matrix, known as biofilm. This is often harmful in industrial environments, and the formation of biofilms on medical instruments is contributing to the development of nosocomial infections.

The Genetics of Biofilms Unit is working to identify the cellular factors required for mature biofilm formation and to demonstrate the characteristic physiological functions and responses of this environment (genetic exchanges, adhesion, interbacterial communication and mechanisms of antibiotic resistance).

This work could also lead to the development of strategies to prevent or control biofilm formation in situations where they represent a health, industrial or environmental risk.

Units are working on bacteria transport and membranes, the means by which they feed. For example, iron is essential for many enzyme reactions, but not very soluble. Bacteria have therefore developed iron solubilization and sequestration systems. The Bacterial Membranes Unit is mainly focusing on research into an original system for the uptake of the iron-containing molecule heme. It is found in the structure of several proteins, including hemoglobin. Research covers both gene expression regulation and identification of the action mechanism of each protein involved in the heme acquisition system.

Bacteria with environmental potential

Cyanobacteria emerged around three billion years ago and are responsible for the presence of oxygen on our planet. They colonize most ecosystems and can be detrimental to humans and the environment, in particular due to their ability to synthesize toxins. The Cyanobacteria Unit is focusing on the genome, physiology and biodiversity of these cyanobacteria to improve understanding of their adaptive capabilities in

Highlights

FIRST SEQUENCING OF A FRESHWATER CYANOBACTERIUM GENOME

The Cyanobacteria Unit has sequenced the genome of a hepatotoxic freshwater cyanobacterium of the genus *Microcystis* that is widespread over all five continents. When *Microcystis aeruginosa* proliferate, a limited number of genotypes are selected from local populations. These changes in genotype composition during proliferation are partly linked to the selection and counter-selection of clones which may or may not be capable of producing hepatotoxins (microcystins). The same result has been observed in another cyanobacterium, *Planktothrix agardhii.*

changing environmental conditions. The aim is to clarify the role and biosynthetic pathways of the secondary toxic and/or bioactive metabolites that they produce, and to exploit their biotechnological potential.

Antibiotic resistance and alternative therapies

The Biology and Genetics of the Bacterial Cell Wall group is studying the metabolism of peptidoglycan (PGN), which is essential for bacterial rigidity and shape. The long-term aim is to develop new therapeutic strategies by targeting PGN metabolism, and to increase understanding of the mechanisms of antibiotic resistance, a serious public health problem.

Bacteria can also alter antibiotic targets or antibiotics themselves. The Antibacterial Agents Unit studies the molecular mechanisms of antibiotic resistance in bacteria — the genetic basis, biochemical mechanisms, heterospecific expression, evolution and dissemination of antibiotic resistance. The unit recently demonstrated a new vehicle for gene transfer from bacteria to mammal cells.

Alternatives to antibiotics are also being investigated. Bacteriophages — viruses that only infect bacteria — have frequently been used by researchers to combat bacteria, as models for research into fundamental cell mechanisms (replication, transcription, regulation, etc.) and, more recently, as biotechnology tools. The Molecular Biology of the Gene in Extremophiles Unit is investigating the relationship between bacteriophages and bacteria. The aim of this research is to improve understanding of how bacteriophages can be used to combat infectious bacteria. This technique is known as phage therapy.

14 units, **1** bacteria collection and **1** fungi collection

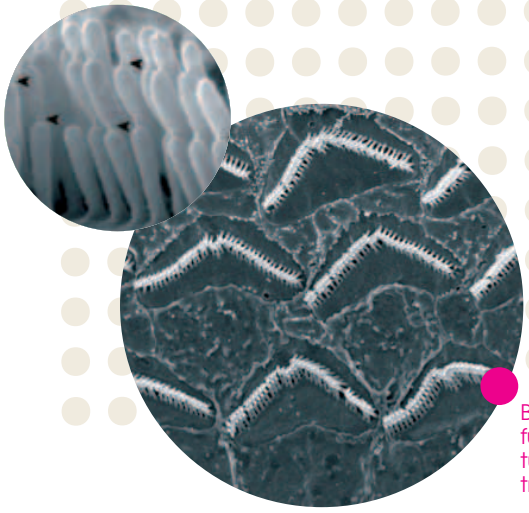
A NEW APPROACH FOR BIOFILM RESEARCH

The Genetics of Biofilms Unit has developed a multidisciplinary approach combining biophysics, flow cytometry and bacterial genetics. This approach enables several parameters to be measured simultaneously during bacteria-surface interactions with a temporal resolution of a few seconds.

This provides new information on the very early stages of adhesion and paves the way for research into the physiology of bacteria in contact with surfaces, a decisive stage in biofilm development.

The department carries out fundamental research to understand the principles governing the nervous system: those which are innate, those acquired and the dialog between the two. Research focuses on several diseases, disabilities and behavioral disorders, including autism, certain neurodegenerative diseases, deafness and nicotine addiction.

Neuroscience



Bottom and top (magnified further), hair cell stereociliary tufts involved in auditory signal transmission in mice.

Over the past few years, genetic analysis carried out by many of the department's units has enabled spectacular progress to be made in understanding the molecular and cell mechanisms which, if impaired, can lead to these disorders. The research teams focus on deciphering nervous system functions in molecules, cells, synaptic communication (synaptic physiology and pathophysiology in autism) and neuronal circuits. The department is also committed to developing imaging, genetic and molecular biology techniques with resolution capabilities that open new fields of investigation.

Detailed knowledge of the central nervous system

••• At molecular level

The Channel Receptors five-year group is looking into the specific receptors in the brain that are activated by acetylcholine and nicotine. Its work has led to the identification and isolation of the ancestors of these proteins in bacteria; the simplified structure of these protein ancestors lends itself to structural research. The group has established the first atomic-resolution 3D structure of a bacterial receptor in its active state (study carried out with the Structural Dynamics of Macromolecules Unit).

••• At neuronal circuit level

The neurotransmitter acetylcholine plays an important role in the central nervous system (where it is involved in memory and learning)

Highlights

DISTORTING SOUNDS TO IMPROVE HEARING

A study carried out by the Genetics and Physiology of Hearing Unit has revealed how the inner ear distorts sounds. This distortion is one of the essential stages in the processing of auditory messages by the ear. These messages are then encoded and transmitted to the brain as electrical signals.

Distortion improves speech intelligibility. This breakthrough should help to improve the interpretation of certain existing hearing tests, used in particular to detect deafness in newborn babies.

and the peripheral nervous system. The Integrative Neurobiology of Cholinergic Systems Unit is studying the way in which acetylcholine alters the dopaminergic networks underlying certain cognitive functions, including what is known as the "reward" function. Unit researchers are also studying nicotine addiction. Their aim is to understand the molecular and cellular composition of the neuronal networks involved, and to establish correlations between the presence of a particular neurotransmitter receptor in a given cell subtype and a particular type of behavior. They have started to explore how the cholinergic system, and therefore nicotine, protects against the neurodegeneration found in Parkinson's and Alzheimer's disease.

••• Plastic and self-renewal properties

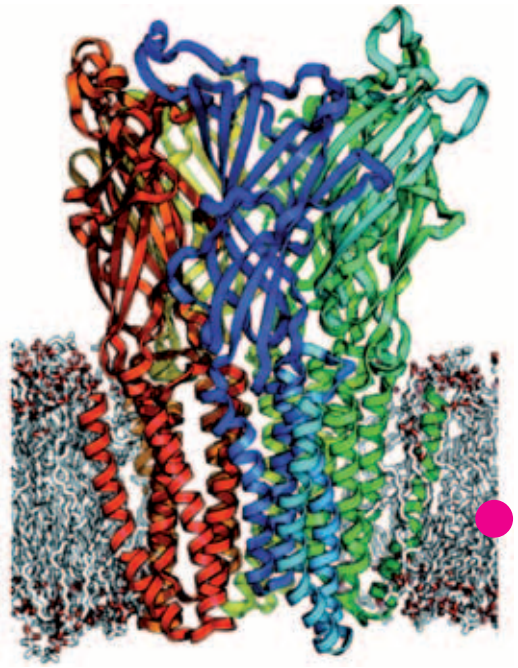
The Perception and Memory Unit has recently identified a new neuron production source in the adult brain. This work demonstrates the brain's intrinsic self-repair capacity. It also opens up unexpected possibilities for the development of therapies, particularly for the treatment of neurodegenerative pathologies such as Parkinson's disease or Huntington's chorea. The team demonstrated that glial stem cells, which are able to transform into neurons, are not only located in the subventricular zone of the brain, but also along a tunnel where new neurons migrate, and in the olfactory bulb. The "neurogenic" regions of the adult brain are therefore much larger than previously believed. This team is also studying the relationship between these cells and existing cellular networks.

A genetic approach to research

••• Increasing knowledge about deafness and the principles governing the auditory system

Severe or profound deafness affects one child in 700 at birth and one child in 500 before adulthood. For children who are profoundly deaf at birth, acquiring spoken language is particularly difficult. One quarter of people aged over 65 are hard of hearing, which interferes with their conversations and can have an adverse effect on their social lives. The Genetics and Physiology of Hearing Unit is

We now know that in developed countries, around three quarters of cases of deafness in young people are hereditary.



3D structure of a bacterial ancestor of nicotine receptors, shown embedded in the outer membrane.

3D STRUCTURE OF A NICOTINIC RECEPTOR HOMOLOG

Together with the Structural Dynamics of Macromolecules Unit, the Channel Receptors five-year group has established the first atomic-resolution 3D structure of a bacterial receptor in its active state, the ancestor of vertebrates' acetylcholine and nicotine receptor. The data obtained opens up many possibilities for understanding the mechanisms responsible for neuronal communication and their modulation by drugs (nicotine and alcohol) and therapeutic components (tranquilizers and general anesthetics). It will also be used to develop new molecules that can target these receptors.

working to understand the molecular mechanisms of the cochlea, the auditory sensory organ. The genetic approach developed has offered an insight into several aspects of its development and functioning, in particular regarding the hair bundle, the structure that receives sound from the auditory sensory cells. The team has identified around twenty genes which, if lacking, lead to deafness. We now know that in developed countries, around three quarters of cases of deafness in young people are hereditary. This research has greatly improved the quality of genetic advice given to families and management of people with hearing difficulties. It enables some forms of hereditary deafness, triggered by certain drugs or exposure to noise, to be prevented, and enables some children to receive a cochlear implant by identifying the impairment in each form of deafness. Usher syndrome, which combines blindness caused by retinal degeneration and deafness, is a major focus of research in this unit, both in terms of fundamental knowledge and the development of therapeutic approaches.

Age-related hearing loss, or presbycusis, is also researched to try to discover the genetic and environmental predisposition factors of this condition, with a view to prevention and treatment.

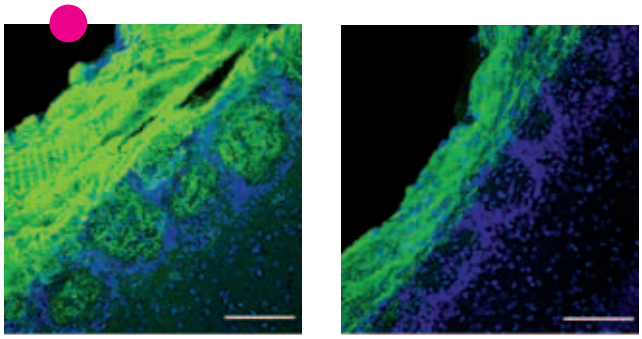
••• Improving the lives of autism sufferers

More than one child in 200 suffers from autism, a complex syndrome characterized by severe developmental problems in communication and social interaction.

Autism cannot be diagnosed before the age of three. In most cases, it is accompanied by mental retardation. If this is not the case, the term "high-functioning autism" is used. There is no therapy for autism. The Human Genetics and Cognitive Functions Unit has identified genetic mutations associated with the condition. It recently discovered *Shank3,* a gene involved in the establishment of contacts between neurons — in other words, the formation of synapses.

The team is also looking into melatonin, a hormone that plays an essential role in regulating biological rhythms. A number of studies have found low levels of melatonin in patients suffering from autism. Researchers in this unit have demonstrated that some young people with autism presented anomalies in the synthesis of this hormone. This discovery has direct therapeutic applications: taking melatonin improves autistic children's sleep.

An olfactory epithelium lesion leads to a lack of olfactory bulb innervation. On the left, the green labeling shows the presence of sensory endings from the olfactory epithelium. In the event of lesions (photo on the right), there are no sensory endings innervating the olfactory bulb glomerular layer.



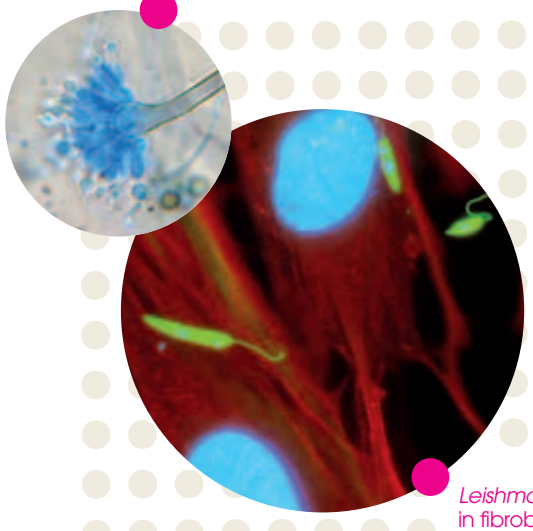
Hopes for gene therapy

••• A therapeutic trial for Sanfilippo syndrome currently in the planning stages

The Retrovirus and Genetic Transfer Unit has demonstrated that gene therapy might be beneficial in Sanfilippo syndrome. This rare genetic disease in children is caused by an enzyme deficiency that leads to an accumulation of saccharides in cells. It is characterized in children from the age of three by behavioral problems which are followed by the onset of mental retardation, gradually leading to loss of speech and walking ability. From the age of seven or eight, children become uncommunicative and are highly dependent. There is currently no treatment for this disease. Having demonstrated in animals that providing brain cells with the missing enzyme restores them to a normal state, the unit is preparing for a gene therapy trial in child sufferers. This trial will be carried out with the Department of Pediatric Neurology at Kremlin-Bicêtre Hospital. In order to judge the efficacy of this treatment in children, researchers are collecting epidemiological data on the natural development of the disease at European level and working to determine biomarkers to measure the effects of the treatment. They are also working to improve their understanding of the disorder at nerve cell level.

The department's research activities are dedicated to three eukaryotic parasites responsible for severe diseases with major health and economic impact in developing countries: *Plasmodium spp* (the malaria parasites), *Leishmania spp* (responsible for leishmaniasis) and *Trypanosoma brucei* (responsible for sleeping sickness), as well as the *Anopheles* mosquito, the vector for *Plasmodium* parasites. The research activities on fungi are focused on the mycosis caused by *Aspergillus fumigatus,* often fatal in immunosuppressed patients (invasive aspergillosis).

Parasitology and Mycology



Aspergillus ustus, a filamentous fungus.

Leishmania (in green) in fibroblasts. In blue, the cell nucleus.

The department's activities combine basic research using *in vitro* and *in vivo* models with biomedical research, field work and clinical vaccine trials. New models and experimental tools are developed to improve understanding of the dynamic interactions that these microorganisms establish with their host, the fundamental basis of parasitism and vector transmission, invasion of the host by fungi, as well as the virulence factors, pathology and survival strategies of these microbes. The department has benefited from the support of the dedicated "Combating Parasitic Diseases" fund, co-financed by Sanofi-Aventis and the French Ministry of Research and Higher Education.

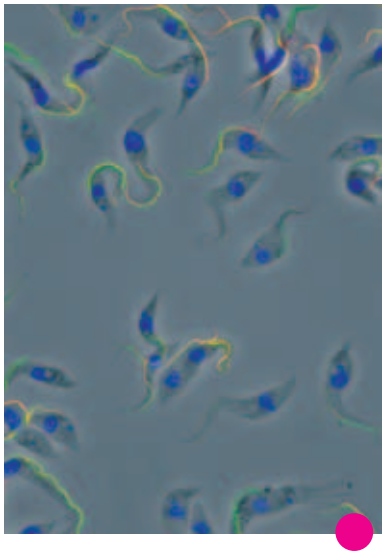
Plasmodium and malaria: a public health priority

Malaria affects some 500 million people worldwide every year and causes 1 million deaths. There is no vaccine currently available. The available drugs are losing their effectiveness as a result of the multidrug resistance developed by *Plasmodium* and *Anopheles* vector mosquitoes are becoming resistant to insecticides. The department is working to improve understanding of the relationship between malaria parasites and their host(s) with the aim of developing new methods of prevention, treatment or control for the disease. Cooperation with the Institut Pasteur International Network is a key of these programs.

Fundamental research to understand the host-parasite relationship

The research scope includes all stages of the *Plasmodium* parasite's biological cycle, from the mosquito to the mammal host.

The Genetics and Genomics of Insect Vectors Unit focuses on the dissection of the genetic bases of transmission of the parasite by the *Anopheles* mosquito. Genetic mapping of the mosquito has allowed them to identify the genes contributing to the mosquito's natural resistance to the parasite. The unit's objective is to develop new tools to prevent or limit transmission by the vector.



Trypanosoma brucei, African trypanosome, responsible for sleeping sickness.

The Institut Pasteur's Center for the Production and Infection of *Anopheles* (CePIA) is a valuable resource for the mass production of various vector mosquito lines. The CePIA also studies the influence of mosquito physiology on transmission.

The pre-hepatic invasion and intra-hepatic development of *Plasmodium* that precedes the development phase in red blood cells, are studied by the Malaria Biology and Genetics Unit. Quantitative imaging in a mouse infection model led the unit to discover a novel parasite development stage, namely a development phase in the skin, and to demonstrate the essential role played by the cell traversal enabling the parasite to develop in the hepatocyte. The unit has developed powerful novel tools for conditional mutagenesis. The liver stage of parasites in humans is studied in the Biomedical Parasitology Unit for the human parasite *P. falciparum*. The unit combines vaccine development with fundamental research on the immune processes interfering with the intra-hepatic and/or blood stages.

The development of *P. falciparum* in red blood cells — which not only causes the disease but also enables the parasites to be transmitted to the mosquito — is analyzed in several *in vitro* models. The Parasite Molecular Immunology Unit works on red blood cell invasion and red blood cell membrane remodeling by parasite proteins. The modification of the mechanical, adhesive and antigenic properties of the infected red blood cell influences parasite handling by the spleen, one of the major players of parasite clearance.

The Biology of Host-Parasite Interactions Unit focuses on the molecular mechanisms by which parasites adhere to endothelial cells and the regulation of the expression of the gene repertoire involved in this process.

Exploring *leishmania-mammal* host interactions, from molecular level to *in vivo* imaging

Leishmania spp, the parasite responsible for leishmaniasis, is transmitted by a hematophagous insect, the female sand fly. Human leishmaniasis — cutaneous and/or visceral leishmaniasis — occurs in tropical and subtropical areas where both sand flies and the wild mammal reservoir are present.

The Immunophysiology and Intracellular Parasitism Unit explores how *Leishmania* hijack or remodel cell niches — macrophages and dendritic cells — and tissue niches — the skin and the draining lymph node — to establish themselves in the mammal host. Using high-content *in vitro* imaging or quantitative *in vivo* imaging methods, the unit has developed experimental systems for screening the efficacy of new molecules targeting intracellular *Leishmania*.

The Parasite Virulence five-year group dedicates its research activities to decipher the signaling pathways which operate during the development of *Leishmania* in mammal cells. The group has identified new protein kinases and a new complex of phosphorylated proteins specific

Highlights

WORKING TOWARDS NEW TREATMENTS AND METHODS TO COMBAT MALARIA

The Parasite Vaccinology Laboratory's activities are centered on vaccine candidates located at the surface of the parasites infecting red blood cells. Research is focused on new formulations designed to increase immune response and preparation of clinical batches of proteins, the folding of which mimics the conformation of the antigen on the parasite surface as closely as possible.

A vaccine aiming to protect pregnant women by preventing placental colonization by parasites that cause the disease is being developed by the Biology of Host-Parasite Interactions Unit. Several vaccines are under development and in clinical trials in the Biomedical Parasitology Unit. The Parasite Molecular Immunology Unit is developing a drug discovery project targeting the proteases

to the parasite's pathogenic stage. These new factors are being studied as new therapeutic targets.

Trypanosomes and sleeping sickness: exploring the biogenesis and remodeling of the parasite's flagellum

Sleeping sickness, a "neglected disease", is present in around 36 countries in sub-Saharan Africa where 50,000 to 70,000 people are infected each year. The trypanosome responsible for this pathology has a flagellum that enables it to move in the blood and nerve tissues. The aim of the research conducted by the Trypanosome Cell Biology provisional Unit is to understand the role of the flagellum in the cell life of the trypanosome, in particular during the early stages of infection in the tsetse fly and the vertebrate host. The unit has developed imaging tools to study infection by fluorescent trypanosomes. The identification and molecular analysis of new membrane proteins and the novel insights into the biogenesis of the flagellum and its sensory elements open new perspectives in research on certain human genetic diseases.

140 people

8 Units working on parasites, including

5 on *Plasmodium,* the malaria parasite

2 on *Leishmania*

1 on *Trypanosoma*

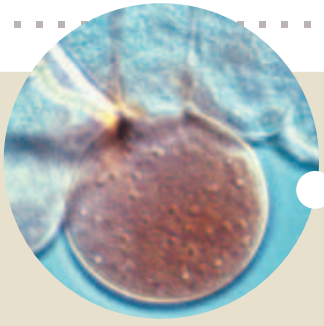
1 Unit working on fungi

1 Unit working on an insect vector, the *Anopheles mosquito*

Research areas in mycology

The *Aspergillus* Unit is studying a fungus, *Aspergillus fumigatus,* whose conidia, present in the atmosphere, are inhaled by humans. This fungus causes severe respiratory pathologies which are often fatal for immunosuppressed transplant patients or those receiving immunosuppressive treatment, despite highly costly antifungal treatments. The unit is exploring the molecular and immunological interactions between the host and the fungus during aspergillosis and the successive steps of cell wall biosynthesis, which is critical for the development of all fungi. This research opens new possibilities for diagnosis and the development of new therapies targeting essential processes.

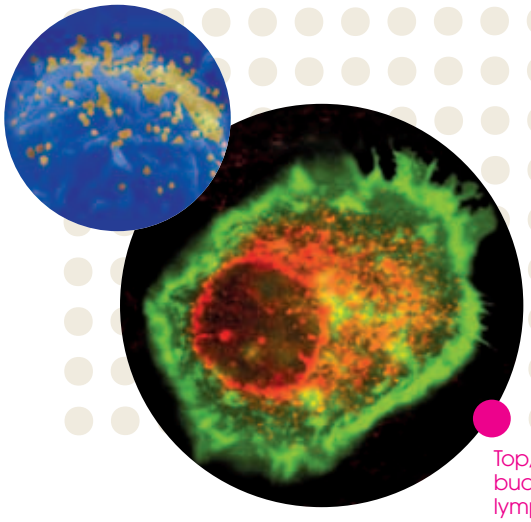
involved in red blood cell invasion. In French Guiana, Cambodia, Senegal, Niger and Madagascar, researchers associated with the Institut Pasteur's Parasitology and Mycology Department are studying the interplay of polymorphism of parasite, vector and human populations in various epidemiological transmission conditions. The impact of control measures is being explored, along with monitoring of resistance to anti-malarial drugs and insecticides.



Plasmodium oocyst, implanted on the wall of the mosquito's digestive tract, containing sporozoites.

The department's 22 units specialize in research into viruses and their molecular organization, virus-host interactions and pathogenicity determinants. The mechanisms of infection by a virus, its entry into the cell, multiplication, propagation in the organism, transmission from one individual to another and dissemination are the focus of the department's research.

Virology



Top, particles of the AIDS virus (HIV) budding at the surface of a lymphocyte. Bottom, cerebral endothelial cells (nucleus in blue) infected by the HTLV-1 virus (viral protein p24 in green).

The viruses studied include arboviruses transmitted by insects that cause diseases such as dengue, yellow fever and Rift Valley fever; retroviruses such as HIV or HTLV; respiratory viruses; viruses that cause cancers, such as papillomaviruses; and the hepatitis B and C viruses.

Understanding viral pathogenesis

Work is being carried out to understand viral pathogenesis and the mechanisms used to cause disease. Understanding host responses to infection, both in the infected cell and in the organism as a whole, can help to clarify these mechanisms. Human papillomaviruses, for example, are the cause of benign lesions (warts or condyloma) but also anogenital cancers, in particular cervical cancer. HPV types from the genus *beta* do not cause lesions in the general population. Researchers from the Genetics, Papillomavirus and Human Cancer Unit have demonstrated that two cellular proteins (EVER1 and EVER2) control infection by HPV. These proteins form a complex with the zinc transport protein ZnT-1 and negatively regulate zinc traffic in the cell and the synthesis of cell factors required for the multiplication of the virus. A viral protein (E5) is capable of inhibiting the EVER and ZnT-1 proteins. The absence of E5 protein in beta HPVs might explain the asymptomatic nature of these viruses in natural conditions.

Working in cooperation with the technological platforms, the department's scientists are developing sophisticated screening assays to

Highlights

NEUROLOGICAL CONDITIONS PARTLY EXPLAINED

The HTLV-1 virus, which infects 15 to 20 million people worldwide, has various clinical characteristics, including certain neurological disorders. It enters the central nervous system by crossing the blood-brain barrier via lymphocytes in the blood circulation. The Oncogenic Virus Epidemiology and Pathophysiology Unit has demonstrated that lymphocytes infected by HTLV-1 can impair blood-brain barrier integrity by increasing its permeability to small molecules. They are also able to migrate through the single layers of endothelial cells, which can themselves be infected by the virus. The correlation of these observations with anatomopathological data can help in the understanding of

identify and validate viral targets that are subsequently used in research for therapies.

Genetic susceptibility to infection

Working with the Genomes and Genetics Department, researchers are studying genetic susceptibility and resistance to infectious diseases, in particular why certain people or certain ethnic groups are more resistant to viruses than others. In the case of HIV, researchers in the Regulation of Retroviral Infections Unit are looking into individuals who are frequently exposed to the virus but are not infected. They are trying to determine whether their natural defenses are the reason for their protection against HIV. This work, carried out with the Institut Pasteur in Phnom Penh, Bangui and Ho Chi Minh City, has already demonstrated the involvement of innate immune cells. Research has also suggested that, in certain individuals, resistance mechanisms in cells targeted by HIV infection play a part in protecting against infection. Restriction mechanisms that affect either viral entry or the stages after entry into lymphocytes in particular have been identified.

Reverse genetics and vaccine candidates

With reverse genetics, we can now introduce mutations into the viral genome and impair the expression of certain viral proteins, such as virulence factors, in order to produce attenuated or avirulent viruses. The Molecular Genetics of

With reverse genetics, we can now introduce mutations into the viral genome and impair the expression of certain viral proteins.

Bunyaviruses Unit is working on the Rift Valley fever virus, which affects ruminants and causes hemorrhagic fever when transmitted to humans. In 2008, the laboratory demonstrated that the virus codes for a non-structural protein, NSs, which inhibits the innate response by repressing the interferon promoter. This repression plays a major role in the virus's virulence. The laboratory demonstrated that a virus in which the NSs gene is eliminated is a very good vaccine candidate.

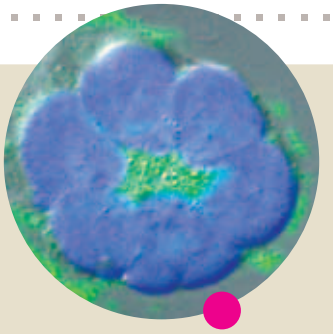
Monitoring and clinical research

Alongside the department's fundamental research, clinical research is also carried out, involving the monitoring of patient cohorts.

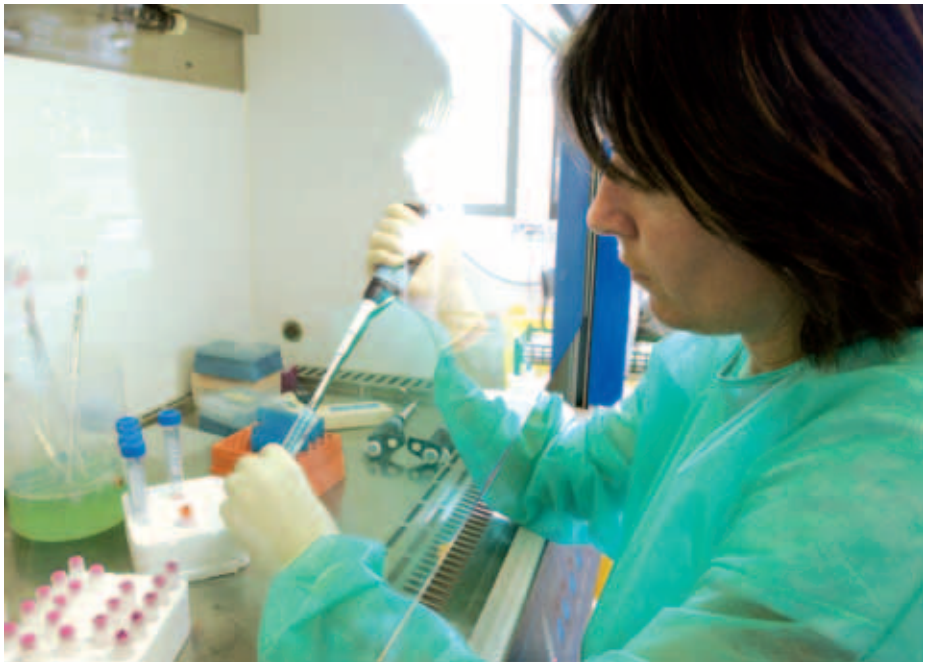
In the 2007-2008 season, for example, the National Reference Center (CNR) for influenza identified the emergence of a virus with natural resistance to Tamiflu, in the absence of use of the drug.

The Molecular Genetics of RNA Viruses Unit then demonstrated that resistance was linked to the mutation of the viral enzyme, which had already

some of the mechanisms involved in blood-brain barrier rupture, a decisive element for a large number of both viral and non-viral neurodegenerative diseases.



Cerebral endothelial cells (nucleus in blue) infected by the HTLV-1 virus (viral protein p24 in green).



been identified as affecting the viability of the virus. A comparison of the enzymatic activities of the enzyme in the strains circulating in 2008 with that of the virus circulating in previous seasons showed a natural evolution with greater affinity for the substrate, along with better enzymatic activity. This result explains the improved viability of the viruses presenting the mutation.

Moreover, the newly created Human Papillomaviruses (HPVs) CNR will contribute, under the aegis of the French National Institute for Health Monitoring (InVS), to the monitoring of HPVs in France. This is of vital importance given the recent arrival of the first vaccines against papillomavirus infection and cervical cancer.

Responsiveness to emerging diseases

As well as its role as a microbiological observatory for known communicable diseases, the Institut Pasteur has a duty to be present in areas where new diseases are emerging. The Virology Department is central to this mission. A group focusing on the discovery of emerging viruses, made up of the Oncogenic Virus Epidemiology and Pathophysiology Unit in cooperation with the CIBU, has been created for the rapid identification of new pathogenic agents responsible for major health crises.

Virology — a translational discipline

The department is developing strong synergies with the Institut Pasteur's other Scientific Departments and groups in the Institut Pasteur International Network.

The Institut Pasteur in Cambodia, for example, is monitoring cases of H5N1, working closely with the Molecular Genetics of RNA Viruses Unit in Paris.

In Madagascar, teams are working on the poliomyelitis virus in collaboration with the Biology of Enteric Viruses Unit in Paris. The insufficient vaccination coverage in this region of the world has led to the virus combining with local viruses, creating new cases of poliomyelitis, a disease that had been all but eradicated.

Highlights

APOBEC3 SURPASSED

Within a cell, the APOBEC3 protein exerts its antiviral power by intervening at the moment of DNA transcription and replication. The emergence of numerous mutations during this process generates totally defective viruses. Using human biopsy specimens, researchers in the Molecular Retrovirology Unit investigated the possible action of APOBEC3 on the genome of the human papillomavirus (HPV), a virus that is responsible for cervical cancer. It was revealed that, while the genomes of HPV1 and HPV16 present mutations typical of APOBEC3 action, in the event of over-expression of this enzyme, the human genome can also be the target. These impairments are generally eliminated by cell correction systems, which here are unable to cope with the excessive range of mutations, leading to the infected cell becoming cancerous.

Biological research increasingly depends on complex, costly and rapidly evolving technologies. The Institut Pasteur has devoted considerable resources to the development of its technological platforms — the Pasteur Genopole Île-de-France, the Imagopole, platforms offering tools and expertise in biophysics, protein sequencing and murine transgenesis, a software and databases group, a Center for Production and Infection of Anopheles, and collections of microorganisms forming the Biology Resource Center.

Technological Platforms

Institut Pasteur Genopole

The rapid development of new molecular and genome analysis technologies has transformed biomedical research. The Institut Pasteur has set up technological platforms to increase access to these technologies and the expertise required for their application. These platforms, which form the Institut Pasteur Genopole, reflect a coordinated approach, ranging from genome sequencing to the characterization of proteins derived from them. These proteins are targets for modern drug and vaccine development. Eighty researchers, engineers and technicians with varied and complementary skills are involved in basic and applied research and public health projects, altogether co-signing over 70 publications in 2008.

Analysis of genetic information is based on the sequencing of complete genomes and the characterization of polymorphisms. Targeted analysis of candidate genes or research into polymorphism at complete genome level have led to the discovery of genes predisposing to different diseases in human beings or model organisms. Whole genome transcriptome analyses using DNA microarrays have improved our understanding of microorganism physiology and host response to infection. These methods are also applied to various issues such as the identification of regulatory micro-RNAs and research into embryo development.

The Genotyping of Pathogens and Public Health Platform, supported by the French public health institute (InVS), cooperates with French National Reference Centers and national microbiological monitoring laboratories to type pathogenic microorganisms and to perform population genetics studies. This platform is also called upon in the event of a bio-emergency and is part of the Institut Pasteur's emergency plan in case of a pandemic outbreak of avian influenza.

Information technology has a major role to play in processing data produced by these high-throughput approaches. The Genome Analysis and Integration team implements IT methods to analyze and manage genomic and postgenomic data in order to facilitate their analysis using various algorithms.

The Genopole offers a full range of technologies, from the production of recombinant proteins to their characterization using physicochemical methods.

The new Illumina high-throughput sequencer enables the Genopole to approach new issues, such as population genomics of pathogenic microorganisms, the characterization of coding and non-coding RNAs and the modification of genomes responsible for epigenetic regulation. Applications range from understanding the phenomenon of emergence and discovering new pathogenic agents, to analyzing cancer development. A research group bringing together computer scientists from different teams has been set up to meet the bioinformatics challenges posed by this new technology.

As for macromolecular analysis, the Genopole offers a full range of technologies, from the production of recombinant proteins in prokaryotic or eukaryotic systems to their characterization using physicochemical methods. Different proteomics and analytical biochemistry technologies are available for analyzing purified proteins or complex preparations. These methods are used to address very different issues relating to post-translational modifications of proteins, cell regulations, intracellular trafficking or the organization of macromolecular complexes. The energetics and dynamics of biological macromolecules, their assembly into complexes, and interaction with ligands can be approached using 15 biophysics instruments. Finally, the automation of crystallogenesis of biological macromolecules has contributed to the development of structural biology in the Institut Pasteur. This coherent set of approaches was recognized in 2008 with the award of the national label IBiSA (Infrastructures for Biology, Health and Agronomy) and by funding from the Région Ile de France and the Canceropole.

Imagopole

The Imagopole or Molecular and Functional Dynamics Center features four "technological platforms" — Flow Cytometry, Dynamic Imaging, Ultrastructural Microscopy and the very recent Center for Human Immunology. It is part of the Institut Pasteur's Technopole. With its 35 permanent research engineers/technicians, the Imagopole is involved in scientific research projects requiring conventional or sophisticated molecular and/or cell imaging techniques. The Imagopole provides the scientific community with its expertise in advanced optical and electronic imaging and cytometry techniques for research into infectious diseases.

The aim of this center is to provide scientists with:

- access to advanced technologies and expertise;
- an original contribution in terms of technological development for given research projects;
- BSL2 and BSL3 approved "biological laboratories" that are specially designed for analyzing biological materials used to conduct experiments on living cells and infectious agents.

At the end of 2007, the Imagopole was awarded ISO 9001:2000 certification for its photonic and electron microscopy and cytometry services. This certification confirms the Imagopole's commitment to continually improving the quality of its services and relations with its users.

••• Infection imaging

The main examples of pathogens targeted by the Imagopole's imaging technologies currently include parasites such as *Plasmodium* (responsible for malaria) and *Leishmania* (responsible for visceral leishmaniasis). The center also investigates infections by viruses such as the AIDS virus (HIV), the hepatitis C virus and human papillomaviruses. Infections by bacteria such as *Listeria* and *Shigella* and the mycobacteria responsible for tuberculosis are also studied. Moreover, imaging technologies are used in research into emerging diseases such as SARS, avian influenza and chikungunya. In order to examine infectious material, more equipment must be installed in high security laboratories, and automated cytometry and photonic imaging methods are required for high-throughput imaging of living cells.

••• Some of our projects

Development of a correlative microscopy approach

Engineers from the Imagopole are working on a correlative approach to combine data obtained from fluorescence (cryo)microscopy with structural information obtained in 2D using transmission (cryo)electron microscopy and in 3D using (cryo)electron tomography. Fluorescence-marked structures are localized on the frozen sample using a new technique available at the Imagopole, fluorescence (cryo)microscopy. This new approach will be applied to different areas at the Institut Pasteur, such as research into isolated pathogenic bacteria or host-pathogen interactions.

Acquisition of imaging systems for screening

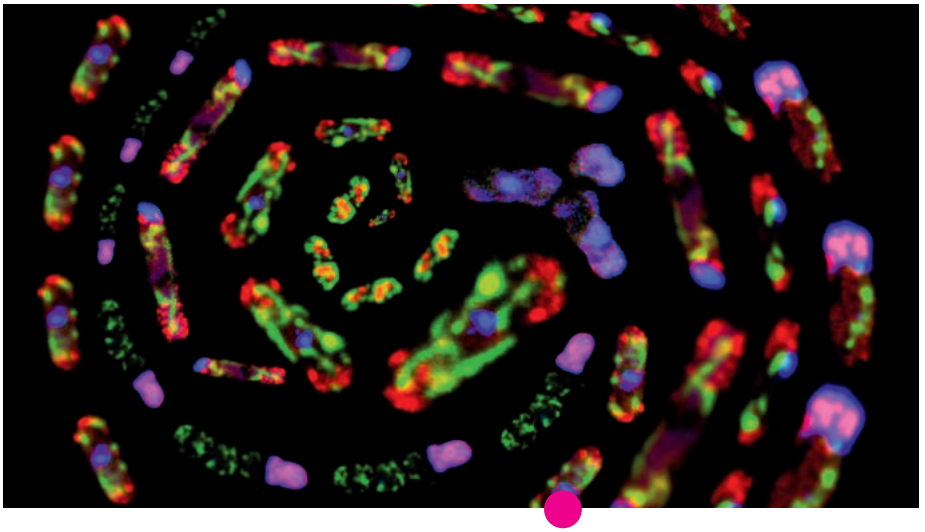
Research into infectious disease processes requires analysis of the dynamics of host-pathogen interactions at molecule and cell level. The localization of these events in living cells, their measurement and their quantification, are mainly based on the use of imaging techniques. These techniques provide significant new information for understanding mechanisms at molecular, functional and structural level. They require quantitative analysis of 2D or 3D high-resolution images, combined with statistically significant sampling.

In 2009, new high-throughput and high-resolution imaging systems for screening adherent and non-adherent cells will be made available to scientists to obtain high-resolution quantitative information in a single cell associated with high sampling. These screening systems will also be linked to a database used to view, analyze and share biological images within the Institut Pasteur. This project is funded by the Greater Paris region (SESAME 2007 project).

Development of a system for studying oxygen distribution in cells

The *Shigella flexneri* bacterium infects the epithelium of the human colon by invading epithelial cells with low pH and low oxygen levels. The bacterium then causes phagocytosis of the cell and induces apoptosis. This leads to bacillary dysentery in humans.

Research focuses on the development of a system used to identify a correlation between bacterial virulence and oxygen distribution in the cells and tissues. By using oxygen-sensitive fluorescent sensors, oxygen distribution in cells and tissues is studied before and during bacterial infection. *Shigella flexneri* will be used as a bacterial model and variations in fluorescence will be monitored by modulating the life span of the fluorescent marker.



Artistic view of *Schizosaccharomyces pombe* analyzed by high-resolution fluorescence microscopy. Acquisition and editing by L. Chatre. (M. Richetti's team, Immunology Department and, since April 2008, Genomes and Genetics Department).


From public health
to **research**
applications
Public health

Since it was founded, the Institut Pasteur has always helped improve health through its discoveries. It has provided the best possible conditions for facilitating and speeding up the transition from "academic research" to practical applications by consolidating clinical research, cooperating with hospitals, and developing partnerships with the industrial world. In addition to the need for faster medical progress, epidemic and pandemic alert situations require an immediate response. Thanks to its specialized structures (National Reference Centers for France and WHO Collaborating Centers for the rest of the world), the Institut Pasteur is a recognized and essential stakeholder for monitoring and characterizing infectious diseases (assessment, diagnosis, monitoring and research).

- Clinical research and public health
- National Reference Centers and WHO Collaborating Centers
- Research applications

The Institut Pasteur has always sought to establish the best possible conditions for turning its discoveries into applications for human health. The role of the Medical Department is to forge links with hospitals to reinforce cooperation in translational and clinical research.

Clinical research and public health

The Medical Department coordinates support structures for clinical research. The Institut Pasteur's desire to coordinate clinical and exploratory research more closely is demonstrated through the setting up of the new Clinical Research Center and the redefined scope of the Biological Resources platform.

Clinical research

••• A Clinical Research Center (PIRC) to support researchers

This center is responsible for:

– following up vaccine candidates currently being developed on campus for malaria, HIV and cancer. The center works closely with the Cochin Clinical Investigation Center (CIC) and industrial partners.

– coordinating the Clinical Research Committee, which examines the regulatory, legal, ethical and organizational compliance of clinical research projects conducted by Pasteurian teams in collaboration with external organizations, e.g. the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) and the Paris Public Hospital Network (AP-HP). Given that the regulatory framework becomes more complex every year, the Clinical Research Committee supports and assists campus and International Network researchers with their procedures as early as possible. In 2008, 35 clinical research projects were examined by this committee.

A biobank is available to research teams and responds to the needs of health authorities.

The Medical Department recruited a clinical research ethics adviser in 2008 to bring expertise to the campus on issues involved in setting up clinical research projects in developing countries.

••• New scope for the Clinical Investigation and Access to Biological Resources (ICAReB) platform

The Clinical Investigation and Access to Biological Resources platform is a key structure for clinical research at the Institut Pasteur. ISO 9001 certified in 2007, it recruits cohorts of people, both healthy volunteers and patients, and manages a biobank of human biological material, stored in optimum conditions with the related clinical and biological data. This biobank is available to research teams and responds to the needs of health authorities.

This platform has been opened up to hospitals and European and international (e.g. WHO) biobank structures in line with new regulations on biological collections and the growing need to access biological material in strictly controlled regulatory and ethical conditions.

The platform is also responsible for the inventory launched by the French Ministry of Research (decree no. 2007- 1220 of August 10, 2007 relating to taking, conserving and preparing human body samples for scientific purposes, in compliance with, in particular, articles L. 1243.3 and L. 1243.4 of the French Public Health Law) for all collections of biological samples of human origin. This is a huge task that concerns all Institut Pasteur research teams on campus and in International Network institutes housing such collections.

Medical Center

••• The first steps towards certification

The Institut Pasteur Medical Center (CMIP) is the only part of the Institut Pasteur that is in direct contact with the general public via its international vaccination and travel medicine center, its infectious disease and allergy clinics and its medical test laboratory.

2008 was marked by the launch of the CMIP certification process, which aims to further

88,347 vaccinations

16,274 consultations for infectious diseases

8,046 consultations for allergies

14,348 medical tests

+20% compared with 2007

3,142 consultations for rabies (with the ability to act immediately in the event of a health alert)

improve the quality and reliability of treatment and promote its work among the general public and health stakeholders.

The Institut Pasteur Medical Center is the first medical center to begin this process and the procedure is being closely watched by the French Authority for Health (HAS), which could use this pilot procedure to encourage other centers to follow the example.

Five working groups comprising CMIP staff, a restricted steering committee and the CMIP Management Committee are involved in this procedure.

••• Continuous medical training

The first continuous medical training session, jointly organized with the Necker Hospital Department of Infectious Diseases, took place this year. It highlights the partnership between the two institutions through the Necker-Pasteur Center for Infectious Diseases.

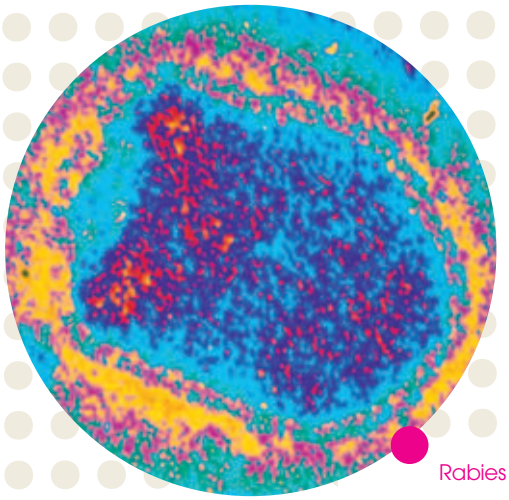
Three sessions were organized for Parisian doctors: "Management of HIV infection: from diagnosis to follow-up," "Vaccinations and advice before traveling" and "Good practices in diagnosing and treating community-acquired infectious diseases."

••• Clinical research

The Medical Center also continued active clinical research work for several projects, including HIV antiretroviral drugs and research into the infectious cause of pathologies such as Verneuil's disease and olfactory disorders.

National Reference Centers (CNRs) act as microbiological observatories for communicable diseases and play an important role in the Institut Pasteur's public health activities. They are partners of the French General Directorate of Health (DGS) and the National Institute for Health Monitoring (InVS).

National Reference Centers and WHO Collaborating Centers



Rabies virus.

Twenty-three Institut Pasteur research units were appointed by the French Ministry of Health for five years (2006-2010 term) as CNRs (21) or associated laboratories (2). Eight World Health Organization Collaborating Centers (WHOCCs) fulfill a similar role for the WHO within an international network of expert laboratories.

The National Reference Centers and WHOCCs draw on the scientific environment of their host units and the various support structures, particularly the Public Health platform and Laboratory for Urgent Response to Biological Threats, to develop tools and conduct research for their respective missions.

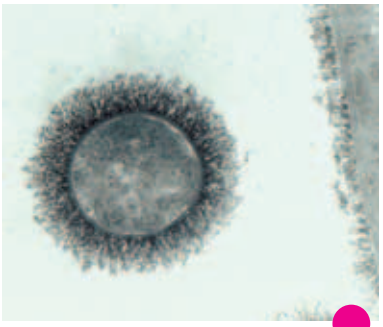
Influenza Virus CNR (France-North)

The Influenza Virus CNR (France-North) monitors circulating strains for vaccine strains and antiviral drug sensitivity purposes.

During the 2007-2008 season, an influenza epidemic of moderate intensity was dominated by the circulation of A(H1N1) influenza viruses and, later, by type B viruses. A(H3N2) viruses were detected only sporadically. As regards antigens, the majority of the A(H1N1) and A(H3N2) viruses, and the type B viruses, were different from the respective vaccine strains. This season was marked by the emergence of A(H1N1) viruses that were naturally resistant to Oseltamivir (Tamiflu®) in France and Europe, with a prevalence rate varying from 1% in Italy to 67% in Norway. In the north of France, resistant viruses became dominant during the season. According to a geographical gradient, prevalence rates were 61% for the North West, 55% for the Greater Paris region, and 40% for the North East.

Anthrax CNR

Three cases of human anthrax were reported in the French *département* of Moselle in December. One of these cases was identified using a strain isolated from the patient. For the other two cases, as no strain was isolated, patients were treated with antibiotics and the retrospective diagnosis was confirmed by serology. The source of contamination was traced to an infected animal (illegal cattle slaughter) and this triggered an epidemiological investigation.



The *Bacillus anthracis* capsule has a hairy appearance. It is the anthrax disease agent which affects hoofed animals (sheep, goats, cattle, etc.) and sometimes humans but it is not contagious (magnification x 35000).

Whooping Cough and other Bordetellosis CNR

The Whooping Cough and other Bordetellosis CNR continued to develop whooping cough diagnostic tools and analyze isolates circulating in France.

Isolates from the pre-vaccine era are no longer in circulation. They have been controlled by vaccinating children with a whole-cell vaccine.

However, other virulent isolates continue to circulate. By replacing the whole-cell vaccine by a vaccine that only targets the virulence, all virulent isolates should be controlled provided that there is sufficiently high vaccine coverage among adolescents and adults. The disease must therefore continue to be monitored, especially as a few isolates have been observed that do not express some virulence factors.

Rabies CNR

In 2008, the Rabies CNR had to handle a high number of alerts and this led to an increase in activity of close to 70%, and a rise in the number of consultations and anti-rabies treatments in France.

Three cases of dog rabies, linked to illegal imports, were identified by the CNR.

• February: one case in the *département* of Seine-et-Marne (imported from Morocco) with retrospective identification of a chain of transmission of two cases of indigenous dog rabies. This case resulted in France losing its status as being free from rabies in terrestrial animals.

• April: one case in the *département* of Var (illegal introduction into Belgium from The Gambia).

• November: one case in the *département* of Isère (adoption in Spain).

The virus was typed very quickly at the CNR and this directly contributed to the epidemiological investigation. The CNR was actively involved in the information campaign and, for the Seine-et-Marne case, it provided information and treated patients and exposed individuals using a mobile unit from the Institut Pasteur's Antirabies Center.

This series of dog rabies cases and the two isolated cases that followed are the first of their kind in France since 1924. They highlight the importance of maintaining a high level of vigilance regarding rabies in France and particularly the risk linked to illegal imports of domestic animals, particularly from North Africa.

Furthermore, in May 2008, the CNR confirmed the diagnosis of rabies in a Guianese resident who died at Cayenne Hospital. The virus identified was a hematophagous bat lyssavirus, an enzootic virus in this region. It was the first human case of this type identified in French Guiana. The CNR was a central stakeholder, providing the health authorities and anti-rabies centers involved with its scientific, medical and epidemiological expertise.

The CNR works to limit the spread of a new epizootic of dog rabies in France and also to limit the public health consequences of existing rabies cycles in mainland France and French overseas departments.

Highlights

CREATION OF THE NATIONAL REFERENCE CENTER FOR HUMAN PAPILLOMAVIRUSES

In 2008, the Institut Pasteur's Genetics, Papillomavirus and Human Cancer Unit became the National Reference Center for Human Papillomaviruses (HPV CNR). The main role of this CNR is to set up a network of virology testing laboratories to monitor the distribution of papillomaviruses in vaccinated and unvaccinated women. Following the recent market launch of the first preventative vaccines against cervical cancer, testing will be used to detect any emergence of new genotypes or variants of viruses present in the vaccines. In addition, epidemiological research conducted among unvaccinated or immunodepressed women should be helpful in

Meningococcus CNR

Since 2003, the *département* of Seine-Maritime has experienced a hyperendemic situation caused by invasive serogroup B meningococcal infections, linked to the circulation of a specific meningococcal strain (B:14:P1.7,16.). There is no vaccine against serogroup B strains.

Three available OMV (Outer Membrane Vesicle)-type vaccines expressing all the epidemic strain envelope proteins were tested in Norway, Cuba and New Zealand. It was discovered that this type of vaccine, and particularly the Norwegian MenBvac™, could possibly help to control the epidemic situation in Seine-Maritime. Based on this information, the CNR demonstrated:

• that the strain used for the Norwegian vaccine was phenotypically and genotypically close to the Normandy strain;

• and, in collaboration with the Norwegian Institute of Public Health (NIPH), that the serum antibodies of individuals vaccinated with the MenBvac™ vaccine presented with bactericidal activity against the local strain that was similar to the activity obtained against the vaccine strain.

These results enabled the Technical Committee on Vaccines (CTV) to recommend the vaccination of the most exposed children and adolescents (1 to 19 years) in the *département* with the MenBvac® vaccine. The CNR then conducted two studies among the vaccinated children (1 to 5 years), which were used to demonstrate the immunogenicity of the vaccine and change the initial vaccine plan from three doses plus a booster to two doses plus a booster. Finally, in 2008, the CNR took part in an asymptomatic carriage study in the same *département* to increase understanding of the circulation of B:14:P1.7,16 strains.

Anaerobic bacteria and botulism CNR

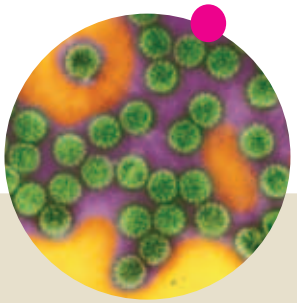
In 2008, eight cases of botulism were diagnosed (five of type A and three of type B). The five type A cases (corresponding to two foci) developed a very severe form requiring intensive care and serotherapy. Two type A foci and one type B case were of foodborne origin. The other cases concerned infant botulism and wound botulism.

Although lower than in 2006-2007, the rate of botulism in intensive poultry farms remained alarming in 2008 (37 positive foci out of 95 analyzed).

Genotyping of Pathogens and Public Health Platform (PF8)

In 2008, three years after it was set up, the first projects undertaken with its partner laboratories (particularly the CNRS) gave rise to 15 articles. A study published in *PLoS Pathogens* shed light on the evolution of *Listeria monocytogenes* strains and their virulence, and a bioinformatics project resulted in a system for standardizing and exchanging microbial genotyping data at international level thanks to the "minisatellite" method.

Papillomaviruses. They cause proliferation of the epithelium leading to generally benign tumors (warts) but sometimes malignant ones (cervical cancer). Colored image.



estimating the prevalence and type of HPVs located in the genital region.

The HPV CNR will carry out assessment, monitoring, alert, training and laboratory technical support activities for the health authorities. It is particularly responsible for assessing the performance of diagnosis tests likely to arrive on the market. It will develop new virus genotyping techniques for diagnosis, and new antibody titration techniques for monitoring vaccinated individuals. This work will provide the French National Institute for Health Monitoring (InVS) with useful data for assessing vaccine policy.

It will also be used to define the genotypes that should be included in second generation vaccines against papillomaviruses.

Research applications

The Institut Pasteur has always endeavored to conduct high quality research while concentrating on its application for public health. The results of its research are used to develop new means of diagnosing, preventing and treating diseases, and they give rise to numerous patents and license agreements. Partnerships are also forged with the industrial world so that the public quickly benefits from these scientific advances.

The Institut Pasteur has retained considerable freedom regarding its lines of research, an advantage that is envied by many research centers. It also forges partnerships with the industrial world so that the public quickly benefits from these scientific advances. More recently it has changed the way it works with industrial partners in the field of health to build joint research programs, an innovative approach to facilitate dialog and ensure efficient research.

An increase in research and development agreements: application and technology transfer

The Institut Pasteur is consolidating its partnership strategy by developing the number and individual amounts of its research and development agreements. The Research Applications and Industrial Relations Department is involved in producing an overview of activities, presenting the Institut Pasteur's fields of excellence, unit by unit.

Whether concerning joint research programs, collaboration between Institut Pasteur and industrial scientists, exclusive information agreements, joint participation in scientific conferences, or international programs, the various different approaches have proved successful.

The year 2008 therefore saw the signing of 39 research contracts supplemented by 20 assessment contracts, 32 contracts for consultancy work performed by Institut Pasteur scientists at the request of industrial partners, 41 biological material exchange contracts, and 86 license agreements enabling, in particular, many diagnosis kits to be launched.

Joint research programs

The research and development programs often involve teams trying to insert a research program into an existing partner program by providing a specific technology, product research, diagnosis tools or a vaccine-based strategy, but this is often a complex task. However, the requirements of industrial partners have changed — they are seeking to

increase their knowledge of fundamental research and develop their traditional research model. The incredible boom in biotechnologies has heightened this trend.

Within this context, the Institut Pasteur is behind a new approach for expertise sharing and strategic discussion, offering industrial partners a joint investigation into their requirements and resulting in the funding of joint research programs. This approach guarantees them privileged access to academic research work that may lead to applications. Requirements are set out by Institut Pasteur scientists and company researchers. The industrial partner then contacts the Institut Pasteur to confirm the knowledge requirement and fundamental research themes that it is interested in. A workshop is organized to freely discuss more specific scientific issues. Lastly, the overall research programs are finalized and agreed by contract. They are as far-reaching as possible and cover a minimum period of three to five years.

This approach, launched six months ago, has led to 16 discussions, some of which should give rise to programs in the coming months.

The Institut Pasteur would like to extend this approach to other industry sectors. There are many requirements in the fields of nutrition and the environment, and partnerships are already underway with Danone, L'Oréal, Saint-Gobain and Vivendi. The creation of a Chair of Innovation — a forum where industrial and social issues meet research — could facilitate dialog between entrepreneurs and scientists, and pave the way for efficient approaches.

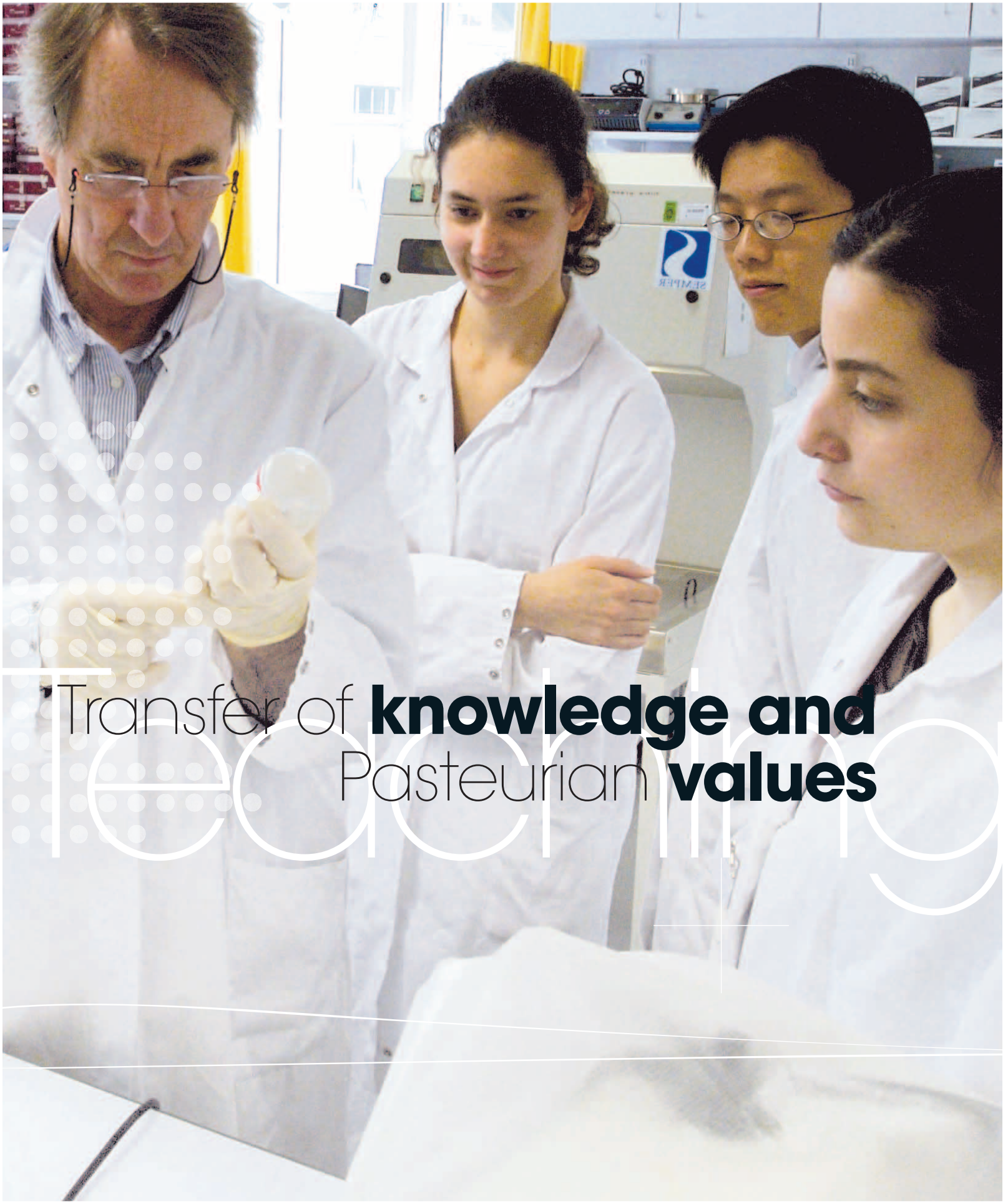
Speeding up applications through suitable funding

The Institut Pasteur has set up a new fund for financing research project proofs of concept. Named Kurma, it will help to speed up the maturing process for scientific programs that are most likely to result in industrial applications, licensing agreements or the setting up of new biotech companies for example. This innovative approach, adopted in partnership with a financial institution, could provide a program with up to €2 M to enable it to reach a regulatory preclinical stage more quickly (in the case of a product) or to demonstrate the importance of more fundamental project concepts. In 2008, two new companies were set up and they join the 15 others created over the last eight years. And continuing along this line, 12 new company creation projects are currently being examined.

Similarly, following its designation as a Carnot Institute two years ago, the Institut Pasteur has access to the joint research development fund, a public fund that facilitates the application of research by the industrial community. Concerted actions between Institut Pasteur research units and external research centers are also facilitated. The higher the number of contracts with industrial partners, the higher the Carnot funding — this is an effective way of boosting partnership strategy.

Protecting research work

Scientific discovery forms the very basis of the Institut Pasteur which innovates both continuously and systematically. A rapid and simplified procedure has been implemented for invention disclosures. Feedback for scientists regarding these patents has also been improved. Ninety-one invention disclosures were submitted, giving rise to 45 priority patent applications, particularly in the field of diagnosis and therapy. Together with representatives from the ten research departments, the Institut Pasteur patent portfolio is regularly assessed to ensure ongoing optimization. Before the costly national procedure begins, the Institut Pasteur has 30 months to assess whether patents are useful or not. On average, one in ten invention disclosures becomes an extended patent that is filed within 30 months.



Transfer of **knowledge and** Pasteurian **values**

Teaching

Ever since the creation of the world's first microbiology course in 1889 — the "microbiological technique course" — teaching has been a priority at the Institut Pasteur. In 2008, 396 students of 53 different nationalities attended its courses. Both theory- and practice-based, they are run by Institut Pasteur teacher-researchers. This year was especially marked by the opening of the new teaching center, the arrival of the first year of Pasteur-CNAM School of Public Health students, and renewed partnerships with universities. The Institut Pasteur constantly updates its courses to meet the expectations of young researchers and the health challenges of tomorrow's society.

A dynamic structure for high quality courses

The Institut Pasteur has worked with French universities for many years in the fields of teaching and research. Twelve Institut Pasteur courses are in fact recognized as second year teaching units for Research Masters in various Parisian universities — René-Descartes (P5), Pierre and Marie-Curie (P6), Denis-Diderot (P7), Paris-11-Orsay and Versailles-Saint-Quentin.

New facilities designed for practical biology courses as well as theory- and IT-based teaching.

Twenty-five courses are available covering a broad spectrum of disciplines ranging from fundamental microbiology (part of the Institut Pasteur's tradition of "prestigious lectures") to more recent fields of research, such as genomics or neuroscience. These courses are intended for graduates of French universities, university teaching hospitals, French *grandes écoles* and foreign graduates.

In 2008, the Institut Pasteur and Pierre and Marie-Curie University (P6) signed a new framework agreement to intensify partner relations for research (cooperation between laboratories, creation of mixed teams/units for joint research), Masters-level teaching (cross-involvement of teachers/researchers and cross-hosting of trainees) and training through research (hosting and supervision of PhD students, joint PhD training initiatives).

The Pasteur School of Infectiology (EPI) offers eight specific lectures on epidemiology and public health in the field of infectious diseases. These lectures form the basis of the Infectious Risk specialization of the Master's in Public Health proposed for the first time in 2008. This Master's degree, recognized by the French *Conférence des grandes écoles* and run in partnership with the French National Conservatory of Arts and Trades (CNAM) benefits from the complementary nature of teaching at the Institut Pasteur (epidemiology, infectious risk) and the CNAM (biostatistics, health economics and law, analysis of health policies, non-infectious risk). Students can choose between several programs within the Infectious Risk specialization — monitoring,

The Institut Pasteur offers an international PhD program in life sciences and biomedicine.

clinical research, vaccinology, entomology and medical microbiology. Following a core curriculum on public health and several weeks of lectures on infectious risks, these students complete a six-month internship in one of the International Network institutes.

This Master's degree also develops cooperation with International Network institutes, which are involved in the lectures and enrich the quality of infectious risk tools and projects.

Optimum conditions for unique teaching that has won recognition

On April 16, 2008, the Institut Pasteur opened its new teaching center in the Louis Martin wing of the former Pasteur Hospital, which was fully refurbished last year with the exception of the façades, which retain their original character.

These new facilities have been designed for both practical biology courses (thanks to rooms fitted out with scientific equipment and microbiological safety cabinets) as well as theory- and IT-based teaching (in rooms featuring video projection equipment and computers).

Students from very different scientific and geographical backgrounds

The Teaching Center welcomes scientists, doctors, pharmacists, engineers and veterinarians from all over the world. In 2008, half of the students were foreign and 53 nationalities were represented. This is why some courses are taught in English.

The Institut Pasteur offers students from foreign universities an international PhD program in life sciences and biomedicine — the Pasteur-Paris University International Doctoral Program. This program, which is due to begin in September 2009, will be spread over three years. It involves agreements with the René-Descartes (P5), Pierre and Marie-Curie (P6) and Denis-Diderot (P7) universities. It will also help to promote French Pasteurian culture worldwide.

Mechanisms of Living Organisms

- **Advanced Immunology:** lectures, practical work and seminars focusing on fundamental immunology.
- **Cellular and Molecular Genetics:** concepts and techniques in somatic and germinal genetics and epigenetics.
- **Development and Plasticity of the Nervous System:** theoretical and practical course on the most recent fields of neuroscience.
- **Genome Analysis:** experimental and bioinformatics approaches for genome research.
- **Molecular Biology of the Cell**
- **Mouse Genetics:** research into genes, their function and product interactions at cell, tissue and organism level.
- **Multiple Roles of RNAs:** study of RNAs (synthesis, maturation and degradation) and their role in gene expression.
- **Protein Biochemistry:** theoretical and practical course on the structural and functional properties of proteins.

Biology of Micro-Organisms

- **Basic Virology:** study of the host cell and various viral families.
- **General Microbiology:** lectures and practical work on the most recent advances in molecular and cellular microbiology.
- **Medical Bacteriology:** study of numerous bacterial genera relevant to medicine, and veterinary and environmental science — morphology, metabolism, biochemistry, antibiogram, and molecular tools for the identification of difficult or non-cultivable bacteria.
- **Medical Mycology:** theoretical and practical course for future university hospital scientists with basic knowledge of practical techniques in medical mycology.
- **Molecular Tools and Epidemiology of Tuberculosis:** theoretical and practical course on the molecular typing of tuberculosis bacilli and its clinico-epidemiological and fundamental applications.
- **Systematic Virology:** theoretical and practical course focusing on the classification of viruses, virus-host relationships, transmission of viral infections and diagnosis techniques, and structural and biological properties of different virus families of medical or veterinary interest.

Epidemiology and Public Health

- **Arthropods and Human Health:** fundamental knowledge of the transmission and control of vector-borne diseases.
- **Circulation of Pathogens and Risk Control:** knowledge of pathogens, their ecosystems, modes of transmission, effects on health and methods of control.
- **Clinical Trials and Infectious and Tropical Diseases:** basic knowledge of epidemiology and biostatistics, and initiation to methods for evaluating diagnosis tests.
- **Data Analysis using Stata:** analysis of univariate and multivariate (logistic regression and Cox models) data using Stata software.
- **Food Safety and Risk Analysis:** theoretical and practical course for quantitative assessment of risks linked to contaminated food.
- **Human Genetics and Infectious Diseases:** epidemiological and population genetics of infectious diseases.
- **Introduction to Epidemiology, Biostatistics and Validation of Diagnostic Tests:** course in clinical trial methodology and practices.
- **Management of Microsoft Access and Epidata Databases:** building and managing databases under Access and Epidata.
- **Research on Human Beings and Applied Ethics:** course on rules of research on human beings, understanding their ethical justification and taking them on board through real-life examples.
- **Surveillance, Alert and Outbreak Investigation:** course to develop the knowledge (surveillance, alert and outbreak investigation) required for decision making.
- **Transfusion Safety — Infectious Diseases:** course on transfusion-transmitted infections.
- **Vaccinology:** the aim of this course is to provide an extensive overview of vaccinology, from scientific, medical and public health data justifying the development of a vaccine to it being made available to populations in rich and poor countries.


The strength of a global cooperation network

Whether setting up major projects in partnership with public or private international organizations, building interfaces in numerous countries or promoting the development of regional centers throughout the world, the Institut Pasteur is recognized as an essential partner in these major scientific programs.

The Institut Pasteur is developing two areas of international cooperation — via European and international partnerships on all the institute's scientific and medical themes, and via the Institut Pasteur International Network (RIIP), which today includes 32 institutes all over the world.

International cooperation

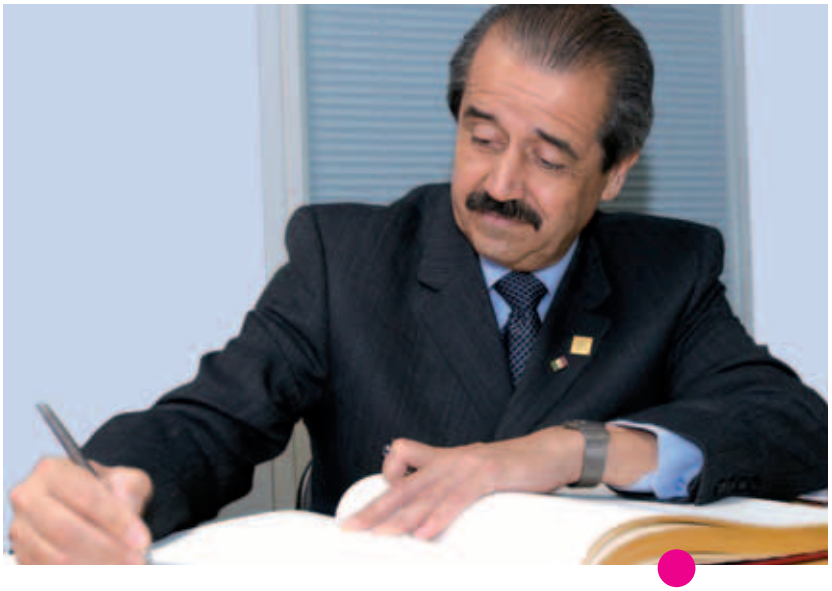
Present on all five continents, the Institut Pasteur is a major strategic partner for WHO missions in the field of infectious diseases. There are eight WHO Collaborating Centers in Paris and ten in the International Network, which also houses 26 recognized National Reference Centers. In January 2008, a visit from Margaret Chan, Director-General of the WHO, consolidated the project to set up a WHO Collaborating Center for Influenza at the Institut Pasteur.

Another major example of Pasteur's international reach is the AmSud-Pasteur Cooperation, a network of 63 partners in Latin America.

A program focusing on bacterial meningitis in Africa (Mali, Burkina Faso and Niger) and a program focusing on influenza in Asia and Africa are being supported respectively by the French Ministries of Foreign Affairs and Health.

In 2008, several agreements were signed or renewed with private foundations, institutes and universities, such as the Wellcome Trust in the U.K., Harvard University in the U.S., the National Institute of Infectious Diseases (NIID) in Japan, Mahidol University in Thailand and the French-Speaking University Agency (AUF). Two partnership agreements were launched with Mexico during visits from the Mexican Minister of Health, J.A. Córdova Villalobos, and J.C. Romero Hicks, Director-General of the Mexican National Council for Science and Technology (CoNaCYT), and they were signed in early 2009.

Finally, the Institut Pasteur also received a visit from Zsuzsanna Jakab, Head of the European Center for Disease Prevention and Control (ECDC) based in Stockholm.



The visit from the Mexican Health Minister, José Ángel Córdova Villalobos, to the Institut Pasteur on May 23, 2008, consolidated partnerships in scientific research between the Institut Pasteur and Mexico in the field of infectious diseases.

The Institut Pasteur International Network

The Institut Pasteur International Network (RIIP) is a partnership of research and public health institutes located on all five continents. Based on Louis Pasteur's desire to fight infectious diseases in the countries where they emerge, the Network

Margaret Chan, Director-General of the WHO, during her visit to the Institut Pasteur in January 2008.

The Institut Pasteur International Network is a partnership of research and public health institutes located on all five continents.

strives to produce high-quality international research.

The wish of Pasteur and the directors who followed him was to contribute to world-class research while protecting populations. The sustainability of this research is assured through the training of local researchers, today mainly based in independent institutes rooted in their national contexts.

It is therefore a voluntary partnership network, united by shared values and reinforced by the transfer of ideas, people, knowledge and expertise. The Institut Pasteur International Network promotes the words of Louis Pasteur: "Science knows no country, because knowledge belongs to humanity."

The activities of the Network cover the three central Pasteurian aims — scientific research, public health and teaching — with a particular focus on:

- the major pandemic diseases (HIV/AIDS, tuberculosis, malaria, etc.) that are an obstacle to achieving the UN Millennium Development Goals;
- upstream research for new vaccines and therapies;
- emerging diseases (dengue, encephalitis, hemorrhagic fevers, chikungunya, etc.);
- health safety (monitoring and alert in the event of epidemics);
- monitoring and research for resistance to anti-infectious agents;
- neglected diseases (rabies, meningitis, diarrhea, leishmaniasis, etc.).

For each of these themes, the Institut Pasteur and the International Network are recognized as essential partners by Ministries of Health in France and abroad, major international organizations such as the WHO and the EU, private foundations and the main research and public health institutes in France (IRD, INSERM, CNRS, CIRAD, InVS) and the world.

Examples of partnerships formed within the RIIP include:

Highlights

INTERVENTION IN THE EVENT OF EPIDEMICS

The Laboratory for Urgent Response to Biological Threats (CIBU) and the RIIP were recently involved in various epidemic situations: avian influenza in Cambodia (Institut Pasteur in Cambodia) and Cameroon (Pasteur Center in Cameroon), yellow fever in Mauritania (Institut Pasteur in Dakar), dengue in Paraguay (Institut Pasteur in French Guiana), meningitis in Niger (CERMES), encephalitis in Vietnam, and fever and dengue in the Ivory Coast.

INTERNATIONAL TEACHING

More than 100 students from the Institut Pasteur International Network supplement their training each year with courses or internships in Paris. Courses and workshops are also organized within the RIIP. In 2008, 16 courses

• The French Development Agency is financing the SISEA (monitoring and investigation of epidemic situations in South East Asia) regional project, which calls on the three Instituts Pasteur in Vietnam in cooperation with Cambodia, Laos and China;

• The French Development Alliance, in partnership with the French Ministry of Foreign Affairs, Veolia and Sanofi, is working with the RIIP in Vietnam in the biological fight against dengue fever using mesocyclopes;

• The US Department of Health and the Institut Pasteur have signed a cooperation agreement for support, consolidation and training as part of a program for influenza monitoring in South East Asia (Cambodia, Laos and Vietnam) and Africa (Ivory Coast, Cameroon, Senegal, Central African Republic and Madagascar).

A BSL-3 laboratory was inaugurated at the Institut Pasteur in Cambodia by Rama Yade, French Secretary of State for Foreign Affairs and Human Rights, and Doctor Mam Bun Heng, Secretary of State for the Cambodian Ministry of Health, on April 25, 2008. Another BSL-3 laboratory is under construction at the Institut Pasteur in Madagascar. Work on the Institut Pasteur in Laos is underway, and the change in status for the future Institut Pasteur Foundation in Dakar is currently being finalized.

Key figures

Grants in 2008

95 grants awarded:

57 for courses

38 for internships

11 RIIP grants:

7 PhDs

4 conferences

8 AmSud-Pasteur grants

6 grants jointly funded with the "Fondation Pierre Ledoux – Jeunesse internationale"

funded by the RIIP were held in 11 different countries, including five in Africa, seven in Asia, three in Latin America and one in the Middle East. Certain regional courses are available every year, such as the Malaria Workshop at the Institut Pasteur in Madagascar, the virology and immunology courses at the Hong Kong University-Pasteur Research Center and courses on the Monitoring of Salmonellosis organized jointly with the WHO in Cameroon and Saint Petersburg. Other international courses, supported by the Institut Pasteur, are organized throughout the world, such as the AmSud-Pasteur regional courses.

The Institut Pasteur's development largely depends on the advancement of the Pasteurian community as a whole, a community that boasts a wide range of disciplines, cultures and arrangements. Particular attention is therefore paid to staff career development, trainee status, training and labor relations.

The Institut Pasteur's financial equilibrium relies on three sources of funding: income from public donations and constituted patrimony, government grants, and contractual resources, particularly from intellectual property agreements. It therefore has a responsibility to its various partners.

Expertise and resources

2008 was mainly marked by the implementation of a skills management policy, illustrated — particularly in terms of training — by a career development plan. Particular focus was also placed on recruitment and hosting activities.

Pasteurian teams: the true wealth of the Institut Pasteur

Vocational training

In 2008, close to 1,100 training activities were organized as part of the annual plan for a budget of €1.3 M.

Support and training for new heads of unit in team management, project management and communications (media relations, etc.) were among the priorities that supplemented regular research-related courses. Efforts were also made to welcome young researchers, particularly non-French speakers, and courses were offered with the support of the *Alliance française*. At the same time, training opportunities designed to meet skill development requirements were introduced this year in partnership with service providers, who are recognized in their field and have a long history of working with the Institut Pasteur, for instance, Paris 7 University and GRETA. These opportunities, which will be continued and expanded next year, apply to all Institut Pasteur laboratories.

And in addition to the activities undertaken as part of the training plan, initiatives taken by the employees themselves were also on the rise, e.g. life-long learning (DIF), recognition of prior learning (VAE) and skills assessment. To optimize this skills management policy, the Training Department has been restructured and will outsource all financial management. This new organization, in place for 2009, will enable the department to focus on its core task.

Recruitment and hosting activity

2008 was marked by a major recruitment drive for both temporary and permanent positions. 63 employees were hired on permanent contracts and 24 others had their fixed-term contracts converted into permanent ones. Close to 280 people were also hired on fixed-term contracts. Half of these temporary contracts were granted to young researchers (PhD students and post-doctoral researchers) with research training grants or bound by an international agreement, or to young foreign researchers temporarily living in France.

In addition, the Institut Pasteur pursued its policy to welcome young apprentices to Pasteurian teams to study for qualifications ranging from

French BEPs (vocational technical diplomas) to vocational Master's degrees. Introduced three years ago, this policy concerns a dozen apprentices each year.

As for our numerous trainees (445 during the year), they are eligible for a training bonus if their internship exceeds three months. This bonus was introduced with the French Equal Opportunities Act and amounted to a budget of €451,000 for 214 trainees in 2008.

Labor relations

As part of the 2008 annual negotiations, several general or category-based measures were introduced regarding pay. A general pay rise of 1.3% therefore became effective on March 1, in addition to a one-off bonus awarded to mark the 120th anniversary of the Institut Pasteur. A budget of 2% of the indexed salary was also allocated to individual pay rises and this figure was increased to 2.2% for research management staff. On average, one in two Pasteurians receives an individual pay rise each year. Finally, a rise was agreed for the lowest salaries in the form of extra index points.

Several major labor initiatives were also launched this year (GPEC — forward-looking management of jobs and skills —, employment of seniors, etc.) and they should take shape in 2009.

A few figures

On December 31, 2008, the Institut Pasteur workforce totaled

2,654 people

1,933 were Institut Pasteur employees

147 were CNRS employees, including **96** researchers

87 were Inserm employees, including **61** researchers

39 employees were university lecturers/researchers

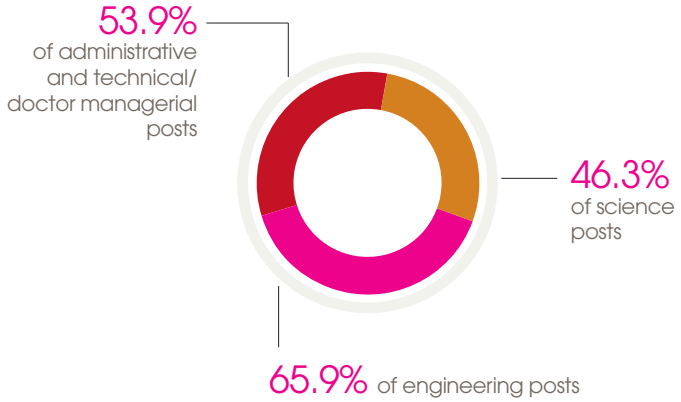
207 trainees of **60** different nationalities were welcomed to the campus

1,933 Institut Pasteur employees, including:

1,173 women **60.7%**

760 men **39.3%**

Women hold **50.7%** of senior positions, including:



Diverse income sources

Current income in 2008 €239.3 M

€94.4 M

Revenue from own activities

43.1%

Industrial royalties (€40.2 M and 18.4% of income) are essential for the Institut Pasteur. They are a direct result of the research carried out on campus. They are up slightly thanks to the renegotiation of existing contracts.

Sales and services (€18.9 M and 8.6% of income) comprise activities linked to business development (expert assessments, advice for industrialists, etc.), public health activities carried out at the Medical Center, and services provided to institutes of the International Network in particular. This income remains stable.

Research contracts (€35.3 M and 16.1% of income) have increased again this year and this increase applies both to public contracts through the increasingly important French National Research Agency (ANR) and key programs designed for institutes of the International Network, and to European and foreign funding.

€67.7 M

Donations, legacies and patrimony incomes

30.9%

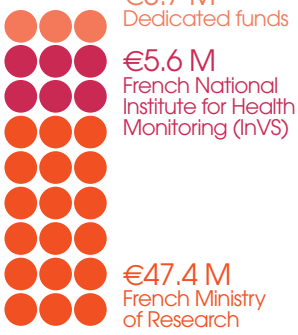
Patrimony incomes (€25.8 M) include current financial revenue, rent from income property and agricultural revenue from estates registered among the Institut Pasteur's assets.

Donations (€41.9 M) include all donations and legacies, and apprenticeship tax. The notable increase in the amount of donations received in 2008 is due both to the development of fundraising campaigns targeted at individuals and communications initiatives conducted throughout the year. Since 2005 and for the final year in 2008, they have included the contribution from Sanofi-Aventis to finance research programs into parasitic diseases. Legacies, as regards the share allocated to current revenue, are down due to a fall in the number of new legacies witnessed over the last few years. The amounts recorded in 2008 correspond to completed legacies, the majority of which were bequeathed in previous years.

€56.7 M

Government contributions

25.9%



They are mostly made up of the grant from the French Ministry of Research which, at **€47.4 M,** is slightly lower than the previous year.

They also include the **annual grant from the InVS,** which covers some of the costs of activities carried out by National Reference Centers: **€5.6 M.**

Since 2005, the Institut Pasteur has received a **government grant of €4 M** from the special appropriation account to support research programs on parasitic diseases, in addition to the funding from Sanofi-Aventis. This funding came to an end in 2008.

€20.5 M

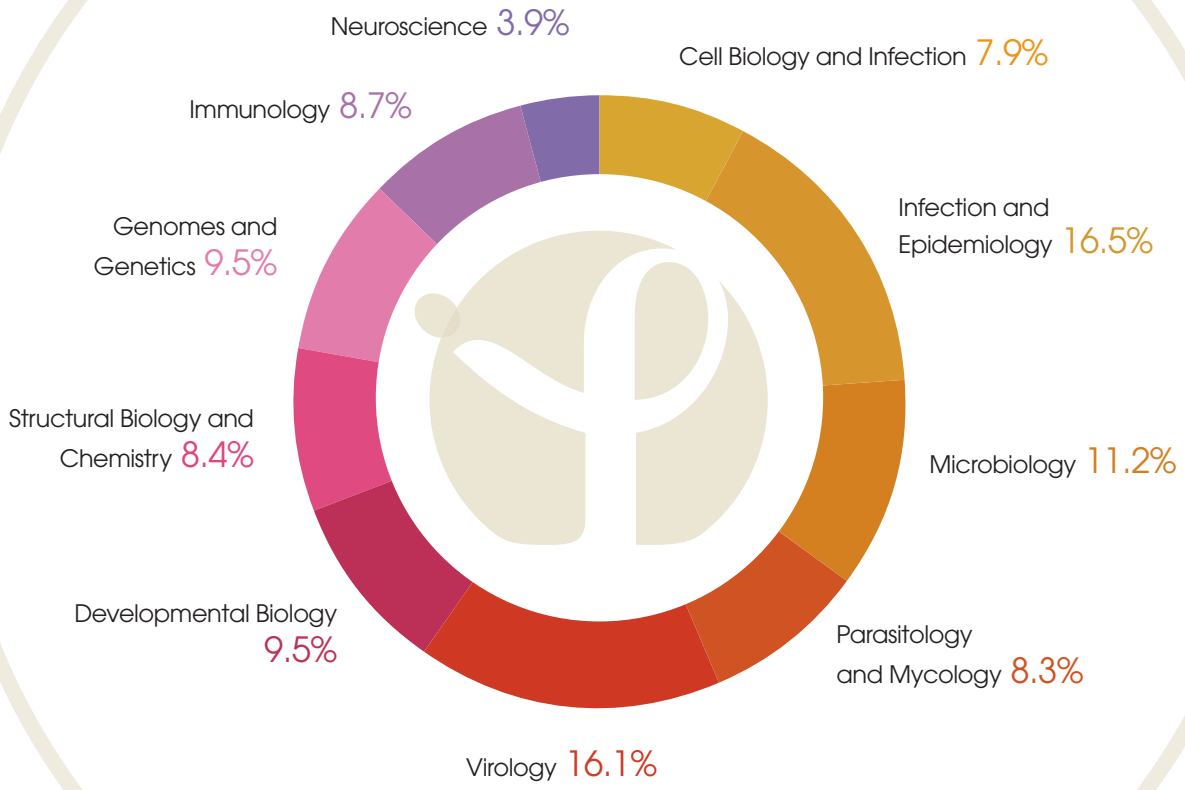
Non allocated

0.1%

This is carry-over of unused income from previous years and recovery of provisions.

Current expenditure in 2008 €237.4 M

€110.7 M	€90.3 M	€10.2 M	€26.2 M
Personnel expenditure	**Operating costs**	**Depreciation**	**Provisions and future commitments**



The structure of research spending shows that over 60% of our budget is earmarked for infectious diseases (viral, bacterial and parasitic diseases).

In 2008, the operating result amounted to €1.8 M, down by €7.3 M in relation to the previous fiscal year. It includes the financial result corresponding to income from investments (€20.5 M) and a transfer of non-recurring income from legacies (€6 M). This year, the net deficit amounts to €111 M and is largely due to significant falls on the global financial markets that have forced us to post €132 M in non-recurring provisions for our long-term investment portfolio.

Financial situation

Current operations

Current revenue increased by 2.2% on average in relation to 2007 with contrasting developments according to the items. Government contributions were down slightly, industrial royalties were up this year and income from donations was noticeably down due to a drop in legacies. These developments clearly show the fragile nature of the Institut Pasteur's current income.

Current expenditure rose by 5.9% in relation to 2007, with a noticeable increase in personnel expenditure, which this year again reflects the recruitment of some twenty additional post-doctoral researchers, who were previously paid using gifts.

Regarding the Institut Pasteur's activities, research accounts for the majority of this expenditure (close to 90%), while public health represents 8% and teaching, 2%.

Non-recurring operations

In 2008, non-recurring operations recorded a deficit of €112.2 M (compared with a surplus of €33.4 M in 2007). The two main factors leading to this result are gifts and the management of investments.

The share of each gift (donation or legacy) under €300,000 is recorded in the accounts as current income. The share which exceeds this amount is reported as non-recurring income (apart from the amount transferred to operating income pursuant to article 19 of the articles of association, i.e. €6 M in 2008). In 2008, the total recorded in the accounts as non-recurring income was €18.5 M (compared with €17.1 M in 2007).

In total, legacies recorded in the accounts in 2008, as both recurrent and non-recurring income, amounted to €41.4 M, compared with €42.3 M in 2007.

The Institut Pasteur's assets are managed by several specialized financial institutions on the basis of management agreements. The long-term allocation of assets corresponds to a balance between shares and bonds. In 2008, the financial markets experienced a turbulent year and the share index collapsed, closing at -18.1%.

The overall return on our portfolio for 2008 was -16.7%, and, although negative, it is slightly above the reference index. The average annual return over the last five years is 1.4%.

On the whole, these results are lower than the previous year and this shows that funding for the Institut Pasteur's current operations remains a challenge. The conditions required to develop the foundation's activities depend on continually high royalties, increased fundraising efforts and continued support from the French government.

Since the very beginning, the generosity of companies and the general public has been crucial to the Institut Pasteur's development. 2008 — the year of the 120th anniversary celebrations — marked a new step in fundraising with a continued increase in donations.

Donations and **legacies**

Donations

With €18 M, 2008 was a historic year for donations at the Institut Pasteur. Donations from individuals and companies were up 10% compared with 2007 and a campaign targeting companies led to a rise in the number of donation agreements signed (Fondation Le Roch Les Mousquetaires, Janssen-Cilag, Orange, Tarifold) and the renewal of important partnerships, with Danone for instance. Other contacts should also soon pledge their support. Including the major contribution from Sanofi-Aventis, company donations exceeded €8 M in 2008.

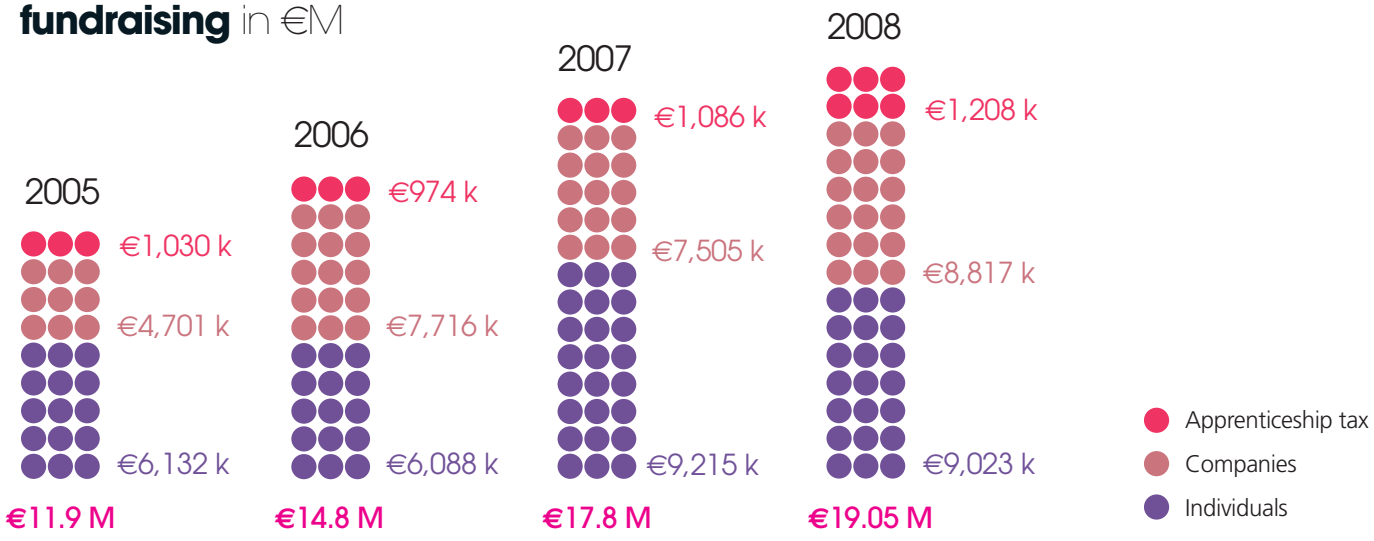
And as regards individuals, 50,000 new donors gave their support to the Institut Pasteur. Furthermore, the number of donors who opted for direct debit donations increased significantly, as did the number of major donors. 2008 also provided the Institut Pasteur with the perfect opportunity to reach out to its various publics — donors, individuals and companies — and invite them to meet its researchers and teams.

Various open days were held to meet the general public, and the *Théâtre des Champs-Élysées* gala evening, organized thanks to the loan of the building by the *Caisse des dépôts* and the support of numerous companies, enabled donors to attend a prestigious evening event while helping to fund Institut Pasteur research.

Legacies, donations and life insurance policies

Public support also took the form of legacies and life insurance policies bequeathed to the Institut Pasteur and such donations are exempt from transfer tax.

Development of fundraising in €M



French Republican Guard concert given at the Institut Pasteur to mark the handing over of a €20,000 cheque by the Versailles Rotary Club on April 17, 2008.

In 2008, the number of donors increased by 10%.

In 2008, 95 legacies and donations were submitted to the bureau of the Board of Directors, representing a total of €26.3 M, a slight increase compared with 2007, although no major legacies were received.

The processing of gifts is much faster following the 2007 reform on legacies that simplified administrative procedures. In the majority of cases, certificates of non-opposition are now obtained in just a few weeks. Gifts recorded in the accounts this year amounted to €41.4 M, a figure which is stable in relation to 2007.

New legislation regarding donations and the new Institut Pasteur articles of association opened up new possibilities in terms of philanthropy (donation funds, sponsored foundations) and the first projects were launched in 2008 and should be completed in the next few years.

International fundraising

2008 saw the continuation of activities by associations of friends of the Institut Pasteur in New York, Montreal, Hong Kong and Tokyo. They work to promote the Institut Pasteur and encourage donations and legacies. In 2008, 15 American, Japanese and Canadian post-doc researchers were present on the campus thanks to funding by these associations.

Thanks to the generosity of Mrs. Anne Cox Chambers, President of the American Advisory Board for the Pasteur Foundation, the Pasteur museum renovated the small dining room in Louis Pasteur's former apartment. In addition, the annual Pasteur Foundation gala evening in New York raised over $1.1 M. The annual gala evening in Montreal and a major conference organized in Tokyo in partnership with the leading Japanese business newspaper *Nikkei* also contributed to the renown of the Institut Pasteur.

Apprenticeship tax

Payment of apprenticeship tax is another way in which companies can lend their support, in addition to donations.

The Institut Pasteur Teaching Center is largely funded by apprenticeship tax and, thanks to major communications initiatives, the amount raised totaled €1.2 M (+9%).

Ethics and transparency

The Institut Pasteur's accounts are inspected by a statutory auditor and are subject to the approval of the Board of Directors. The Institut Pasteur's fundraising activities are also assessed by the *Comité de la Charte,* an independent ethics committee, which promotes the transparency and efficient management of affiliated organizations. Finally, donors are regularly informed of the institute's activities, in particular via the newsletter *La Lettre de l'Institut Pasteur* and the dedicated Institut Pasteur website: aiderpasteur.fr. Each year, they receive their tax receipt, a statement of the accounts and, on simple request, the full annual report.

2008 was a great year for the Institut Pasteur as regards image and renown as it was awarded the "Major National Cause" title. The 120th anniversary celebrations also provided the ideal opportunity for communications initiatives, for promoting the Institut Pasteur as a recognized cause among various publics, and for actively increasing the money raised in aid of research.

Communications

Striving for recognition in fundraising circles

The Institut Pasteur enjoys undeniable recognition and renown. Though often cited as a major stakeholder in the fight against infectious diseases, it was seldom present in philanthropy and donation circles. The communications strategy implemented since 2006 aims to develop the renown and ranking of the Institut Pasteur among the major causes to be supported. The long-term objective is to feature among the top donor choices. The Institut Pasteur has applied this strategy to all publics over the last three years, combining all regular forms of communications: brochures, *Pasteur Le Mag'* magazine, websites, talks, advertising campaigns and more innovative fundraising initiatives. This strategy culminated this year with the 120th anniversary celebrations.

2008, taking center stage for the 120th anniversary

With over €19 M raised in 2008, an increase in donations from individuals, major donors and companies, and a particularly strong media presence, the results for 2008 are very positive. The Institut Pasteur achieved greater visibility among the public and consolidated its image of excellence in research.

With over €19 M raised in 2008, the results are very positive.

109 lectures for the general public organized throughout France in 2008,

9,750 delegates

The second Pasteurdon raised close to €1 M.

The 120th anniversary provided a real boost for communications initiatives. Numerous events called on scientists, donors, political figures, the media and the general public, including Pasteurdon, the laying of the first stone of the Integrative Biology of Emerging Diseases Center, the classical music concert given at the *Théâtre des Champs-Élysées* in aid of research, and scientific talks. The open days, held on November 22-23, brought the celebrations to a successful close and were attended by close to 20,000 people on the campus. And the Institut Pasteur also benefited from the Nobel Prize for Medicine being awarded to Professors Françoise Barré-Sinoussi and Luc Montagnier. This exceptional event highlighted the excellence of Pasteurian research by focusing on one of its main missions — the fight against viruses.

The renewed success of Pasteurdon

Supported by Danone, Total, the Fondation Le Roch Les Mousquetaires and their eponymous boutiques, and the leading national radio stations, the second Pasteurdon raised close to €1 M. It also helped to promote the Institut Pasteur. Over the space of a week, radio stations featured various scientists, promoted the Institut Pasteur's core missions, explained the Institut Pasteur's need for donations, and encouraged listeners to support its research programs. Through two radio shows broadcast live from the campus on stations France Inter and RMC, researchers were able to explain their research and make it more accessible to the public. Many local councils and associations throughout France also organized events to raise money for Pasteurdon and they invited speakers from the Institut Pasteur for the occasion.

Communications initiatives directed at the public

The Institut Pasteur continued to promote its research amongst the public. Out of around 30 press releases published this year, 15 focused on advances in research work. Many talks were also organized for the general public on campus and throughout France.

The "Mysteries of Science" and "Mr Pasteur's Way" lectures, in particular, met with great success. Throughout the year, Pasteurians also worked with schools as part of the "dirty hands/clean hands" operation to raise awareness of hygiene and scientific careers among children. To mark the 120th anniversary, dozens of talks were held for the general public throughout France. A conference held 120 years to the day since the Institut Pasteur was inaugurated — "Health: a major challenge for sustainable development in the world" — attracted a particularly high number of visitors. It received support from Sanofi-Aventis, a partner of the operation.

The communications campaign for the 120th anniversary of the Institut Pasteur won the "Prix Empreinte Corporate Santé" medical advertising prize.

03

An organization driving research

The Management, Board of Directors and General Assembly enable the Institut Pasteur to carry out its missions by combining an effective management policy with a successful response strategy.

The President is responsible for general policy and the smooth running of the Institut Pasteur that she represents outside the campus. Appointed by the Board of Directors, she is assisted by an Executive Board and a Scientific Council.

Through its proceedings, the Board of Directors settles Institut Pasteur matters. It gives its opinion on the strategic policies set out by the President. It votes on the budgets, approves the accounts and sets the budgetary headcount.

The General Assembly has three main tasks — approving the Annual Report from the Board of Directors, electing the 16 members of the Board of Directors, and voting on changes to the articles of association upon Board proposal.

General organization of the Institut Pasteur

Board of Directors

May 2009

Board of Directors bureau

Chairman
François Ailleret
Honorary President of EDF

Vice-Chairman
Alain Fischer
Pediatric Immunology and Hematology Unit,
Necker Enfants Malades Hospital

Vice-Chairman
Bernard Guirkinger
Executive Vice-President,
Suez environnement

Treasurer
Vincent Berjot
Head of Department in the Budget
Division of the French Ministry of the Budget,
Public Accounts and Civil Service

Secretary
Claude Leclerc
Head of the Immune Regulation
and Vaccinology Unit

Bureau member
Bruno Rémond
Chief Adviser to the French Government's
Accounting Office

Other members of the Board of Directors

Catherine Bréchignac
President of the CNRS (French National
Center for Scientific Research)

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

Antoine Gessain
Head of the Oncogenic Virus Epidemiology
and Pathophysiology Unit, Institut Pasteur

Carine Giovannangeli
Directorate-General of Research,
French Ministry of Research and Innovation

Didier Houssin
Director-General for Health,
French Ministry for Health and Sports

Bruno Latour
Scientific Director, *Sciences-Po*
(French School of Political Science)

Benoît Lesaffre
Head of the "strategy and research" mission
for the French Ministry of Health

Jean-Bernard Levy
Chairman of the Board of Directors, Vivendi

Daniel Louvard
Director of the Institut Curie Research Division

Isabelle Pelletier-Doucement
Engineer in the Biology of Intestinal Viruses
Provisional Unit, Institut Pasteur

Christine Petit
Head of the Sensory Deficit Genetics Unit,
Institut Pasteur

Didier Sicard
Chairman of the IDS (Health Data Institute)
Committee of Experts, Former Head of Internal
Medicine, Cochin Hospital

André Syrota
Director-General of Inserm (French National
Institute for Health and Medical Research)

Patricia Tortevoye
Engineer in the Oncogenic Virus Epidemiology
and Pathophysiology Unit, Institut Pasteur

Lionel Zinsou
Managing partner, PAI Partners

Executive Board of the Institut Pasteur

Anthony PUGSLEY
Senior Vice-President responsible for Scientific Affairs

Alice DAUTRY
President

Christophe MAURIET
Senior Vice-President responsible for Administration

Armelle DELECLUSE
Vice-President Human Resources

Valérie GADAUD
Vice-President Financial Affairs

Alain GUEDON
Vice-President Research Applications and Industrial Relations

Muriel ELIASZEWICZ
Vice-President Medical Affairs

Sylvain COUDON
Vice-President Communication and Fundraising

Marie GLOMET
Vice-President Legal Affairs

Isabelle SAINT GIRONS
Vice-President Teaching

Alain ISRAEL
Vice-President Scientific Assessment

Yves CHARPAK
Vice-President International Affairs
(not pictured)

Scientific Council

Elected Pasteurian Members

Alain Jacquier, Chairman
Head of the Macromolecular Interaction Genetics Unit

Nancy Guillen, Vice-Chairman
Head of the Cell Biology of Parasitism Unit

Patrick Trieu-Cuot
Head of the Biology of Gram-Positive Pathogens Unit

Appointed Pasteurian Members

Arnaud Fontanet, Secretary
Head of the Epidemiology of Emerging Diseases Research and Expertise Unit

Pierre-Marie Lledo
Head of the Perception and Memory Unit

Jean-François Nicolas
Head of the Molecular Biology of Development Unit

Olivier Schwartz
Head of the Virus and Immunity Unit

External Members

Lynn W. Enquist
Professor
Department of Molecular Biology, Princeton University

Jörg Hacker
Professor
Robert Koch-Institut (RKI), Berlin

Gabriel Waksman
Professor
School of Crystallography, Birkbeck College, London
Department of Biochemistry and Molecular Biology, University College London

Per Brandtzaeg
Professor
Department of Pathology, University of Oslo

Soren Brunak
Professor
Head of the Center for Biological Sequence Analysis, Technical University of Denmark, Lyngby

Richard Moxon
Professor
Weatherall Institute of Molecular Medicine
John Radcliffe Hospital, Headington, Oxford

David Sibley
Professor
Washington University School of Medicine
Department of Molecular Microbiology, St. Louis, USA

Michel C. Nussenzweig
Professor
Laboratory of Molecular Immunology
The Rockefeller University, Howard Hughes Medical Institute, New York, USA

Design and layout: avantgarde +33 (0)1 45 74 61 61 • **Photo credits:** The Nobel Foundation 2008/Hans Mehlin (Nobel Prize Award Ceremony) • Institut Pasteur/Thérèse Couderc, Marc Lecuit, Gérald Späth, Philippe Bastin, Imagopole • Jacques Grison • William Beaucardet • TBWA/Corporate/Non Profit • Getty Images.

Institut Pasteur
Department of Communication and Fundraising
25-28 rue du Docteur Roux
75724 Paris Cedex 15 FRANCE

www.pasteur.fr

Institut Pasteur
Department of Communication and Fundraising
25-28 rue du Docteur Roux
75724 Paris Cedex 15 FRANCE
www.pasteur.fr

Institut Pasteur