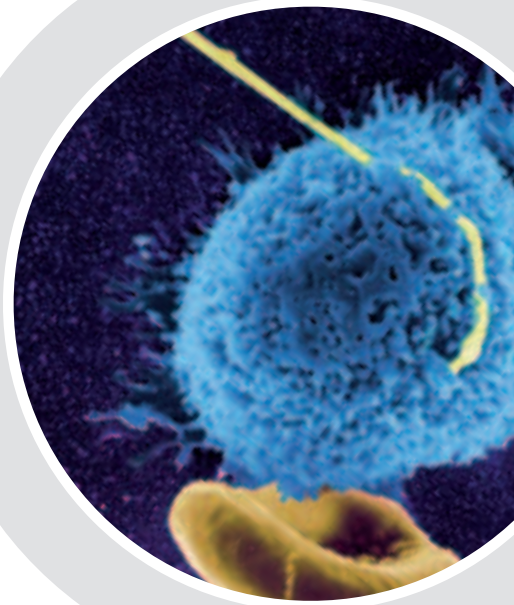
ANNUAL REPORT 2009



Meeting the major challenges of biomedical research and human development

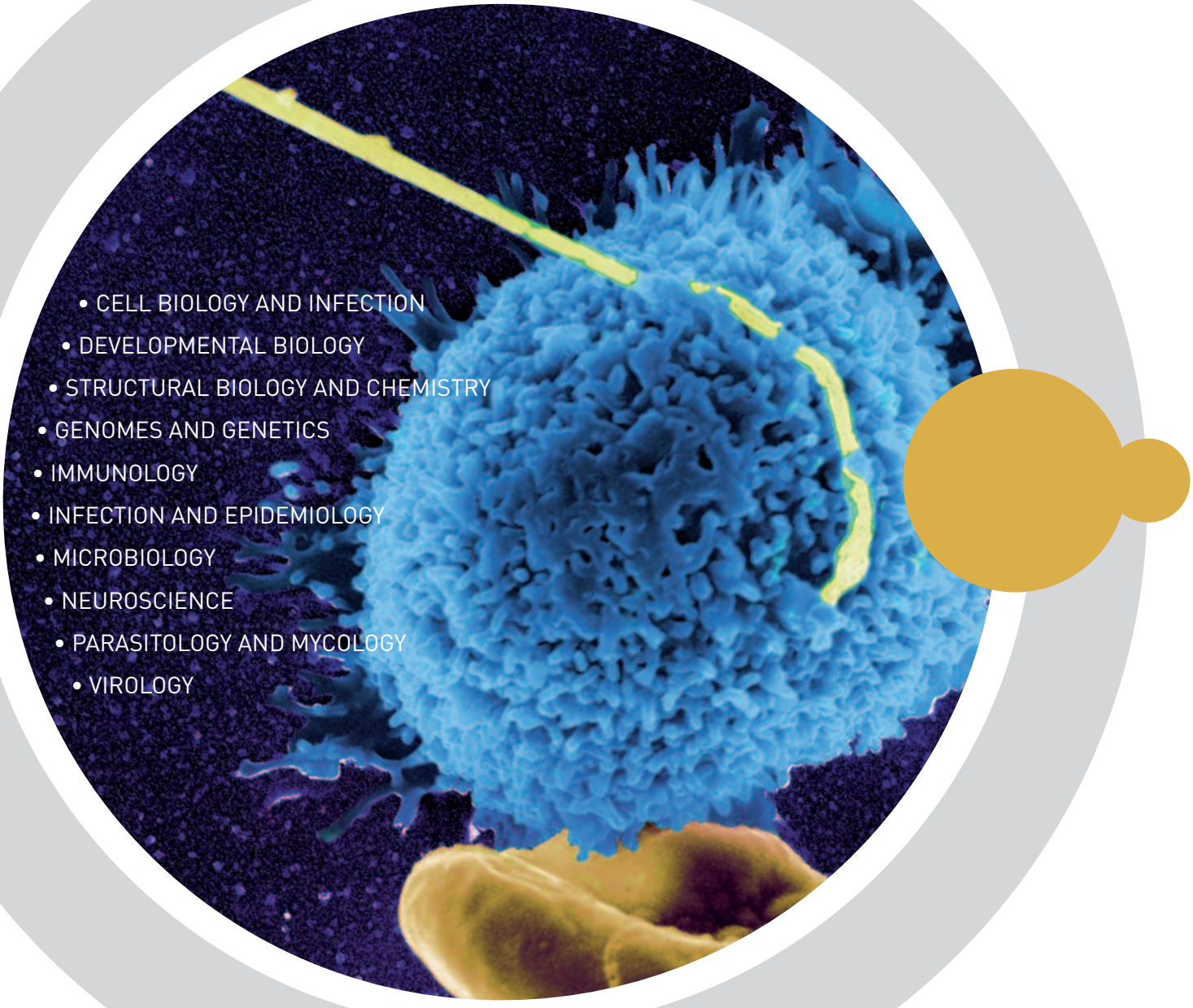
Institut Pasteur

the essence of the Institut Pasteur

challenges

8 billion humans in 2020

The scientific strategy of the Institut Pasteur is firmly rooted in major global health priorities and is based on developing new topics for biomedical research, enhancing multidisciplinarity and improving the transfer of scientific discoveries to applications. The Institut Pasteur is at the forefront of the major research areas and is devoted to finding effective solutions for the problems raised by the emergence of new diseases, working tirelessly to strengthen the response of its teams.


• CELL BIOLOGY AND INFECTION
• DEVELOPMENTAL BIOLOGY
• STRUCTURAL BIOLOGY AND CHEMISTRY
• GENOMES AND GENETICS
• IMMUNOLOGY
• INFECTION AND EPIDEMIOLOGY
• MICROBIOLOGY
• NEUROSCIENCE
• PARASITOLOGY AND MYCOLOGY
• VIROLOGY

research

10 research departments

The Institut Pasteur sets the international standard of excellence in infectious diseases, striving daily to combat all the microorganisms that cause them, whether viruses, bacteria, parasites or fungi. Neuroscience, genetics and genomics, and developmental biology complete this scientific hub where 130 Institut Pasteur research units work tirelessly, often in cooperation with the major stakeholders in international research.

teaching

525 students from 55 countries

The Institut Pasteur has an international reputation for quality teaching that attracts students from all over the world who wish to further their knowledge or supplement their degree programs. Twenty-eight courses with a strong emphasis on practical work focus on three main areas: Mechanisms of Living Organisms, Biology of Microorganisms, and Epidemiology and Public Health. These courses can also be taken as part of Masters programs with various universities and the specialized Masters program at the Pasteur-CNAM School of Public Health.


• Abidjan
• Algiers
• Antananarivo
• Athens
• Bangui
• Brussels
• Bucharest
• Casablanca
• Cayenne
• Dakar
• Hanoi
• Ho Chi Minh City
• Hong Kong
• Laval
• Lille
• Montevideo
• Nha Trang
• Niamey
• Noumea
• Paris
• Phnom Penh
• Pointe-à-Pitre
• Rio de Janeiro
Yaoundé •
Vientiane •
Tunis •
Tehran •
Sofia •
Shanghai •
Seoul •
Saint-Petersburg •
Rome •

international

32 institutes on 5 continents

The Institut Pasteur is at the center of an international network of 32 institutes located on all five continents. They have all signed a charter declaring their commitment to Pasteurian values, and they are united in the fight against infectious diseases. The Institut Pasteur is also involved in numerous projects with major international scientific bodies such as the World Health Organization, along with several major universities and research institutes worldwide.

public health

85,000 vaccinations each year

The Institut Pasteur hosts 21 National Reference Centers and 7 WHO Collaborating Centers, all of which are vital observatories for infectious disease monitoring. The Institut Pasteur Medical Center, which specializes in travel medicine, vaccinates over 85,000 people each year and provides advice and treatment during medical consultations, particularly for infectious diseases.

fundraising

€41.7 M

The economic model of the Institut Pasteur – a private, state-approved, non-profit foundation – is based on three separate sources of funding, in which public generosity and proceeds from assets play an important role. Government contributions, research contracts and the development of business from Pasteurian research supplement this budget, which is unique in terms of its sources and distribution – a feature which guarantees the independence of Pasteurian research policies and places the burden of responsibility on the institute with respect to its partners.

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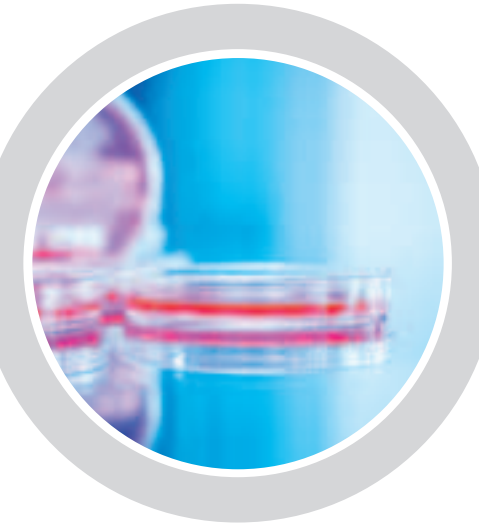


François Ailleret,
Chairman of the
Board of Directors

"These are difficult times for everyone, but the Institut Pasteur has been protected by its **diverse sources of funds.**"

Was the Institut Pasteur affected by the major global economic crisis of 2009?

Yes, it was, but to a lesser extent than most companies and institutions. These are difficult times for everyone, but the Institut Pasteur has been protected by its diverse sources of funds. The public has remained generous. The French policy to boost research nationwide, together with the quality of the projects conducted by Institut Pasteur scientists, has led to an increase in funds from the government and the European Union. However, revenue from patents and licenses is slowly heading in the other direction. Finally, our spending management has been particularly rigorous, resulting in a reduction of almost €7 M in operating costs.

Can you give us some figures that sum up the 2009 budget?

In 2009 we had an operating revenue of €212 M, a decrease of 3%, with an operating result of €1.2 M.

Furthermore, our investment budget remained high, €41 M, particularly for the Integrative Biology of Emerging Diseases Center – for which building work is on schedule. Fundraising (public donations and contributions from companies) was in the region of €19.8 M, an increase of 10.6% compared with the previous year. Legacies (€26.7 M) remained constant.
In short, I can say that the 2009 financial year was in line with budget forecasts and was therefore satisfactory, despite the difficult economic context. That said, it confirmed the general trends such as a fall in industrial revenue, a fall that is set to continue for several years and will have to be offset by a higher level of funding from the government and the European Union, and an increase in donations from businesses and the general public if we are to avoid reducing institute activities.
The Board of Directors has approved a tight but balanced 2010 budget that, if we all work together, will allow us to maintain a high level of activity in the various areas in which the Institut Pasteur is involved: fundamental research and its applications, public health, higher education and international cooperation.

Was 2009 marked by extraordinary events?
Yes it was. Half way through the year, the Board of Directors decided to reappoint the Institut Pasteur's President, Alice Dautry, for a second four-year term. This decision was taken following a rigorous selection procedure that, as had been decided in 2005, was open to international applicants. After a first positive term, and with new priorities set out in the medium- and long-term strategy approved by the Board of Directors, Alice Dautry has four years to implement the adaptations and changes required as a result of the rapid and extensive developments in the research, public health and higher education sectors, in France and worldwide. Furthermore, this must be done in a difficult context, both financially and managerially.
Of course, I should also mention the contribution made by the Institut Pasteur during the influenza A(H1N1) pandemic. It played its role, remarkably in my view, but I will let the President address that subject in more detail.

You are known for keeping a close eye on the role and activities of the Institut Pasteur International Network. What are your impressions of its work?
This network of 32 institutes on all 5 continents is unique worldwide. It is a valuable asset that is vital for the Institut Pasteur. It reflects the diversity of different regions and countries worldwide and the public health problems facing them. It carries out its work in close cooperation with the Institut Pasteur in Paris, in the spirit intended by Louis Pasteur when he created the institute 120 years ago.
In 2009, I was able to visit some of the institutes, in particular in Seoul for the inauguration of buildings and equipment of the highest international standard, and in Dakar, where the institute has now become a foundation under Senegalese law, opening up a host of new possibilities. The building work to construct the center for the recently established Institut Pasteur in Laos will begin in 2010.

What are your final reflections on this year?
On behalf of the Board of Directors, I would like to thank all those who, in one way or another, have contributed to the Institut Pasteur. Without them, it wouldn't exist. I also wish to thank all the Institut Pasteur researchers for their commitment and for the progress and results achieved, and to underscore their sense of responsibility, because it is their efforts, their professionalism, their excellence, their open-mindedness and mutual respect, and their ability to accept changes to working methods and organization that will determine the future of the Institut Pasteur.
Finally, I would like to express my thanks to all the board members for their contribution to the Board of Directors, to the bureau and to the various committees. Their expertise and sense of responsibility enable the Board of Directors to take the vital decisions with which it is entrusted, year after year, with insight and confidence.

Alice Dautry,
President

"Independence through interdependence.'
I like this phrase because it characterizes the Institut Pasteur."

What were the major achievements of the scientific policy and strategy pursued by the Institut Pasteur in 2009?

2009 saw a number of successes for the Institut Pasteur. As is the case every year, we issued international calls for tenders to set up new teams. A new unit was created in the field of neuroscience, and leading young scientists joined us to form two new five-year groups.

At the same time, the quality and creativity of Pasteurian research were recognized by the European Research Council (ERC). Two groups of young researchers and two groups of experienced researchers were awarded grants by the "Ideas" program, part of the 7th Research and Development Framework Program.

Finally, a study carried out by the Science and Technology Office on the quality of scientific output in the field of life sciences gave the Institut Pasteur a very high national and international ranking in the areas of fundamental biology and medical research.

2009 witnessed a number of significant highlights…
Firstly, in terms of public health, we responded to the influenza A(H1N1) pandemic as soon as the first alerts were issued. The rapid efforts of our teams enabled a diagnostic test to be developed in under 15 days; this test was then made available to hospitals in France and laboratories in the International Network. I would like to congratulate all the teams who worked day and night from the moment the first cases emerged in France at the end of April.
In the area of industry, we signed an agreement with the Institut Mérieux to pool our resources for research projects to combat infectious diseases. The Kurma Biofund for life sciences, of which we are a partner together with the Institut Curie, will provide us with a new tool to finance innovation that makes it easier for researchers to set up biotech companies with the aim of transferring their discoveries to applications. This is also one of the results of research – creating companies and jobs.

"As scientists, **we are always looking to the future…** The future is also about young people and their training."

We are also a founder member of Aviesan, the French National Alliance for Life and Health Sciences, alongside INSERM, the CNRS, the CEA, INRIA, INRA, the IRD and the French Conference of University Presidents. The idea is to improve synergies between these organizations with the aim of consolidating the position of French research.
Despite the economic crisis, we have continued to benefit from the generosity of the general public and businesses. We have never before enjoyed such a high level of support. I would particularly like to thank Sanofi-Aventis, Total and Danone, our loyal partners for many years. Their support and trust are essential to the very existence of Institut Pasteur research.

At an international level, the Institut Pasteur has a major role to play in the field of public health. What is your strategy?
Thirty percent of our scientists come from abroad, representing a wide range of nationalities. Half of our scientific publications result from cooperation with European and international groups. In addition to these joint efforts, we have the advantage of being at the center of an international network of 32 Instituts Pasteur, a global platform for monitoring numerous diseases that provides a comprehensive view of health issues. Just as health is international, so are our activities. Half of our research areas focus on diseases in developing countries.
We are constantly seeking to implement a strategy of openness with regard to our activities. The agreement signed with the Centers for Disease Control and Prevention demonstrates this; it provides a framework for joint and sustainable initiatives for public health and health safety worldwide. We decided to establish closer links with this US federal agency to coordinate our efforts so that we can ensure optimum response during epidemic emergencies.

Training is also a core Pasteurian priority…
Training is part of Pasteurian culture! As scientists, we are always looking to the future. The future is also about young people and their training. We are not officially a "university", but the Institut Pasteur is like an integrated campus. Every day, over 200 young people prepare for their PhDs and 220 complete their postdoctoral training, not forgetting all the students from across the world who complete courses at the Teaching Center. Wherever I travel, it is rare for me not to run into former Institut Pasteur trainees.

What is the vision for the Institut Pasteur in the coming years?
The Institut Pasteur must remain focused on its core activities: research, teaching and public health. "Independence through interdependence." I like this phrase because it characterizes the Institut Pasteur. We are independent, with our own projects and our specific characteristics, but highly interdependent with national and international stakeholders, society, industry and the political world. Today, the economic situation is a cause for concern and, like all organizations and companies, the Institut Pasteur is fragile. If we are to survive and to continue top-level research, we need more support from the government, from our donors and from our sponsors. It is our future that is at stake. All over the world, everyone knows the Institut Pasteur – it is our pride and joy!

Personal accounts... Behind the scenes at the Institut Pasteur

The top quality research and ambitious scientific projects carried out in the Institut Pasteur's laboratories are made possible by a team of people who are of vital importance to the institute. Here are some portraits of those involved in Pasteurian life.

Françoise Barré-Sinoussi, Head of Unit, 2008 Nobel Prize in Medicine

"I had never seen so many smiles and joy on all those faces. That sense of sharing was what made me happy…"

An VIH life

"I hope that I haven't changed…" Françoise Barré-Sinoussi has never liked being the center of attention. But when she identified the AIDS virus in 1983 she emerged from the shadows, and went on to share the Nobel Prize in Medicine with Luc Montagnier 25 years later. Today she admits to feeling a great responsibility on her shoulders. *"I would like to try to be the spokesperson for a community, the HIV/AIDS community. I get the impression that they are somehow counting on me…"* She gives a hearty laugh.

The day the announcement was made, on October 6, 2008, Françoise Barré-Sinoussi was on an assignment in Cambodia. It was a complete surprise: *"I wasn't expecting this award at all. My first thoughts went to my husband, who had died eight months previously."* On her return to the Institut Pasteur, the researchers were all there to welcome her: *"I had never seen so many smiles and joy on all those faces. That sense of sharing was what made me happy…"*

During the global struggle against the virus, she has never given up and has been very much involved with patients. *"I remember a patient who was very depressed and didn't want to leave my office. I couldn't promise him anything. After a short while I said: 'You need something to occupy your mind. Why don't you try joining the community of fellow patients?' He left, telling me that he would give it some thought. A few weeks later, he sent me a gift with this message enclosed: 'Thank you for your help. I took your advice and joined an association.' But I was even more delighted when I received another letter twenty years later to congratulate me on my Nobel Prize and let me know that he was still working for patient groups!"*

Today, she still gets up at 5am every day and never takes a weekend off. For Françoise Barré-Sinoussi, life as a researcher also required her to make certain choices, such as the decision not to have children. *"It was a personal decision. I don't know how I could have lived with the frustration of watching my children be raised by other people or not putting all my efforts into my research. I chose research, and my husband understood my decision."* In the evenings, when she opens a book, she tends to fall asleep. *"I am a happy Nobel Prize winner… and a rather tired one…"* No, she hasn't changed, and neither has she stopped laughing!

Loïc Chartier,
Biostatistician

"No matter what country we travel to, we are struck by the worsening global health situation."

People and numbers

It is easy to imagine a biostatistician shut away behind a computer compiling elaborate statistics. At the Institut Pasteur it doesn't work like that. For seven years, Loïc Chartier, aged 30, has been working as a biostatistician in the Research and Expertise Unit for the epidemiology of emerging diseases in developing countries. He can't hide his enthusiasm, smiling as he explains *"I provide technical assistance and support to the epidemiology units in the Institut Pasteur International Network. This means that I often have to travel to the areas plagued by diseases such as malaria, AIDS and tuberculosis."*

After completing his studies, he went into medicine simply because he wanted to help others; he also harbored an interest in research, for three good reasons: *"To tackle diseases, to meet people who are passionate about what they do, and to help move research forward."*

At the Institut Pasteur, this young biostatistician has more than one string to his bow. Loïc is also a computer scientist, and this enables him to develop the tools needed to gather data from clinical trials. At the same time, he helps develop course modules at the institute and trains partners in countries in Asia and Africa. *"During clinical trials, it is vital to meet the partners in the field. The aim is to train them so that they can work independently and can in turn develop their own IT tools."*

When he goes on assignments, Loïc accompanies two or three members from the unit, including a researcher, project manager, etc. *"No matter what country we travel to, we are struck by the worsening global health situation."* Each year, Loïc is involved in around five assignments, during which he particularly appreciates the fact that he can combine mathematics and human contact. This kind-hearted man got married just north of Oporto, Portugal, in July 2009. *"My wife is Franco-Portuguese and I wanted to take the opportunity to give my family a taste of another culture."*

In another sign of his openness to different cultures, Loïc has done capoeira for the last four years. *"It's not merely a martial art but a form of artistic expression. It teaches you to sing and dance and is an opportunity to meet people, to discover and share another culture."* Loïc has even started taking Portuguese lessons!

Sylvie van der Werf, Head of the Influenza National Reference Center

"When there are pandemic situations, work takes up so much of my time that my family life suffers."

All hands on deck!

At the Institut Pasteur, one laboratory often conceals another. It's not easy to find who you're looking for in this maze of corridors. Sylvie van der Werf is Head of the Molecular Genetics of RNA Viruses Unit and the Influenza National Reference Center (Northern-France), where around twenty people work on respiratory viruses, particularly influenza, each day.

Since 2003, Sylvie van der Werf has been working to track down and dissect viruses so that they can be tackled more effectively: *"We were closely involved in the SARS – severe acute respiratory syndrome – epidemic. Then, in 2004, we were called to work on H5N1 avian influenza. In 2006, this virus was observed in turkeys found dead in the French* département *of Ain. In 2007-2008 we encountered a totally unexpected phenomenon: seasonal influenza viruses of the H1N1 subtype became naturally resistant to one of the antivirals. This created a great deal of work, a certain amount of concern, and above all made us want to understand why it had happened."*

Sylvie van der Werf and her teams developed a diagnostic test for the 2009 pandemic H1N1 influenza virus, but where viruses are concerned there is always more work to do. *"The wave of pandemic H1N1 2009 has subsided, but we need to remain vigilant as we are dealing with influenza viruses that never cease to surprise us. We can never be sure that a virus won't evolve…"*

Sylvie van der Werf devotes much of her time to research, but also teaches. With such a busy working life, this mother of four children aged between 14 and 23 finds it hard to reconcile her family life and her research. *"When there are pandemic situations, work takes up so much of my time that my family life suffers,"* she explains.

She escapes from day-to-day realities with a spot of sailing – a passion that she regrets not being able to spend more time on. *"The sea is probably the only place where I can switch off completely. It is important to be able to unwind, as nowadays, with the internet and emails, we are constantly connected to our work."* Sylvie van der Werf can finally change tack and put the wave of influenza out of her mind…

Pierre-Jean Corringer,
Head of a five-year group

"It is important to keep your mind as open as possible; that way you will make unexpected discoveries…"

The brains behind the research

If he doesn't know what he'll be doing in a year's time, it's because of his research! *"I will continue working in the area of brain receptors, but my plans could change if there is a new discovery,"* explains Pierre-Jean Corringer, Head of the Channel Receptors five-year group – a group which could serve as a springboard to a research unit within five years. *"I have been working with six people since 2008 to bring this challenge to fruition. Our initial plan focused on nicotine receptors."* This chemical engineer and CNRS employee first started working at the Institut Pasteur in 1993. *"There is a truly multidisciplinary approach here, which makes it one of the best places for research."*

He is particularly interested in molecules. He talks about receptors and their architecture, and asks the inevitable question, *"Do you know how it works? "It's a macromolecule which is very difficult to manipulate, which is why we took homologs from the ancestor of these nicotine receptors – bacterial proteins already present in bacteria that lived between one and three billion years ago. The discovery of bacterial receptors in 2005 opened up many possibilities."*

For Pierre-Jean Corringer, dreams and research are inseparable. *"But of course researchers mustn't keep their heads in the clouds all day long,"* he adds, with a hint of humor. The true quality of a researcher is also being able to identify the most promising avenue to explore – to get it wrong at times – and to keep at it until you succeed. *"It is important to keep your mind as open as possible; that way you will make unexpected discoveries…"* Like many other researchers, Pierre-Jean Corringer can't imagine working as anything else. Except maybe a cabinetmaker or craftsman: *"When we are working on the lab table, we enter another world; we think with our hands in much the same way as a craftsman…"*

Pierre-Jean Corringer also admits that he is a fan of Go, a Chinese strategy game. Go involves concentration, calculation and memory, and also a level of strategy that incorporates esthetic considerations. Despite this, he intends to introduce his five-year-old son, Raphaël, to the oldest known combinatorial game, and at the same time to "Go" all out to turn his five-year group into a unit!

Andrea Puhar,
Postdoctoral fellow

"It's a bit like travelling without travelling. Everyone describes what daily life is like in their own country… Unfortunately there comes a time when we have to go our separate ways. But it means that we have friends throughout the world."

On the Pasteur road

"Since my childhood I have always been a foreigner. But now I feel like a European." Andrea Puhar, 32, was born in Graz, Austria, and speaks fluent French with just a hint of an accent and a lot of laughter. She grew up in Lugano, Switzerland, taking trips back to Austria during her school holidays. At high school, she learned about the history of microbiology and was particularly fascinated by one of its pioneers, Louis Pasteur. *"Just before taking my high school diploma, my school organized a trip to Paris, where we stayed in a hotel that was a stone's throw from the Institut Pasteur! Some months later, I enrolled to take a biology course at university with the dream of working in this famous place."* She went on to complete her degree in Zurich.

In 2003, she travelled to Padua, Italy, to prepare for her PhD. During her doctoral studies, she spent several months in Germany on an inter-university exchange. *"As we spent a lot of time in the labs, that's where I ended up meeting my partner, who is Mexican."*

She successfully completed her PhD on protein bacterial toxins and became a postdoctoral researcher, or "post-doc". *"You never stop learning. Taking a postdoctoral fellowship also means changing laboratories – ideally changing subjects – and also changing countries to gain international experience."* In February 2008, Andrea Puhar came to France and the Institut Pasteur, where she joined the Molecular Microbial Pathogenesis Unit. *"I work on the Shigella bacterium, which causes bacillary dysentery, an infection which affects 150 million people worldwide and kills around a million children each year. There are around 5,000 cases in France each year. This disease is closely linked to hygiene, which is why it is much more prevalent in poorer countries."*

Grouped under the same roof, the postdoctoral fellows from different countries speak to each other in English. *"It's a bit like travelling without travelling. Everyone describes what daily life is like in their own country… We even cook together. Unfortunately there comes a time when we have to go our separate ways. But it means that we have friends throughout the world."*

2009

significant highlights

The influenza A(H1N1) pandemic, international agreements, fundraising – in 2009, the Institut Pasteur worked to accomplish its various tasks successfully and to develop new partnerships, while making every effort to combine good practices and rigorous research. A look back at the key episodes of the past year.

Influenza pandemic

The Institut Pasteur responded to the influenza A epidemic as soon as the first alerts were issued in France and abroad, deploying its expertise and calling on all its teams to tackle the problem.

As soon as the first cases of influenza A emerged in France and abroad, the Institut Pasteur's teams, via the Influenza National Reference Center (Northern-France), directed by Sylvie van der Werf, and the Laboratory for Urgent Response to Biological Threats (CIBU), coordinated by Jean-Claude Manuguerra, set to work. They began by developing a diagnostic test that enabled the first strains of the new virus to be identified and characterized. They then diagnosed the first cases and systematically confirmed the diagnoses of laboratories within the hospital network.

On May 5, 2009, the Institut Pasteur announced that it had developed a test that would detect the new A(H1N1) virus in 12 hours. At the request of the French General Directorate of Health (DGS) and in partnership with EPRUS, the public body that responds to public health emergencies in France, the institute distributed the reagents required for the implementation of this test in approved laboratories in mainland France and the overseas departments and territories so that the new virus could be diagnosed. Around fifteen institutes in the Institut Pasteur International Network, some of which are influenza national reference centers or laboratories (Algeria, Morocco, Tunisia, Cameroon, Ivory Coast, Senegal, Madagascar, Niger, Central African Republic, Romania, Cambodia, Shanghai, Vietnam and Hong Kong), were also sent the reagents and the protocol.

Operational structures

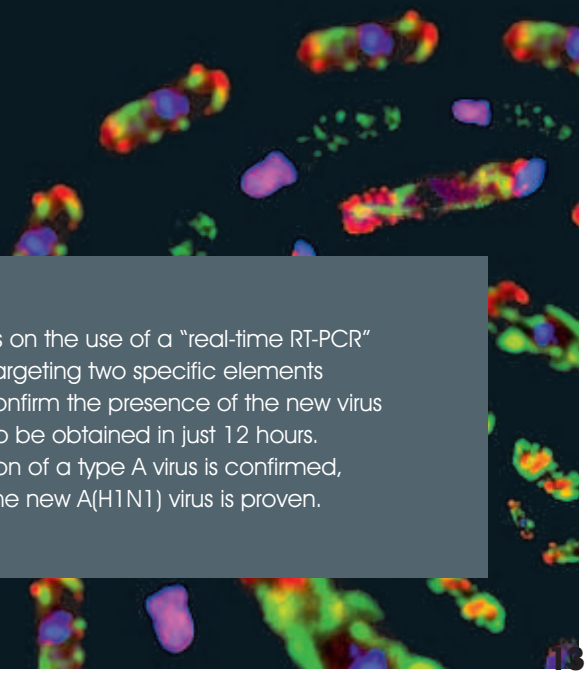
Four Institut Pasteur structures are involved in the French National Plan to Prevent and Combat the Influenza Pandemic. They work in close cooperation with the French Institute for Public Health Surveillance (InVS in French).

- **The Influenza National Reference Center (Northern-France) at the Institut Pasteur,** regularly called on by the French Health Ministry to centralize the monitoring of influenza cases in Northern France, analyzed all the suspected cases in Northern France. The Center developed the rapid diagnostic test and also identified mutations of the virus that occurred in December 2009, some of which were associated with resistance to oseltamivir.

- **The Institut Pasteur's Laboratory for Urgent Response to Biological Threats (CIBU)** was set up in 2002 to provide a real-time response for ensuring that the causative pathogenic agent or agents are detected and identified as quickly as possible in the event of an epidemic. It works in close cooperation with the National Reference Center to analyze suspected cases of influenza A(H1N1).

- **The Genotyping of Pathogens and Public Health Platform** is called on to sequence viral strains involved in the diagnostic process. Its main aim is to provide scientific and technical support to the French monitoring and microbiological expertise laboratories in the fields of infectious diseases, particularly in the event of microbiological emergencies that represent a threat to public health nationwide.

- **Finally, the Antiviral Immunity, Biotherapy and Vaccines Unit** is involved in several clinical trials together with the Cochin-Pasteur CIC to assess immune response to the virus and to the pandemic vaccine used to protect pregnant women and immunosuppressed and HIV-infected patients against this new A(H1N1) virus.



Focus: how is the new A(H1N1) virus detected?

The method behind the detection test, developed at the Institut Pasteur, relies on the use of a "real-time RT-PCR" technique (amplification of the genetic material of the virus in the sample), targeting two specific elements of the H1 gene of the new virus. With this more sensitive test, it is possible to confirm the presence of the new virus without the need for the viral genome sequencing stages, enabling a result to be obtained in just 12 hours. Identification of the new virus involves three simultaneous operations: detection of a type A virus is confirmed, the presence of a seasonal influenza virus is ruled out, and the presence of the new A(H1N1) virus is proven.

International

March 2009 – During the French President's visit to Mexico Professor Alice Dautry signed partnership agreements with the National Science and Technology Council of Mexico and the Mexican Health Ministry. These agreements will strengthen the links and partnerships that the Institut Pasteur has enjoyed for many years with Mexican stakeholders in research and health.

May 2009 – The Institut Pasteur and the US federal agency, Centers for Disease Control and Prevention (CDC) signed a Memorandum of Understanding at the meeting of the Assembly of the World Health Organization (WHO) in Geneva. The aim of this agreement is to pool the efforts of these two organizations, leaders in the field of overall public health, by providing a framework for joint and sustainable initiatives for international public health and health safety worldwide.

May 2009 – The Institut Pasteur signed up to the recommendations set out by the European Commission in the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers. The purpose of these two documents is to generalize good practices in terms of recruitment, terms of employment and working conditions for researchers in Europe.

September 2009 – The Institut Pasteur in Dakar has become a foundation under Senegalese law. This new status will not only offer the institute greater visibility but also provide access to new sources of funding and new partnerships. The ambitious projects of the Institut Pasteur in Dakar include the construction of a new yellow fever vaccine production unit to meet the needs of the African continent. This initiative is supported by UNICEF, the World Health Organization and the French Development Agency (AFD).

Institutional partnerships

April 2009 – With the creation of Aviesan, the French National Alliance for Life and Health Sciences, the CNRS, INSERM, the CEA, INRA, INRIA, the IRD, the Institut Pasteur and the French Conference of University Presidents are taking a major step to enhance coordination in the field of life and health sciences. This alliance is part of a policy pursued by the French government to reform the country's research system and improve coordination between the various stakeholders. The aim is to strengthen the position of French research in this sector through a concerted program of action.

September 2009 – The Paris Public Hospital Network (AP-HP) and the Institut Pasteur signed a four-year agreement to strengthen cooperation in the areas of healthcare and fundamental, clinical and epidemiological research, particularly through joint research programs.

Joint and sustainable initiatives for international public health

Industrial relations

May 2009 – By signing a long-term joint research agreement, the Institut Pasteur and the Institut Mérieux (composed of the companies bioMérieux, Transgene, Shantha Biotechnics, ABL and Silliker) have decided to pool their resources and efforts in joint large-scale research projects to combat infectious diseases.

November 2009 – Natixis Private Equity and CDC Entreprises joined forces to launch Kurma Biofund, a fund for venture projects in the area of life sciences that was set up as a result of a strategic partnership between the Institut Pasteur and the Institut Curie. To boost financial performance and encourage innovation in this market, Kurma Biofund will mainly be dedicated to establishing partnerships with major biomedical research institutes in Europe and generating an economy of knowledge and innovation with a focus on financing assets with quick rotation.

Fundraising

November 2009 – The first conference on philanthropic trusts, organized by the Institut Pasteur, was attended by specialists in current issues relating to trust funds. The event brought together over 300 influential figures from the banking sector, financial advisors and independent asset managers, notaries, tax lawyers, insurance companies, major donors and founders. It was an opportunity for the Institut Pasteur to unveil its new program for major sponsors and philanthropists, "Campus philanthropes", launched in the first half of 2010.

December 2009 – BNP Paribas Corporate & Investment Banking (CIB) decided to renew its partnership with the Institut Pasteur, once again offering its support this year to the global efforts to combat infectious diseases. BNP Paris CIB is providing financial support in 26 countries to research teams from the Institut Pasteur and the Institut Pasteur International Network or to laboratories working in cooperation with the Institut Pasteur.

Ethics

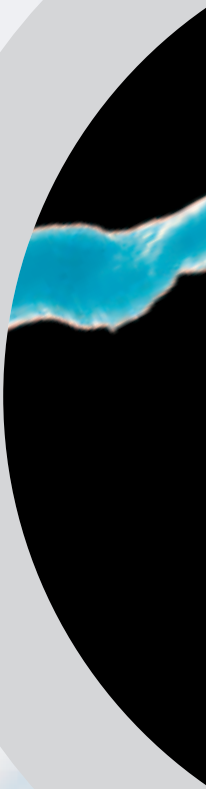
December 2009 – The Institut Pasteur adopted an Ethics Charter based on the work of the Ethical Vigilance Committee, chaired by Professor Jean-Pierre Changeux with Professor Françoise Barré-Sinoussi as deputy chair. This charter is a series of regulations and reference texts for the Institut Pasteur and all those who work there, regardless of their position; every member of staff must comply with the charter.

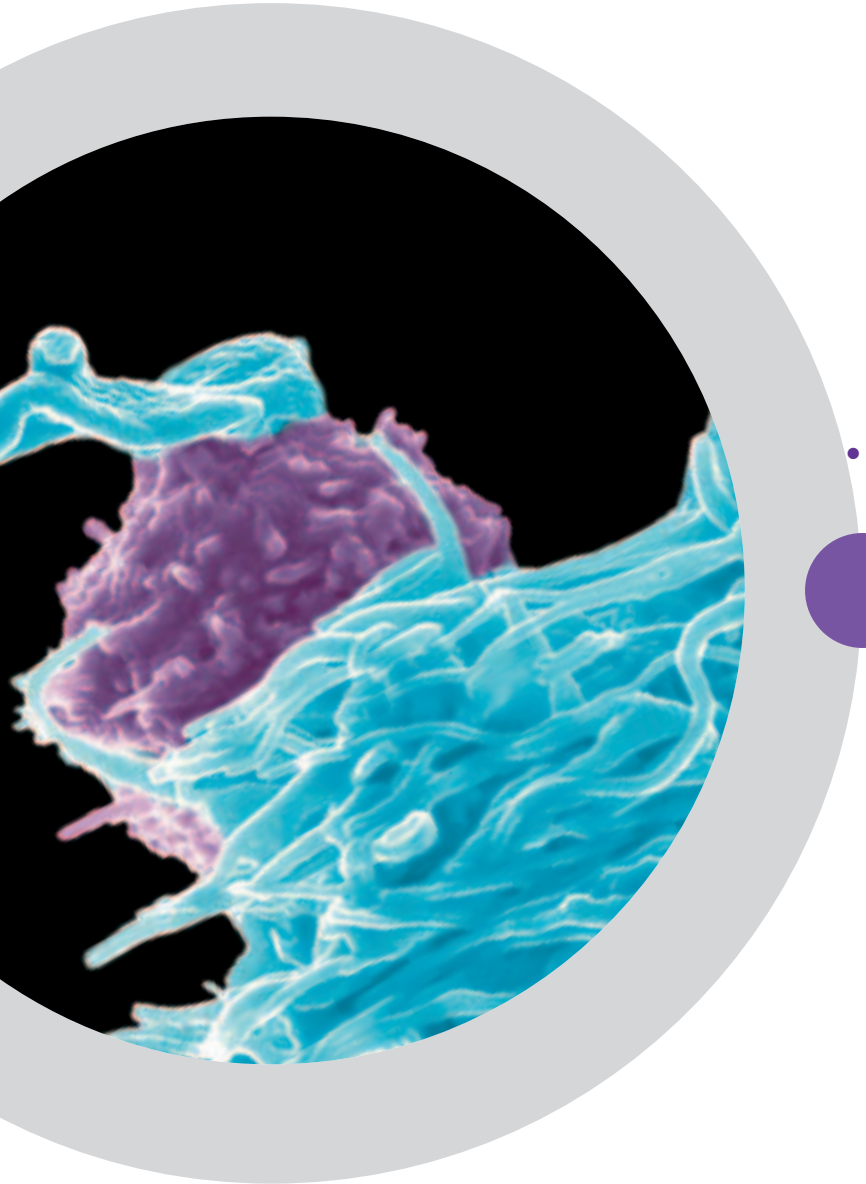
A new program for major sponsors and philanthropists launched in the first half of 2010.

scientific discovery for sustainable health

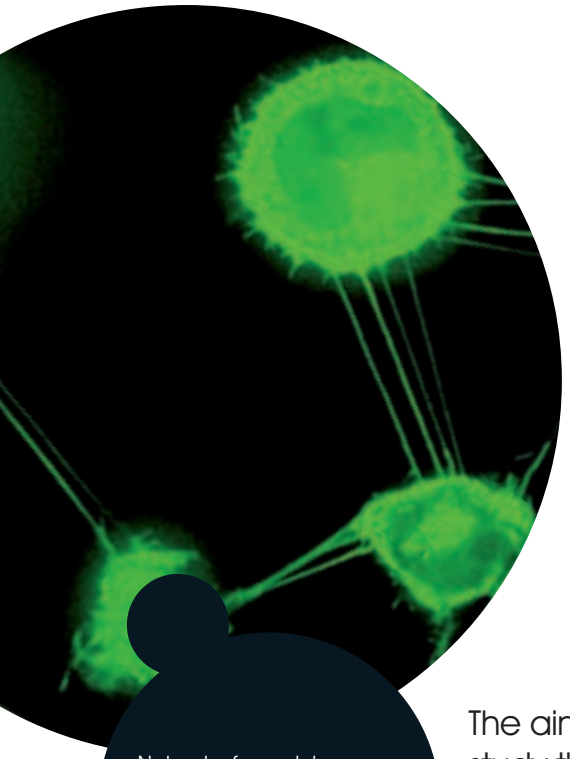
RESEARCH

effective multidisciplinary research





Ten scientific departments, 130 research entities and 14 technological platforms, with over 900 articles published in international scientific journals in 2009. The flexible structure developed by the Institut Pasteur provides a fertile setting for multidisciplinary, innovative, effective research.



Network of nanotubes established between neuronal cells expressing the non-infectious prion protein.

Cell Biology and Infection

●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

The aim of the department is to study the interactions between pathogens and their targets – cells and tissues – at all stages of infection. Some teams focus their research on infectious agents, while others concentrate on gaining in-depth knowledge of the cell in a non-infectious context.

Understanding infectious mechanisms requires extensive research into how cells function during infection and in conditions of balance between the commensal flora and the host. The department's aim is to develop analysis of the interface between microorganisms and cells/tissues. To achieve this aim, three priorities have been set:
– to strengthen the integration of cell biology, cell microbiology, genomics and imaging for a more effective analysis of bacterial, viral, parasitic and prion infections;
– to develop expertise in tissue microbiology by using in vivo imaging technologies and further understand infection at the whole-animal scale;
– to foster close links with immunologists and cell biologists in other departments.
These activities are closely related to the development of new techniques such as imaging, image analysis, genomics and post-genomics.

● THE GENOME OF THE *LISTERIA* BACTERIUM REPROGRAMMED DURING INFECTION

Listeriosis is a food-borne bacterial infection caused by *Listeria monocytogenes.* This bacterium is widespread in nature (in water, soil, plants and animals) and can contaminate a large number of food products. It can lead to septicemia, meningitis or encephalitis in those at risk, such as pregnant women, the elderly and immunosuppressed patients, and is fatal in 20 to 30% of cases.
Using new DNA micro-arrays, which allow whole-genome expression analysis of the bacterium, scientists from the Bacteria-Cell Interactions Unit (Inserm Unit 604, INRA USC2020), in cooperation with other groups from the Institut Pasteur* and a Swedish team, compared the activity of all the bacterium's genes in its inoffensive state and its pathogenic state.
The results of this analysis showed that when the bacterium reaches the inside of the intestine, and then the bloodstream, it radically changes the activity of its genome and successively activates various groups of virulence genes. Of the 50 small RNAs identified, some are missing from the non-pathogenic species *Listeria innocua* and at least two contribute to the virulence of *L. monocytogenes.* The researchers discovered a series of new types of regulatory RNAs which probably also exist in other bacteria.
This work paves the way for a full understanding of Listeria's adaptation mechanisms when the bacterium moves from the environment to the infected host. It especially opens up new possibilities in the highly competitive field of RNA regulation, in all species of the living world.

Philippe Sansonetti, Head of the Molecular Microbial Pathogenesis Unit, and Pascale Cossart, Head of the Bacteria-Cell Interactions Unit, are both winners in the "Advanced Grants" section of the ERC (European Research Council) "Ideas" program, part of the 7th Research and Development Framework Program. This program funds "frontier research", and selects projects based solely on scientific excellence. The respective projects of Philippe Sansonetti and Pascale Cossart are HOMEOPITH – "Homeostasis and rupture of the gut epithelium in the presence of commensals and pathogens" – and MODELIST – "Understanding the infection by the bacterium *Listeria monocytogenes* as a way to address key issues in biology".

Pascale Cossart and Philippe Sansonetti, Heads of Unit

● A FUNDAMENTAL CELL MIGRATION CONTROL MECHANISM IDENTIFIED

Cell polarity determines a cell's ability to orient itself correctly depending on its environment. This is important in the organization of the various stages in a cell's life, such as division, differentiation and migration. Cell polarity is disrupted in cancer cells, particularly in gliomas, which are brain tumors derived from cells in the central nervous system such as astrocytes. Gliomas are highly invasive tumors that are difficult to treat. Their considerable potential for invasion, migration and division could result from a loss of cell polarity.

Researchers from the Cell Polarity and Migration five-year group studied the role of intercellular contact in controlling astrocyte polarity and migration. They demonstrated that the distribution of adhesion junctions involving cadherin molecules determines the polarity axis of astrocytes. Glioma cells are often lacking in cadherins. Suppressing the cadherin in normal astrocytes makes them unable to orient themselves in relation to one another, and they lose their capacity for regulated, coordinated migration. The absence of cadherins therefore leads to cellular disorganization similar to that observed in glioma cells and probably responsible for these cells' invasive migration.

The next stage involves restoring the expression of cadherin in glioma cells and observing their behavior. Would this restore cell polarity and migration, and stop tumor invasion? To be investigated further.

● PRION PROPAGATION IN THE ORGANISM EXPLAINED

After arriving in the intestine via contaminated food, the prion, the infectious protein responsible for Creutzfeldt-Jakob Disease, reaches the brain by means of the lymphoid system (spleen, lymph nodes, etc.). Despite the existence of several theories on the mode of transport used by the prion, its mode of propagation from cell to cell had previously remained unknown.

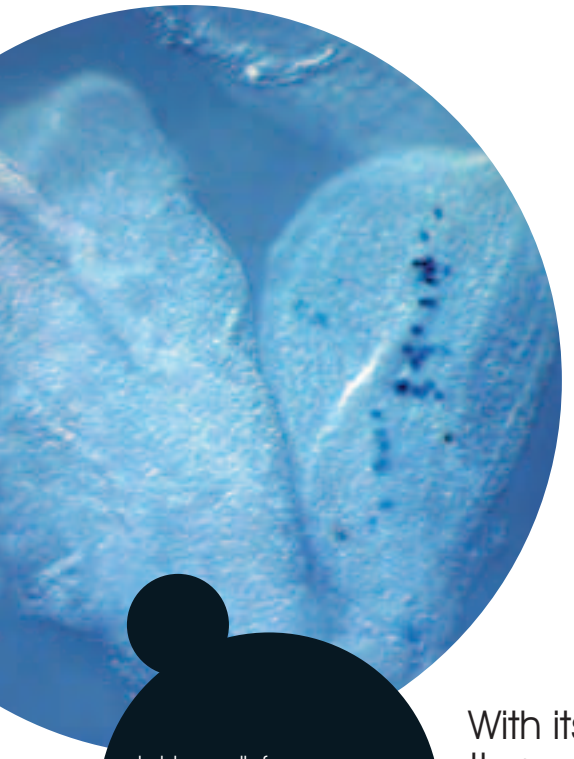
Researchers from the Membrane Traffic and Pathogenesis** Unit focused their efforts on the dendritic cells in the immune system, whose characteristics favor the spread of prions towards the brain. These cells are extremely mobile and use nanotubes, very thin intercellular bridges which form and retract, enabling cell material to move from one cell to another. These nanotubes are the favored vectors of lipid-anchored membrane proteins, the protein category which includes prions.

By using a fluorescent marker, researchers demonstrated in vitro the transfer of the prion from infected dendritic cells to non-infected neuronal cells, where it contaminates normal prion proteins, which in turn multiply and spread to neighboring cells. Conversely, they demonstrated that by using dendritic cells that are unable to produce nanotubes, the infection did not spread.

This work, which the researchers will now attempt to validate in vivo, significantly improves our understanding of Creutzfeldt-Jakob Disease and the therapeutic methods that should be investigated to fight the disease.

7 units
4 five-year groups
2 technological platforms

** Microbes and Host Barriers Group, INSERM Avenir 604; In Silico Genetics provisional unit, Institut Pasteur Genopole*
*** In cooperation with the Quantitative Image Analysis Unit, the Mycobacterial Genetics Unit, the Dynamics of Host-Pathogen Interactions Group and the Universities of Regensburg and Naples Federico II.*



In blue, cells from a mouse embryo deriving from a bipotent stem cell.

Developmental Biology

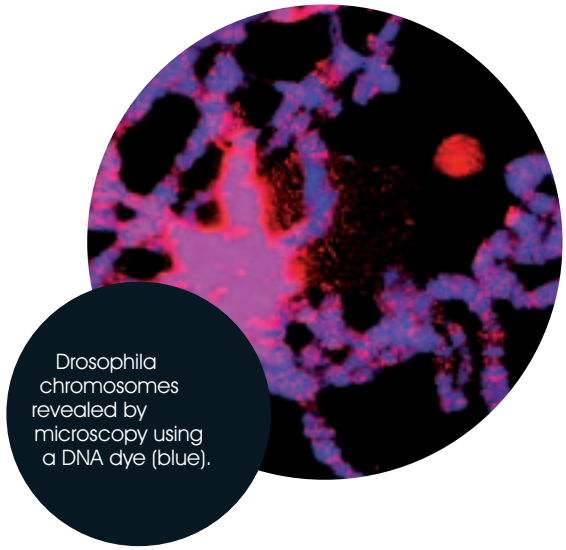
●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

With its research spanning through from the cell to the entire organism, the work conducted by the Developmental Biology Department covers a wide spectrum of multidisciplinary research.

The aim of the Developmental Biology Department is to understand how a highly integrated multicellular organism such as a human being develops from a single cell, the fertilized egg.
The research topics of the eight units, two provisional units and one five-year group can be divided into four main areas:
– identifying the cell movements and migrations of the embryo needed for organ and tissue formation, and the informational exchanges used during this process;
– determining how the identity of each cell is established and maintained through specific programming mechanisms;
– establishing the role of stem cells, which play a dominant role not only in embryogenesis but also in the regulation and maintenance mechanisms of adult tissues;
– clarifying the respective roles of innate and non-genetic factors in the phenotypes developed by the individual, and their genetic contributions to the host's resistance to infectious diseases and/or congenital and metabolic diseases.

● STEM CELLS PLURIPOTENT FOR LONGER

One cell, then two, four, eight... Once fertilized, the egg divides without interruption until the complete multicellular organism has been formed. The gastrula stage, six days after fertilization in mice, is considered to be a nevralgic point in embryonic development, from which stem cells specialize into three distinct cell lineages. These lineages which are organized into three superimposed layers give rise to all the different body tissues.
In 2009, the research of the Molecular Biology of Development Unit, which involves the dynamic mapping of the origins of tissues at each stage of development, challenged part of this theory. The study, carried out on mice, demonstrated that although the inner and outer layers – known as the endoderm and surface ectoderm – do differentiate during gastrulation, the central layer – the mesoderm – continues to share cells with properties in common with the ectoderm until it reaches a much more advanced stage of development.
This discovery demonstrates the continuing presence of bipotent stem cells much later than was first believed, challenging the basis of our knowledge on the early stages of embryogenesis. It provides unexpected avenues for investigation and sheds new light on the possibility that we might one day be able to control the differentiation of stem cells.



Drosophila chromosomes revealed by microscopy using a DNA dye (blue).

A NEW ROLE FOR SMALL RNAs

Small RNAs, originally known for their antiviral properties, have recently been associated with the regulatory mechanisms for vital cell processes such as development, cell proliferation and apoptosis. The Drosophila Genetics and Epigenetics five-year group has recently added a new string to their bow by identifying the crucial role of small RNAs in genome regulation.

The researchers demonstrated for the first time in a superior organism – Drosophila – the role of small RNAs in the formation of large blocks of heterochromatin, regions of the genome composed of inactive DNA in which gene expression is silenced. By controlling the formation of heterochromatin around the centromere – the center of the chromosome – these small RNAs restrict the expression of nearby genes.

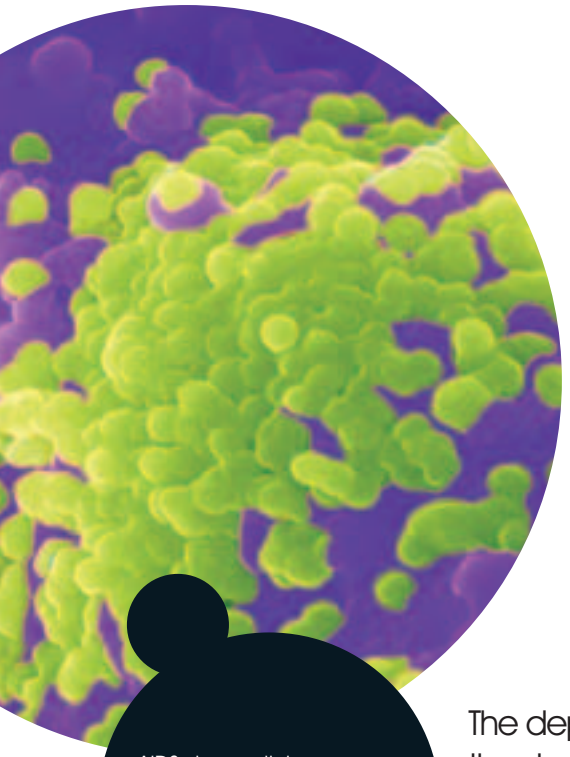
This mechanism results in some genes being completely silenced. If it could be transposed to humans, it would offer new possibilities for understanding genetic diseases and cancers. Ongoing research in mice and chickens will contribute to this work.

CENTRAL ANIMAL FACILITY RENOVATED

The use of animal models remains a necessity for much of the scientific research conducted at the Institut Pasteur, in various fields of biomedical research. The Institut Pasteur takes its responsibilities of ensuring the regular upkeep of its experimental facilities, which are mostly housed at the Central Animal Facility, attached to the Developmental Biology Department, very seriously. As part of its long-term development program, two animal houses in the Central Animal Facility were renovated between 2007 and 2009. These facilities provide the environment and logistics required to raise laboratory animals in strict compliance with European and French regulations.

The Central Animal Facility's 47-member teams, which include 4 veterinarians, one research engineer, one assistant, 18 technicians and 23 animal keepers, make sure the animals are well treated throughout the period of experimentation. The Institut Pasteur is attached to an ethics committee, which examines the experimental protocols and sees that the "3R" approach – *replace, reduce, refine* – is followed. The "replace" refers to using in vitro systems wherever possible. 'Reduce' to efforts to "reduce" the number of experimentation animals used to the strict minimum required. Finally, laboratory practices are "refined" to make sure that the animal's wellbeing is taken into consideration as far as possible.

This code of conduct was included in the *Ethics Charter of the Institut Pasteur*, signed in October 2009. This demonstrates the Institut Pasteur's commitment to going above and beyond its basic regulatory obligations and to ensuring optimal guidance and support for its staff in this important area.



AIDS virus particles at the surface of a lymphocyte.

Structural Biology and Chemistry

●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

The department mainly studies the structure and properties of molecules of biological interest, particularly in the context of their role in human pathology. Identifying links between the structure and function of these molecules is essential for the development of new therapeutic strategies.

The department studies the three-dimensional structure of molecules so as to understand their functions in cell physiology and their role in the development of infectious diseases (tuberculosis, Chagas disease, malaria, etc.), genetic diseases and cancers. It uses and develops cutting-edge technologies:

– molecular modeling plays a key role in determining structures and making use of them;

– crystallography enables the 3D structure of a molecule to be displayed. It is an ideal technique for carrying out drug-design studies on potential targets;

– nuclear magnetic resonance (NMR) enables researchers to access the structure of smaller molecules and provides information on their movements and the molecular interactions studied.

The department combines structural approaches and biochemical and biophysical research to reveal the molecular mechanisms involved in pathological and infectious processes, and to design chemical tools that interfere with these processes.

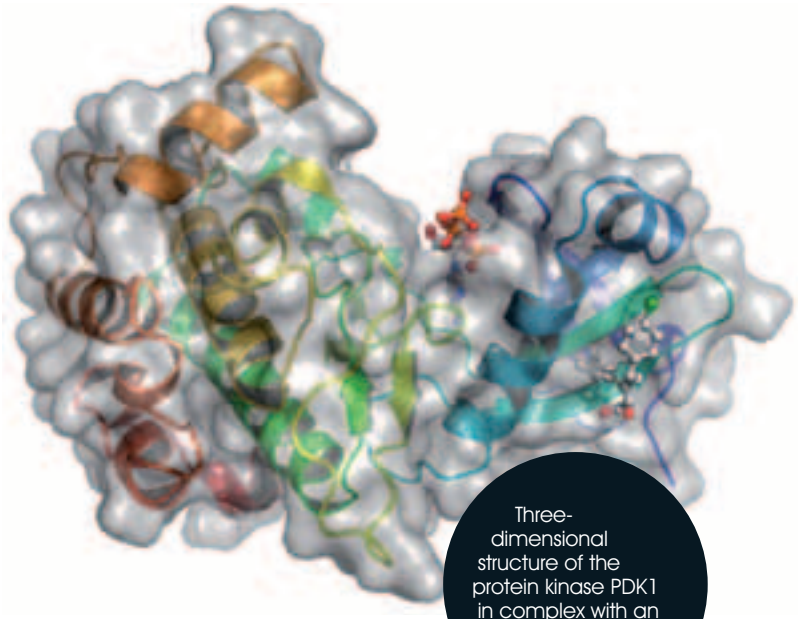
● A NEW MOLECULE AGAINST HIV

The development of some 25 therapeutic molecules has considerably increased the survival rate of patients suffering from the AIDS virus. Most of these molecules target the replication of the virus in the cell, but none of them enable it to be completely eradicated.

Researchers from five organizations*, including the Chemistry of Biomolecules Unit, worked together to develop a molecule capable of blocking entry of the virus into the cell by neutralizing the glycoprotein gp120. This glycoprotein, located on the HIV membrane, could be a prime pharmacological target because it enables the virus to recognize a receptor on the cell, the CD4 molecule. Binding gp120 to the cell's CD4 receptor frees up a new recognition site. The gp120 protein can then bind to one of the co-receptors (CCR5 or CXCR4), and the virus can enter the cell.

The researchers managed to develop a new molecule known as CD4-HS, which has the unique characteristic of simultaneously blocking the CD4 molecule binding site and the co-receptor binding site. Tests for antiviral activity confirmed that this molecule inhibits various HIV strains very effectively.

Work is under way to simplify the structure and synthesis of this molecule. The next stage will be to conduct *in vivo* tests.



Three-dimensional structure of the protein kinase PDK1 in complex with an activator (bottom right).

● ACTIVATION MECHANISM OF SOME ENZYMES IDENTIFIED

Protein kinases are enzymes which play a crucial role in controlling cell proliferation and survival. Their dysfunction plays a role in several cancers, which has led to research being conducted in recent years into molecules capable of modulating (increasing or reducing) the activity of these enzymes. To date, around ten kinase inhibitors are already used in cancer treatments, and several others are in clinical trials to treat autoimmune and inflammatory diseases. However, although it is relatively simple to identify kinase inhibitors, it has proved much more difficult to find small molecules that are able to activate these enzymes.

The work of the Structural Biochemistry Unit, conducted in cooperation with German researchers, has identified a new family of chemical compounds that are able to increase the activity of the human protein kinase PDK1 by binding to an allosteric site** in the enzyme. This has shed light on the molecular basis of the activation mechanism.

These results offer new possibilities for the rational design of kinase modulators, which represent an important tool for researching the functions of these proteins in the cell, and in the long term should also enable the development of new approaches for the design of future cancer drugs.

● DNA TRANSFERS UNDER THE SPOTLIGHT

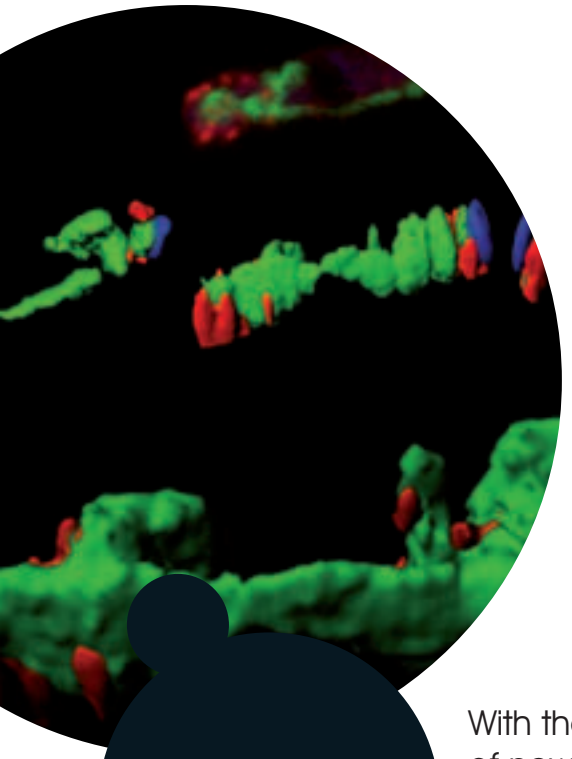
Since October 2009, the Structural Biology and Chemistry Department has housed a new five-year group called Structural Biology of Bacterial Secretion. This new four-member team specializes in X-ray crystallography and in the use of high-resolution electron microscopy. Its aim is to study the membrane protein systems that allow DNA to move from one bacterium to another. These phenomena enable bacteria to acquire new functions that can help them adapt to their environment.

DNA transfer between bacteria is common practice. Three mechanisms by which genetic information is carried have been identified. One of the best-known is transduction, which enables two bacteria to exchange DNA through the intervention of a viral vector. Conjugation, the process whereby a plasmid – a circular piece of DNA – is transferred from one cell to another, and transformation, the system that enables the bacterium to acquire naked DNA from the outside environment, are completely separate processes whose membrane transporters have not yet been characterized.

Researchers in this new group hope to understand the molecular architecture of these protein complexes derived from model bacteria, such as *Streptococcus pneumoniae* and *Bacillus subtilis*. By analyzing each protein subunit, then determining how the entire complex is assembled, the scientists hope to shed light on how these "bridges" work, thereby improving our knowledge of these phenomena whereby bacteria acquire genes resistant to antibiotics.

6 units
2 provisional units
1 five-year group
6 technological platforms

** CEA/CNRS/Institut Pasteur/University Joseph Fourier/University of Paris-Sud 11.*
*** This refers to the binding site of a molecule that activates or inhibits the enzyme. The binding of an activator or inhibitor at this allosteric site, away from the active site, causes a conformational change in the enyzme which triggers a rapid acceleration or a deceleration, or even a complete stoppage of enzyme activity.*



3D reconstruction of *Schizosaccharomyces pombe* yeast cells.

Genomes and Genetics

●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

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

The Genomes and Genetics Department explores the genetic information of the human organism and microorganisms such as yeast and bacteria. The genomes of the tuberculosis bacilli, streptococci, *Vibrio, Legionella* and other pathogenic bacteria or models are studied in depth with the aim of understanding how they live and what determines their pathogenic nature. Yeasts are also studied, both for their own properties and as models to help us understand human genetics. The department is also looking into the evolution of infectious agents and the selective pressures that they have exerted on human genes over time. The success of these research programs benefits greatly from the current progress being made in new sequencing and genotyping technologies.

● THE EFFICACY OF MULTI-ANTIBIOTIC RESISTANCE EXPLAINED

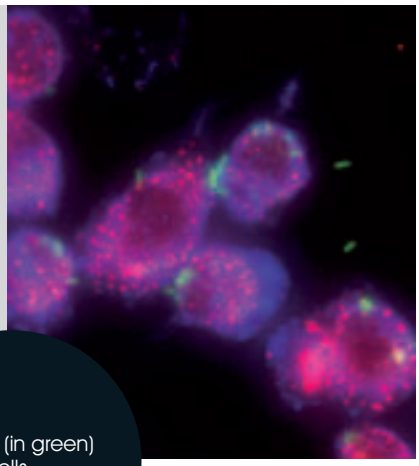
Bacterial resistance to multiple antibiotics – multiresistance – is a phenomenon that appeared in the 1950s when these drugs began to be used. It was subsequently discovered that resistance genes were easily captured, disseminated and exchanged from one bacterium to another by a system involving genetic "copy - paste" of the structures containing these genes, known as integrons. But the dynamics of these exchanges, governing the development of multiresistance in bacteria, remained unknown.

The Bacterial Genome Plasticity Unit has revealed how bacteria acquire these multiresistance properties: the antibiotics themselves trigger the synthesis of the bacterial enzyme that captures the resistance genes and enables their expression in the integron. This enzyme also promotes the random rearrangement of the resistance genes within the integron. When a new rearrangement occurs, triggered by the intake of an antibiotic, for example, they are likely to be moved to the first positions, expressed at higher level, and to give the bacteria the required resistance to this drug. The bacteria with the right "combination" of genes will therefore be able to survive and ensure that the resistance potential is maintained from one generation to the next.

This work shows the extent to which strategies of bacterial adaptation to antibiotics are effective, in both the short and the long term. These strategies will have to be overcome by future public health measures that aim to tackle the problem of multiresistance.

A public health issue

In October 2009, the Institut Pasteur hosted the 7th international conference on *Legionella*, the bacteria responsible for legionellosis. Leading the "*Legionella* 2009" steering committee, Carmen Buchrieser, head of the Biology of Intracellular Bacteria unit, brought together the leading specialists on the subject to review the latest developments: *"Genomics is constantly improving our knowledge of the evolution of these bacteria and of legionellosis. It has enabled significant progress to be made in the field of detection and diagnosis. The new technologies that have been developed to help control* Legionella *could provide valuable data during future epidemics."*



Legionella (in green) infecting cells.

A BENEFICIAL GENETIC MUTATION AGAINST MALARIA IN SOUTH-EAST ASIA

A large-scale evolutionary and epidemiological genetic survey carried out over an eight-year period in Thailand has enabled the Viral Pathogenesis and Human Evolutionary Genetics Units, in cooperation with Mahidol University in Thailand, to demonstrate that a mutation that is particularly widespread in some South-East Asian populations offers a higher level of resistance to malaria. The results of this work revealed an increased survival rate for carriers of this protective mutation, and that it is associated with a significant reduction in the number of parasites in the blood.

The mutation, named *G6PD-Mahidol487A*, affects the gene of the G6PD enzyme. A deficiency in this enzyme – particularly frequent in South-East Asia, where 18 to 25% of the population is affected – leads to disorders of varying degrees of severity, including jaundice and anemia.

As well as demonstrating the protective effect of the mutation against *Plasmodium vivax*, the malaria agent, the study also enabled researchers to date back its emergence in the human genome. It first occurred 1500 years ago in South-East Asia, coinciding with the expansion of rice cultivation, which required extensive deforestation and therefore brought humans and mosquitoes, vectors of malaria, into closer contact. Given this increased "infectious pressure" due to a greater exposure to mosquitoes, those who carried the *G6PD-Mahidol487A* mutation had an advantage, and more were able to survive.

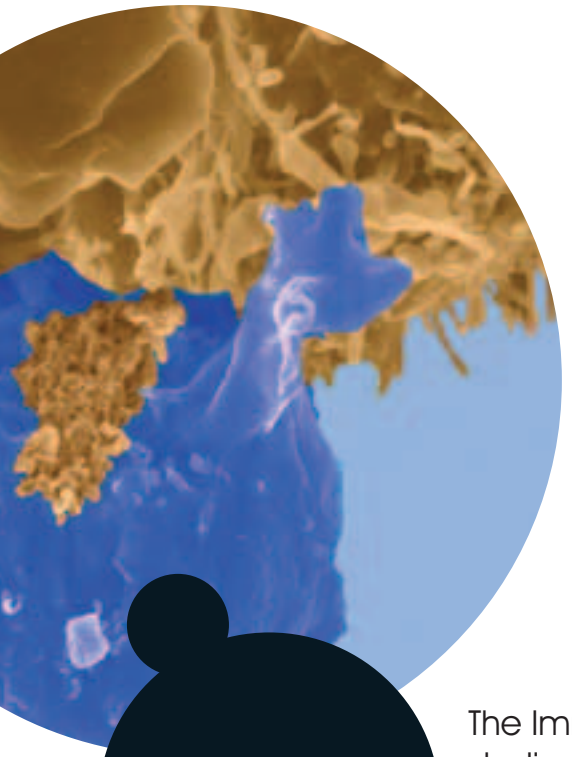
INCREASINGLY INNOVATIVE AND EFFECTIVE TOOLS

With the spectacular progress being made in new technologies – particularly in the area of sequencing – genomics and research into overall gene expression have experienced considerable developments over the past few years. Barely five years ago, sequencing the genome of a bacterium cost 50,000 euros and required several months' work. Today, new high-throughput sequencing techniques have significantly reduced that cost to a few thousand euros, and the time required to just a few days; moreover, these new techniques have also provided an opportunity to revise our approaches to genomes and genetics.

The new Next Generation Sequencing (NGS) platform acquired by the department's Sequencing Platform has revolutionized analysis techniques and approaches in genetics. Sizeable investments in experimentation equipment, increased capacities for calculation and storage, and the involvement of the department's IT experts have enabled the Institut Pasteur to support all its researchers in these new research areas. For example, several groups in the department have been able to sequence the genome of several strains of *Escherichia coli*, a number of *Vibrio,* and some of their variants. For each line, genotype changes could be observed to the nearest base.

In one single experiment lasting a few days, the entire map of the bacterial genome was revealed, and the precise evolutionary pathways were retraced. Given these new possibilities, even more ambitious projects will be launched in the coming months, meaning that the sequencing capacities are already proving limited. A new machine is currently being purchased.

7 units
3 provisional units
1 five-year group
2 laboratories
3 platforms
1 software and databases group



Biofilm formed by the HTLV-1 virus on the surface of a cell.

Immunology

●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

The Immunology Department studies the development of the immune system, conducting research into physiologic and pathologic immune responses. It also creates humanized mice to model the human immune system *in vivo*.

The work of the Immunology Department can be grouped into three main areas:
– development of the immune system. Several teams are working on the differentiation of immune cells, the formation of lymphoid organs and cell dynamics during the immune response;
– innate and acquired immunity. Innate, non-specific and immediate immunity, together with adaptive, specific and acquired immunity, contribute to immune responses. Teams are studying these responses, the cells responsible and their interactions;
– immune responses and pathology. Some teams are studying protective, anti-infectious and anti-cancer immunity; others are studying immune disorders such as allergies or autoimmune diseases. The aim is to strengthen the former and correct the latter.

● BIOFILMS: DISCOVERY OF A NEW MECHANISM OF VIRUS PROPAGATION

The HTLV-1 virus (human T-cell leukemia virus type 1), which infects 15 to 20 million people worldwide, causes adult T-cell leukemia/lymphoma. The dissemination of HTLV-1 was known to occur via cell-cell contact, but the transmission mechanism itself remained a mystery.
Researchers from the Institut Pasteur and CNRS, in the Lymphocyte Cell Biology Unit, in collaboration with the Oncogenic Virus Epidemiology and Physiopathology Unit and with the Imagopole, recently identified, for the first time in viral research, "biofilm"-like structures, formed by the HTLV-1 retrovirus on the surface of infected cells. HTLV-1 is far more easily transmitted in this biofilm – an effective protective and adhesive barrier – than in its free, isolated state. By removing the viral biofilm from the surface of the infected cells, researchers achieved an 80% reduction in infection rates, thus underlining the importance of this mode of transmission for HTLV-1.
Scientists are currently seeking to characterize the mechanisms of viral biofilm generation, and to determine whether viruses other than HTLV-1 form this kind of structure. For such viruses, new therapeutic strategies could be envisaged which would target not only the virus itself but also the formation of these viral biofilms.

MICROBES THAT PROTECT US

It is estimated that several billion bacteria colonize a human being each day, in perfect symbiosis. This relationship, which benefits humans and microbes alike, guarantees a number of vital functions such as digestion, detoxification from certain toxic elements, and protection from other microorganisms. It is a fragile balance obeying very strict rules, which, if not respected, can lead to serious diseases such as inflammatory intestinal diseases.

The Lymphoid Tissue Development Unit specializes in researching the processes that govern the interactions between the intestinal bacterial flora and the host immune system. The 10-member team recently demonstrated how microorganisms in the intestine triggered the formation of lymphoid tissues and cells such as lymph nodes, where there is a proliferation of immune defenses. This team is seeking to understand the complex dialogue between symbiotic bacteria, the molecular motifs that they produce and the immune system, and to understand how impairments to this dialogue can lead to inflammatory diseases. Their work, which enabled this five-year group to become an Institut Pasteur research unit in 2009, is producing important new information on how the immune system operates in relation to these intestinal microbes and revealing new targets for the development of new therapeutic approaches.

OF MICE AND MEN

The Immunology Department is involved in the development of mice whose immune system is partially or fully replaced by its human equivalent. Mice with HLA molecules or human antibody receptors have been or are being created in the department. A particularly ambitious project involves replacing the mouse immune system with a functional human immune system. This project led to the creation in 2009 of Axenis, a start-up which aims to establish models for preclinical trials in immunology and vaccinology that can be used in industry and public research. This technological expertise, involving four of the department's units*, now offers *in vivo* research models for the study of human immune responses in mice.

11 research units

1 laboratory

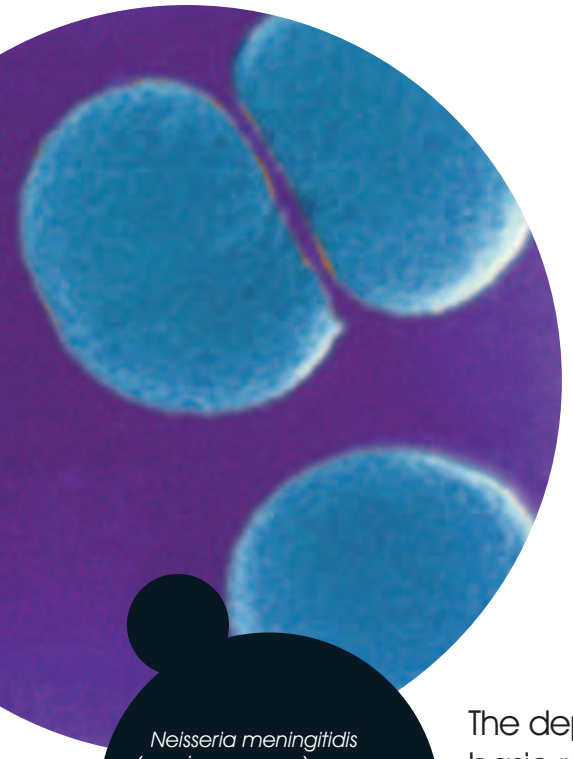
1 technological platform

The Center for Human Immunology

Matthew Albert,
Head of the CIH

The Center for Human Immunology (CIH) was set up to develop "translational" research projects, enabling concepts developed in experimental models to be applied to clinical situations. It also enables researchers to develop experimental models to answer questions raised by human pathologies. *"The CIH is open to researchers and clinicians on and off campus, with the aim being to enable human subject studies; specifically we are interested in supporting research that will improve human health through a better understanding of human physiology and disease pathogenesis,"* comments Matthew Albert, head of the CIH.

** Cytokines and Lymphoid Development Unit, Lymphocyte Population Biology Unit, Molecular and Cellular Allergology Unit, and the former Antiviral Cell Immunology Unit.*



Neisseria meningitidis (meningococcus), capable of triggering infections such as septicemia and cerebrospinal meningitis, especially in young children. Colored image.

Infection and Epidemiology

●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

The department is conducting basic research on infectious diseases, while particularly concerned with public health issues. This commitment is demonstrated by the centers of expertise hosted in units of the department and its constant resolve to stay grounded in clinical reality.

This multidisciplinary department uses immunology, epidemiology, bacteriology and virology for its research into infectious diseases: reservoirs, transmission modes and the virulence factors of pathogens, physiopathological processes in the host, the innate immune response and the role of vaccines. With its units specializing in epidemiological risks, the nine National Reference Centers and three WHO Collaborating Centers that it hosts, the Medical Center and the Vaccine and Biomedical Research Center, the department plays an active role in public health. It conducts a number of clinical and epidemiological studies with clinicians from partner hospitals so that its research can be successfully applied in humans. The Laboratory for Urgent Response to Biological Threats (CIBU) attached to the department provides an emergency response to potential epidemics. In the case of the influenza A virus, teams have been actively working since April 2009 to characterize and identify the first strains of the virus, in cooperation with the Influenza National Reference Center (Northern-France) and the Genotyping of Pathogens Platform.

● ANTIBIOTICS ARE NO LONGER AUTOMATIC!

As part of the nationwide plan "To preserve the efficacy of antibiotics", launched by the French Ministry of Health, the "Antibiotics are not automatic" campaign conducted by the Health Insurance Fund from 2002 to 2007 aimed to reduce the use of antibiotics in France by 25% over five years. It particularly targeted respiratory viral infections in young children, in whom over 50% of antibiotic prescriptions were considered unnecessary.

The impact of the nationwide campaign was analyzed by the Pharmacoepidemiology of Infectious Diseases Unit. This work was based on individual, computerized and anonymous patient data from health expenses refunds made by health insurance funds. In total, over the 2002-2007 period, more than 450 million individual antibiotic prescriptions were analyzed by the researchers. They observed a 26.5% fall in antibiotic use during winter, this figure increasing to 30.1% in children under 6, and above all a decrease of over 40% in the link between flu-like diseases and the prescription of antibiotics.

While France has previously been identified as being among the countries with the highest rate of bacterial resistance to antibiotics, these extremely promising results underline the huge efforts of the French scientific community and health authorities to combat one of the major infectious phenomena to emerge over the last 10 years, and demonstrate the importance of epidemiology.

"Our attention is particularly focused on the host-pathogen interaction. By considering the host as a whole, bearing in mind the clinical reality and using experimental models and clinical or environmental strains rather than collection strains to study the complex biology of pathogens and their interactions with the host, our teams are applying the principles of multidisciplinary, translational research (from patient to laboratory and from laboratory to patient)."

Françoise Dromer,
Head of the Infection and Epidemiology Department

● EFFECTIVE VACCINE COVERAGE AGAINST WHOOPING COUGH

By comparing bacteria circulating in different regions of the world that have undertaken mass child vaccination campaigns against whooping cough, in 2008 the team from the Molecular Prevention and Therapy of Human Diseases Unit demonstrated that the whooping cough vaccine enabled strains similar to those contained in the first-generation vaccine composed of whole bacteria to be controlled, but that other strains, just as virulent, were still in circulation.
The researchers also put forward the theory that the use of a new vaccine that specifically targeted the virulence of *Bordetella pertussis*, the bacteria responsible for the disease, could enable all virulent strains to be brought under control. In 2009, a genetic analysis of isolates collected in France enabled the scientists to confirm their theory. In 2007, for the first time, *Bordetella pertussis* strains no longer expressing some of the bacteria's virulence factors emerged.
These observations support the French policy of vaccination against whooping cough pursued since 1960, with a new vaccine that specifically targets bacterial virulence factors being introduced for children and adolescents in 1998 and for adults in 2004. High vaccine coverage will undoubtedly be able to bring whooping cough under control more quickly.

● THE MAJOR CELL MANEUVERS OF *NEISSERIA MENINGITIDIS*

Each year, between 700 and 800 cases of invasive meningococcal infections (meningitis and septicemia) are recorded in France. These often fatal infections are caused by the bacteria *Neisseria meningitidis*. It is believed that 10 to 25% of the population (source: WHO) are carriers of *N. meningitidis* which naturally resides in the human pharynx without inducing any symptoms in the host.
A study conducted by the Invasive Bacterial Infections provisional unit shed light on the mechanism responsible for this double life of the bacteria, which can be either commensal – when the host and the bacteria co-exist asymptomatically – or invasive – when the bacteria cause disease. The presence of bacteria in the pharynx is detected by the host cell. In the case of virulent strains, detection triggers the cell signal that results in programmed cell death, or apoptosis. Non-virulent strains divert the signal, however, thereby protecting their ecological niche (the human pharynx) from apoptosis.
This work, first conducted on laboratory strains, was then validated on clinical isolates from patients, so as to maintain a link with real clinical concerns. The scientists are currently seeking to elucidate the signaling pathways involved, both in the bacteria and in the host.

13 units
1 five-year group
1 platform

Escherichia coli (enterobacteria) undergoing division.

Microbiology

●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

Bacteria are the cause of a vast number of infectious diseases and have always been important research models at the Institut Pasteur. The Microbiology Department and its various entities are continuing this tradition.

Scientists in the Microbiology Department study various microorganisms (bacteria and Archaea) and their viruses as model systems for fundamental research in genomics, genetics and metabolism, etc. Our scientists also focus on the mechanisms that enable some of these microorganisms to be virulent and to escape the host immune system and/or to develop resistance against antibiotics. This work can improve our understanding of how pathogens live and interact with the environment. Understanding the molecular mechanisms of virulence is essential for the development of new tools for diagnosis and new therapies (antibiotics and vaccines) to treat bacterial infections.

● A NEW IRON UPTAKE MECHANISM IN BACTERIA

Microbes that colonize vertebrates are provided with 80% of their iron requirements through hemoglobin. This iron is found in the heme contained in hemoglobin and is recovered by highly effective bacterial systems. The transfer generally occurs in several successive stages, including red blood cell lysis, heme extraction from hemoglobin, heme transport through the cell envelope, and its degradation in the bacterial cytoplasm to release the iron.

The Bacterial Membranes Unit has discovered and characterized a new heme uptake mechanism. This mechanism is based on the secretion of small proteins, hemophores, which are able to effectively acquire heme from the hemoglobin and transfer it to receptors located on the bacterial surface. The three-dimensional structure of this hemophore/heme/receptor complex has been determined, making it possible to view the molecular collision between the hemophore and the receptor which causes the heme to be transferred to the receptor.

The team has also identified new proteins in the cell envelope that are able to directly extract the iron from the heme without absorbing or destroying it.

This mechanism, initially described in *Escherichia coli,* was also characterized at the cell surface of Gram-positive species. As heme acquisition systems are essential for the virulence of these pathogens, this system could emerge as a potential new target for antibacterial molecules.

9 research units

2 provisional units

1 five-year group

4 collections of microorganisms

5 National Reference Centers

1 WHO Collaborating Center

● THE BACTERIAL CAPSULE, A SWISS KNIFE OF VIRULENCE

Bacillus anthracis is the bacterium responsible for anthrax. To escape the control of the infected host, it produces two toxins that paralyze the immune system and a capsule that covers the entire bacterial surface and protects it against the host's defenses.

The work of the Toxins and Bacterial Pathogenesis Unit has demonstrated a new function of this capsule. This structure enables *B. anthracis* to interact specifically with the surface of blood vessels, particularly in the liver. By adhering to the vascular endothelium, the bacterium enters certain target organs, where it multiplies by forming microcolonies. The toxins are secreted in this microenvironment where they can exert their toxic activity.

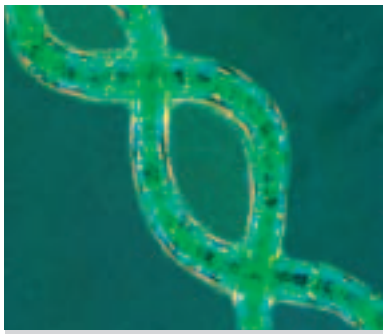
This observation sheds light on the interactions between *B. anthracis* and its host. Continued research in this area will help us understand the mechanisms by which *B. anthracis* spreads in the infected host, and to develop targeted therapeutic strategies to prevent the dysfunction of the target organs.

● BACTERIAL CILIA INVOLVED IN BIOFILM FORMATION

Streptococcus agalactiae is the main cause of infection (pneumonia, septicemia, and meningitis) in newborn babies. This pathogen possesses filamentous structures, designated pili, on its surface which in other bacteria like *Escherichia coli* are involved in various processes including adhesion, conjugation, and the secretion of bacterial effectors.

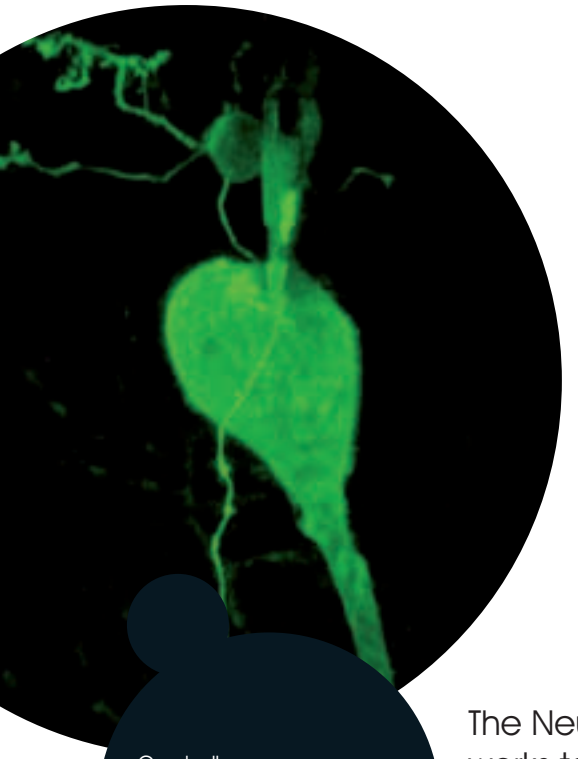
The Biology of Gram-positive Pathogens Unit has demonstrated the importance of the pilus in biofilm formation and in the adhesion of *S. agalactiae* to pulmonary epithelial cells. In this organ, the bacteria are permanently subjected to the mucus flows generated by specialized lung cells to clear the bacteria. The pilus serves as an anchor for these bacteria, offering optimum exposure for the adhesin, the protein of the pilus responsible for bacterial attachment to the lung cells. The study revealed that in the absence of the pilus, the adhesin – normally located at the tip of the bacteria – remains stuck on the bacterial surface, where it is masked by the bacterial capsule. This masking of adhesin means that the bacteria loses all efficient means of anchorage to the lung epithelium.

In the search for new strategies to combat this pathogen, pili seem to represent a prime vaccine target, due to both their ability to induce an immune response and their highly exposed location.



Cyanobacteria

The Cyanobacteria Collection houses the Pasteur Culture Collection of Cyanobacteria (PCC) and carries out various service activities (acquisition and preservation of these microorganisms, distribution of strains, and advice). This biological resource is also used for research programs relating to the biodiversity of cyanobacteria and the diversity of the secondary metabolites, particularly cyanotoxins, produced by these microorganisms.



Cerebellum neurons marked with a fluorescent molecule for optical recording of electrical signals.

Neuroscience

●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

The Neuroscience Department works to describe the mechanisms of the nervous system from molecules, cells, synapses to neuronal circuits. This fundamental research frequently leads to significant therapeutic breakthroughs.

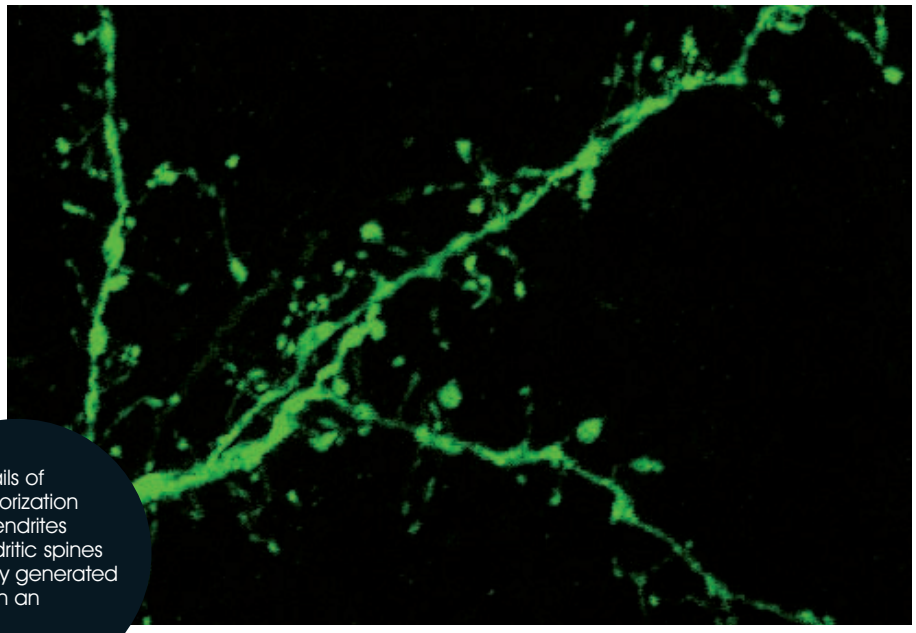
Several of the department teams specified their research interests through previous genetic studies of poorly understood human pathologies, such as deafness, autism and addictions. Molecules identified in these studies provide the entry point to deciphering the molecular assemblies that ensure the complex functions of neurons or sensory cells, and the re-organization of these assemblies over time that ensure nervous system plasticity and adaptation to the environment. The focal point of the department teams is the understanding of adaptability, whether that of the form of chemical receptors, of cell skeleton, of synapses, of neural networks, of newly formed neurons, or of a child's behavior in the environment.

● ADAPTATION IN IMAGES

The brain contains billions of neurons which communicate with each other by means of specialized contacts known as synapses. Synaptic dysfunctions are responsible for many neurological disorders, such as memory disorders experienced by Alzheimer's disease patients. The properties of synapses, and in particular their ability to modulate the strength of communications with other neurons in a network, are essential for learning and memory. These phenomena are traditionally explored using electrophysiological methods.

A new team set up this year, the Dynamic Neuronal Imaging Unit, has taken on the ambitious task of developing and applying optical tools to recording neuron activity in the brain, in particular synaptic behavior in the neuronal compartments that cannot be explored using other methods. Analyzing synaptic transmission using these new observation methods removes a number of spatio-temporal obstacles and enables scientists to view and manipulate synaptic activity as close as possible to the synapse itself.

The researchers hope to be able to identify new cell mechanisms involved in information transfer and to gain a better understanding of the ability of neurons to incorporate these mechanisms.



Details of the arborization of the dendrites and dendritic spines of a newly generated neuron in an adult.

THE BENEFITS OF YOUTH!

Contrary to the widespread theory that once a neuron has been lost it will never be replaced, the Perception and Memory team has demonstrated that the adult brain is capable of producing new nerve cells throughout its life. In 2009, the same neurobiologists identified an unexpected property of these new neurons – during the first 12 weeks of their life, a crucial period for their integration in nerve circuits, these young cells are particularly reactive to stimulation and exhibit high learning capacities. This hypersensitivity is subsequently lost, and neurons end up with similar properties to those of other cells. Moreover, two weeks after they are formed, only 50% of these cells have successfully integrated neuronal circuits, an essential condition for their survival.

Consequently, it appears that only some new neurons – perhaps the most active ones – succeed in establishing new connections; the others are eliminated to ensure the constant, progressive renewal of neurons in the olfactory bulb.

This discovery, if proven for other brain structures, would shed light on the difficulties currently encountered in cell transplantation trials for neurodegenerative diseases. If new neurons only demonstrate significant properties for a few weeks, attempts at recovering certain brain functions through cell transplantation have limited chances of success. These results suggest that it would be better to look towards approaches based on the stimulation of natural brain capacities to continuously produce new neurons.

A POSSIBLE TREATMENT FOR NEURODEGENERATIVE DISEASES IN CHILDREN

Although neurodegenerative diseases most often affect the elderly, they do exist in children, where they are usually caused by a genetic metabolic disorder. Sanfilippo syndrome is one of the most dramatic; this condition causes progressive mental retardation in a few years, with no possibility of remission.

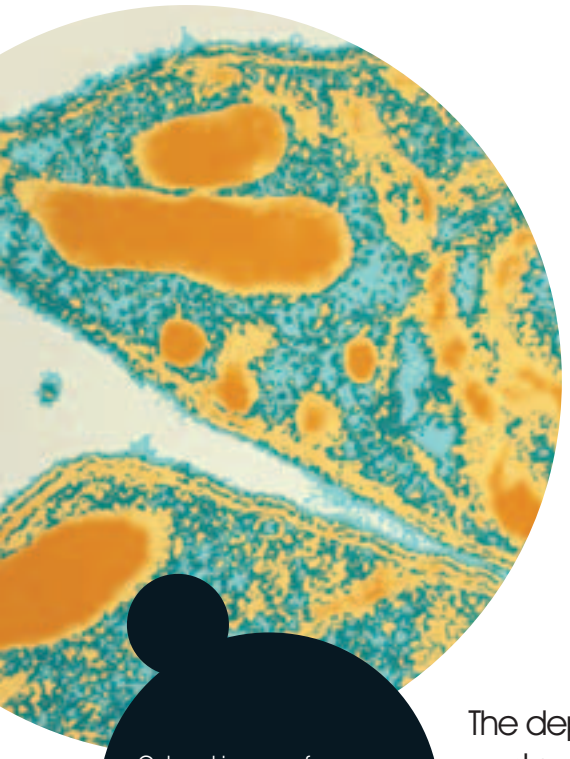
Researchers from the Retrovirus and Genetic Transfer Unit have demonstrated that it is possible to halt the degenerative process using gene therapy. An intracerebral injection of suitable viral vectors can correct the genetic deficit that causes the disease. The efficacy and safety of this treatment, applied to around 30 dogs presenting the same pathology as the affected children, have been proven. This program was supported by the French Muscular Dystrophy Association (AFM).

Following the encouraging results obtained in affected animals, efforts now focus on clinical trials in humans. Given the complex regulatory context surrounding the preparation of gene therapy trials, this study is being set up with the expert help of the Clinical Research Center, which has many years' experience in the area of infectious diseases. The conclusions of this clinical trial will be known only after children enrolled in tolerance trials and followed up in efficacy trials have been monitored for several years. These clinical studies will indicate to what extent this treatment halts the degenerative process or even thwarts the disease before the first symptoms appear.

4 units

1 provisional unit

2 five-year groups



Colored image of *Plasmodium falciparum*, the agent responsible for severe forms of malaria (magnification x 75,000).

Parasitology and Mycology

●●● **FOCUS** ON 4 SIGNIFICANT HIGHLIGHTS

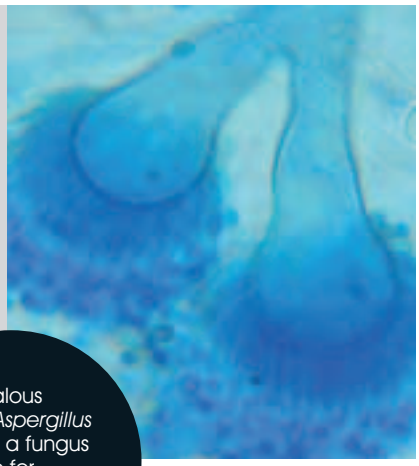
The department studies the biology and survival strategies of parasites and fungi and investigates the biology of the mosquito vector. This research is at the heart of global public health challenges and addresses the needs for better prevention, control and treatment of parasitic and fungal diseases.

The department is conducting research into three key eukaryotic parasites responsible for diseases of major burden in developing countries, in both health and economic terms: *Plasmodium* spp, which cause malaria; *Leishmania* spp, the leishmaniasis agents; and *Trypanosoma brucei,* responsible for sleeping sickness. The *Anopheles* mosquito – the *Plasmodium* vector – is also studied. Mycology research focuses on *Aspergillus fumigatus*, responsible for mycoses which can be fatal in immunosuppressed patients, and *Cryptococcus neoformans*, which causes severe respiratory infections.
The department's work combines fundamental research on *in vitro* and *in vivo* models with biomedical research, fieldwork and clinical trials of vaccines. New experimental models and tools are developed to dissect the dynamic interactions between microorganisms and their host, to identify the fundamental bases of parasitism and transmission by vectors, to reveal the mechanisms by which fungi invade the host, and to determine the virulence factors, pathology and survival strategies of these organisms. Biomedical research includes vaccine development and drug discovery.

● A PROTECTIVE SHIELD FOR THE IMMUNE SYSTEM

Aspergillus fumigatus is a fungus responsible for severe respiratory pathologies, among which invasive aspergilloses, which often prove fatal in immunosuppressed patients. Its spores are present in the atmosphere and are constantly inhaled by humans, where they enter the lungs.
Researchers from the *Aspergillus* Unit looked into how aspergillosis is introduced into the lungs and the interactions between *Aspergillus* and the host, particularly investigating why the *Aspergillus* spores, which are akin to bombs filled with antigens and allergens, do not trigger an immediate innate immune response. This research unit demonstrated that the RodAp amyloid hydrophobin layer – present on the surface of the conidia in an organized structure known as "rodlets" – is responsible for this lack of immune recognition. Tests conducted *in vitro* on human dendritic cells and *in vivo* in mice show that, unlike dormant spores, spores lacking in RodA – either as a result of mutation or by means of chemical treatment – or spores germinated and naturally lacking in RodA, trigger a strong immune response. This confirms the role of this protein in the lack of an immediate response from the host.
As well as improving our understanding of the virulence mechanisms of *A. fumigatus* in humans, this work opens up interesting pharmacological possibilities: in therapeutic treatments, the RodA protein could be used to encapsulate drugs and prevent a negative response to these therapeutic molecules from the immune system.

The Pasteur Infectious Diseases Carnot institute is supporting two projects with potential industrial applications, on which teams from the Parasitology and Mycology Department are working together with teams from the Institut Pasteur campus and from the Institut Pasteur International Network. The project called "Optimization of antimalarial compounds: a rational approach aimed at several new-generation parasite targets" is co-ordinated by Jean-Christophe Barale from the Parasite Molecular Immunology Unit. The second project, "Identification of new drug combinations to treat systemic fungal infections" involves the *Aspergillus* Unit directed by Jean-Paul Latgé.



Bicephalous head of *Aspergillus fumigatus,* a fungus responsible for severe respiratory pathologies.

● THE INVASION MECHANISM OF APICOMPLEXA REVEALED

Apicomplexa are parasites capable of penetrating their host cell in a matter of seconds. *Plasmodium*, the malaria agent, and *Toxoplasma*, which infects more than a third of the world's population, are major examples. Collaborative work carried out by the Institut Cochin and the Institut Pasteur's Malaria Biology and Genetics Unit has demonstrated that these parasites that have their own mobility system, also need the help of the host cell to penetrate the cell.
The parasite causes de *novo* polymerization of the host cell actin, which stabilizes the parasite-cell junction used by the parasite as an anchor to propel itself into the cell. Teams are currently seeking to identify the cell regulation pathways used by Apicomplexa during cell penetration.

● RESISTANCE OF *ANOPHELES* TO *PLASMODIUM*

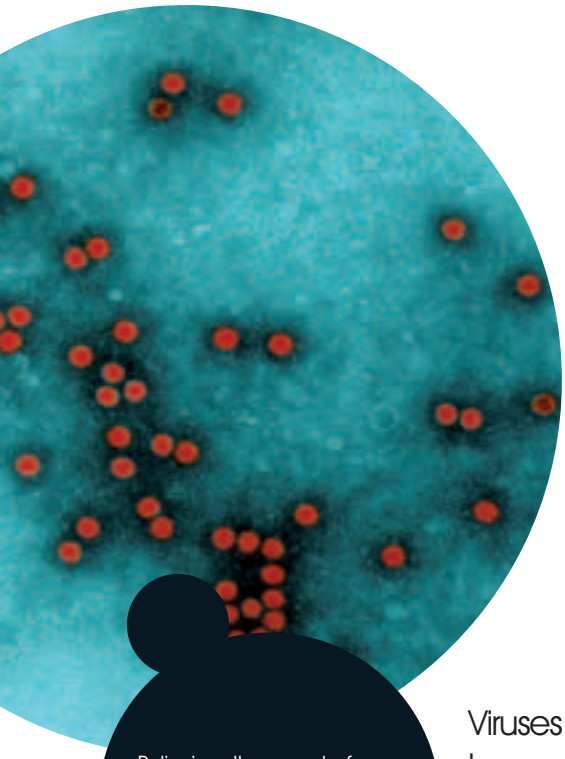
The *Anopheles gambiae* mosquito is the main vector of *Plasmodium falciparum,* responsible for severe forms of malaria which cause around 1 million deaths each year. In natural populations of *An. gambiae,* a significant number of individuals are resistant to the parasite and therefore do not transmit it to humans. Collaborative work carried out by the Genetics and Genomics of Insect Vectors Unit, the CEPIA* platform and an IRD team (Institute for Research and Development) in Cameroon has confirmed the essential role of the APL1A gene in mosquito resistance to the human parasite, and the role of APL1C, a related gene in resistance to rodent parasites. This study identified the first gene involved in the specific resistance of *Anopheles* to the human parasite and revealed the specific adjustment in the mosquito's response depending on whether it is facing parasites infecting humans or those infecting rodents.

● A NEW UNIT TO HELP FIGHT AGAINST SLEEPING SICKNESS

Trypanosoma brucei is the parasite responsible for sleeping sickness, a disease for which no vaccine is currently available. Trypanosomes are also prime model organisms for research into cilia and flagella. In this context, the Trypanosome Cell Biology Unit is developing two areas of research.
The first involves studying the Trypanosoma cycle and the dynamics of infection, particularly during the first three weeks of contamination, when the parasite cannot be detected in humans. The second focuses on in-depth research into their flagella. Some human cells themselves have flagella or cilia with a highly conserved structure and molecular composition in eukaryotes. The researchers therefore decided to use *T. brucei* as a research model for the suspected genes in genetic diseases (such as polycystic kidney disease affecting almost one person for every thousand) linked to a defect in the workings or structure of these complex systems.
In 2009, this work enabled the Trypanosome Cell Biology provisional unit to become a permanent research unit in the Institut Pasteur.

8 units
1 five-year group
1 technological platform

** Institut Pasteur Center for the Production and Infection of Anopheles.*



Poliovirus, the agent of poliomyelitis, of which humans are the only natural host (magnification x 160,000). Colored image.

Virology

●●● **FOCUS** ON 3 SIGNIFICANT HIGHLIGHTS

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

The department's work focuses on research into viruses: their molecular organization, interactions with their host, and pathogenicity determinants. The viruses studied include those that cause cancers such as papillomaviruses or the hepatitis B and C viruses; retroviruses such as HIV and HTLV; enteroviruses; arboviruses, transmitted by insects and responsible for severe diseases such as dengue ("tropical flu"), yellow fever and Rift Valley fever; hemorrhagic fever viruses such as arenaviruses; and respiratory viruses.

To improve their understanding of the infection mechanisms of these viruses and their modes of propagation in an organism, virologists are developing a number of partnerships within the Institut Pasteur and with the Institut Pasteur International Network. The department houses 4 of the 21 National Reference Centers and plays a major role in the epidemiological monitoring of infectious diseases. The Influenza National Reference Center (Northern-France), which conducted the first rapid detection test for the A(H1N1) virus in France, played a central role in the national strategy to prevent and combat this pandemic. (See "Significant highlights" p. 13).

● THE POLIOMYELITIS VACCINE CORRUPTED BY AN INOFFENSIVE VIRUS

The poliomyelitis vaccine, administered during large-scale vaccination campaigns organized by the World Health Organization since 1988, has virtually eradicated the wild viruses responsible for this disease, reducing by almost 99% the number of cases of poliomyelitis worldwide (source: WHO). However, recent poliomyelitis epidemics caused by the circulation of virulent strains derived from the vaccine have been reported in countries where vaccine coverage was lower.

Teams from the Biology of Enteric Viruses Unit, working together with teams from the Medical Virology Unit of the Institut Pasteur in Madagascar, have demonstrated that these new virulent strains came from the genetic recombination of the attenuated virus in the poliomyelitis vaccine with certain phylogenetically related enteroviruses, the Coxsackie A viruses. Analysis of field samples confirmed the frequent presence of these viruses in children, and therefore their circulation. In addition to the mutations caused, this recombination of the vaccine poliovirus with a Coxsackie virus, a virus which in theory has little or no pathogenicity for humans, is turning the recombinant virus into a virulent pathogen.

As well as highlighting the importance of pursuing sustained vaccination policies in all world regions, this research demonstrates the numerous genetic exchanges that exist between viruses circulating in the same environment. This example of emerging viral coevolution should be taken into consideration to prevent future poliomyelitis epidemics.

Marco Vignuzzi, Head of the Viral Populations and Pathogenesis five-year group, and Carla Saleh, Head of the Viruses and RNA Interference five-year group, saw their research projects recognized in the "Starting Grants" category of the European Research Council's "Ideas" program, part of the 7th Research and Development Framework Program. The aim of this program is to fund "frontier research", and it selects projects based solely on scientific excellence. Two grants, to be paid over a five-year period, have been allocated to the "RNA virus population diversity, virulence, attenuation and vaccine development" project led by Marco Vignuzzi and the "RNAi-mediated viral immunity in insects" project led by Carla Saleh.

Carla Saleh and Marco Vignuzzi, Heads of five-year groups

A KEY STRUCTURE OF THE BRONCHIOLITIS VIRUS CLARIFIED

Respiratory syncytial virus (RSV) is responsible for over 70% of winter bronchiolitis cases in young children. Despite the efforts of the scientific community over the last 50 years, there is no vaccine for this virus, and the available treatments are relatively ineffective. RSV stores its genetic material on a single-stranded RNA molecule enveloped by a protein, the nucleoprotein. When the virus penetrates the lung cells, the role of the nucleoprotein is both to protect the viral RNA from the host's immune defenses during its journey inside the cell, and to participate in its proliferation by presenting the RNA to the viral enzyme, which copies it.

To study how the nucleoprotein works, researchers crystallized it and used X-ray diffraction to reconstruct a detailed, high-resolution image of its three-dimensional structure. The nucleoprotein is composed of two domains which close around the RNA like claws. The scientists put forward the theory that during viral replication, the claws open on contact with the polymerase, allowing it to read the genetic information of the RNA sequence. The viral RNA remains protected within the nucleocapsid. The detailed image of this 3D structure, for which a patent application has been filed, should enable the development of effective therapeutic agents through the creation of "tailor-made" molecules capable of blocking the opening of the nucleoprotein and therefore inhibiting viral replication.

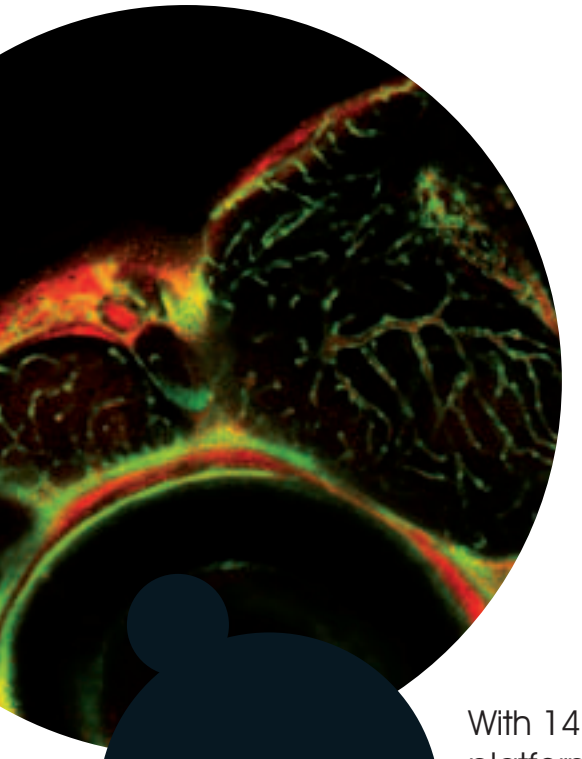
WHEN THE RABIES VIRUS TAKES UP RESIDENCE IN THE NEURONS

When the rabies virus infects a neuron, it stores its proteins and genetic material in the form of large spherical aggregates known as Negri bodies. The Negri bodies are formed in a zone close to the nucleus where all the cellular machinery needed for the multiplication and assembly of the virus is accumulated. The virus sets up a "virus factory", turning to its own advantage the resources and mechanisms of the neuron that it infects.

Researchers from the Viral Neuro-Immunology Unit have recently demonstrated the sequestration of one of the neuron proteins, the TLR3 protein, within Negri bodies, and have shown that this protein is essential for the formation of Negri bodies.

In a neuron, the TLR3 protein appears to have two functions; it is responsible for cell defense against viral infection and for restricting the growth of axons. It therefore seems possible that the sequestration of TLR3 in Negri bodies may not only promote multiplication of the rabies virus by allowing it to form Negri bodies, but that it may also help keep the infected neuron alive, firstly by shielding it from the defense mechanisms implemented by the cell, and secondly by promoting axonal regeneration.

15 units
2 provisional units
2 five-year groups
3 laboratories



Zebrafish embryo (LM).

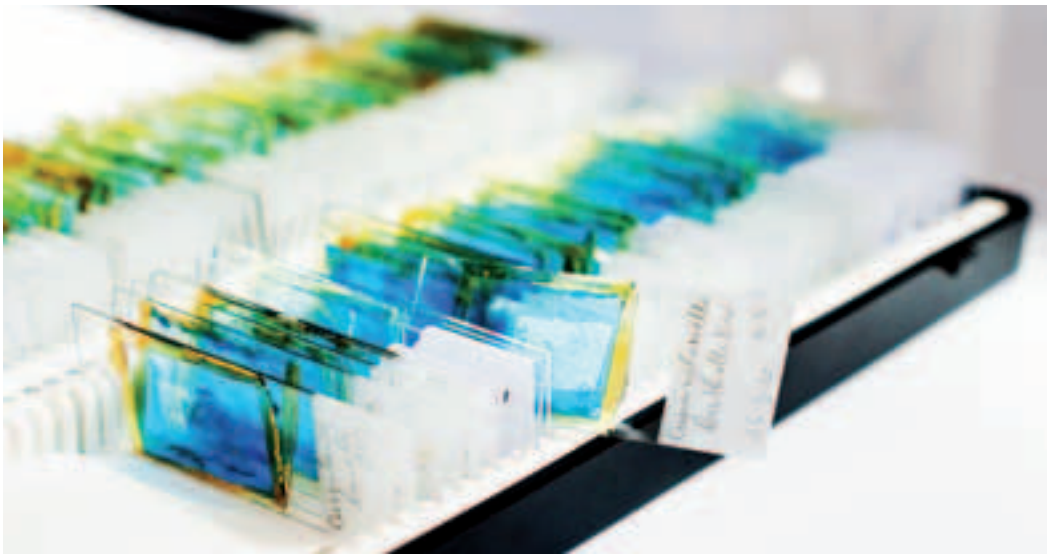
Technological Platforms

With 14 technological platforms, a Center for the Production and Infection of Anopheles, a Software and Databases Group and microorganism collections in the Biology Resource Center, the Institut Pasteur is constantly investing in the state-of-the-art equipment required for research projects, particularly in the area of infectious diseases.

INSTITUT PASTEUR GENOPOLE

The rapid development of new molecular and genome analysis technologies has transformed biomedical research. The ten technological platforms of the Institut Pasteur Genopole provide access to these technologies and to the expertise required for their application, from genome sequencing to research into how genomes function and the physicochemical characterization of the resulting proteins. Eighty researchers, engineers and technicians with wide-ranging skills are involved in fundamental research and public health projects, and co-authored more than 65 publications in 2009. The Genopole's platforms, organized into two clusters – Physicochemistry of Macromolecules and Genomics – were awarded the GIS-IBiSA label in 2008 and 2009 respectively.

New sequencing techniques, a thousand times faster than previous ones, have revolutionized the analysis of genetic information. They allow the sequencing of hundreds of genomes and characterization of polymorphisms on a very large scale. Targeted analysis of candidate genes and research on polymorphism at the complete genome level have led to the discovery of genes predisposing to various diseases in humans or model organisms. Large-scale transcriptional analysis combining sequencing and DNA microarrays has improved our understanding of the physiology of microorganisms and the host response to infection. These methods are also applied to more fundamental issues such as the identification of small regulatory RNAs and research into embryo development, and enable scientists to study epigenetic processes at genome level in normal or pathological conditions.



Eighty of the Genopole's researchers, engineers and technicians with wide-ranging skills are involved in fundamental research and public health projects, and co-authored more than 65 publications in 2009.

The Genopole offers a full range of technologies for the analysis of macromolecules, from the production of recombinant proteins in prokaryotic or eukaryotic cells to their characterization using physicochemical methods. Various proteomic and analytical biochemistry techniques are used to address a wide range of questions related to post-translational modifications of proteins, cell regulations, intracellular trafficking and the organization of macromolecular complexes. Fully automated crystallogenesis of biological macromolecules has contributed to the development of structural biology at the Institut Pasteur. The energetics and dynamics of biological macromolecules, their assembly into complexes, and interaction with ligands can be studied using 15 biophysics instruments.

The Genome Analysis and Integration team uses IT methods to analyze and manage the genomic and post-genomic data produced by high-throughput approaches so as to facilitate their analysis using multiple algorithms. The application of new-generation sequencing requires developments in terms of IT, which have been carried out in close cooperation with the research teams on the campus.

With the financial backing of the Greater Paris region, the Genopole is coordinating a proteomic study on parasitic diseases and a network aiming to apply new-generation sequencing in clinical microbiology.

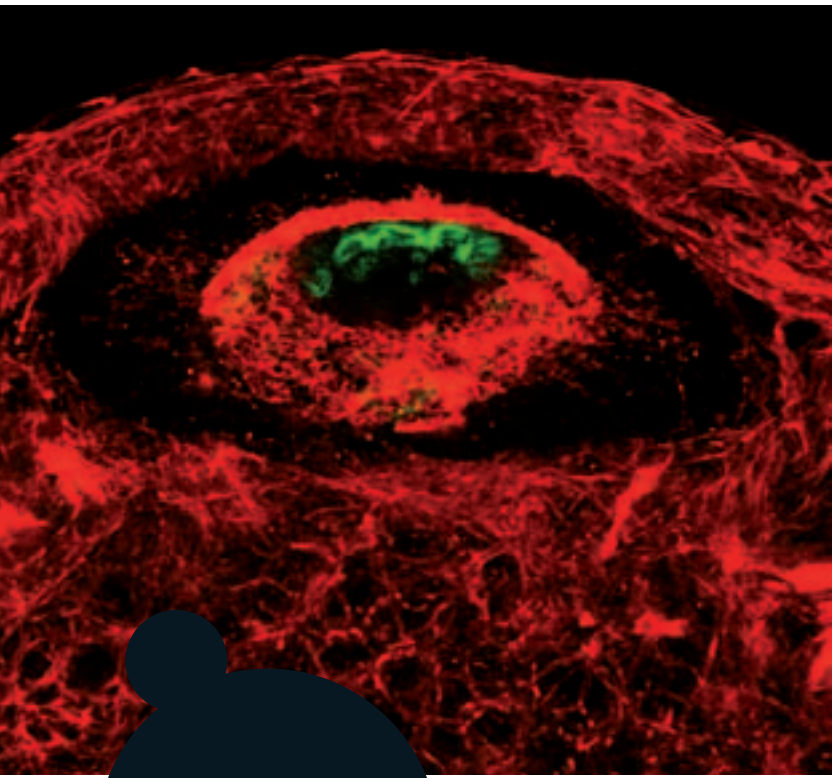
● THE IMAGOPOLE

The Imagopole, or Molecular and Functional Dynamics Center, features four "technological platforms": Dynamic Imaging, Ultrastructural Microscopy, Flow Cytometry and more recently the Center for Human Immunology. With its 35 engineers and 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 researchers with:

– access to advanced technologies and expertise;
– an original contribution in terms of technological development for given research projects;
– officially accredited BSL2- and BSL3-level "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 9001:2009 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.



Surface of a mouse ovocyte (LM).

ISO 9001:2009 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 currently targeted by the Imagopole's imaging technologies 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, 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 EXAMPLES OF PROJECTS

Development of a correlative microscopy approach

Engineers from the Imagopole are working on the introduction of 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 cryomicroscopy. This new approach will be applied to various areas of study at the Institut Pasteur, such as research into isolated pathogenic bacteria and host-pathogen interactions.

Acquisition of imaging systems for screening

Research into infectious disease processes requires analysis of the dynamics of host-pathogen interactions at both 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 the molecular, functional and structural level. They require quantitative analysis of 2D or 3D high-resolution images, combined with statistically significant sampling. Since 2009, new high-throughput and high-resolution imaging systems for screening adherent and non-adherent cells have been made available to scientists to provide high-resolution quantitative information in a single cell associated with high sampling. These screening systems are also linked to a

14 technological platforms

1 Center for the Production and Infection of Anopheles

1 software and databases group

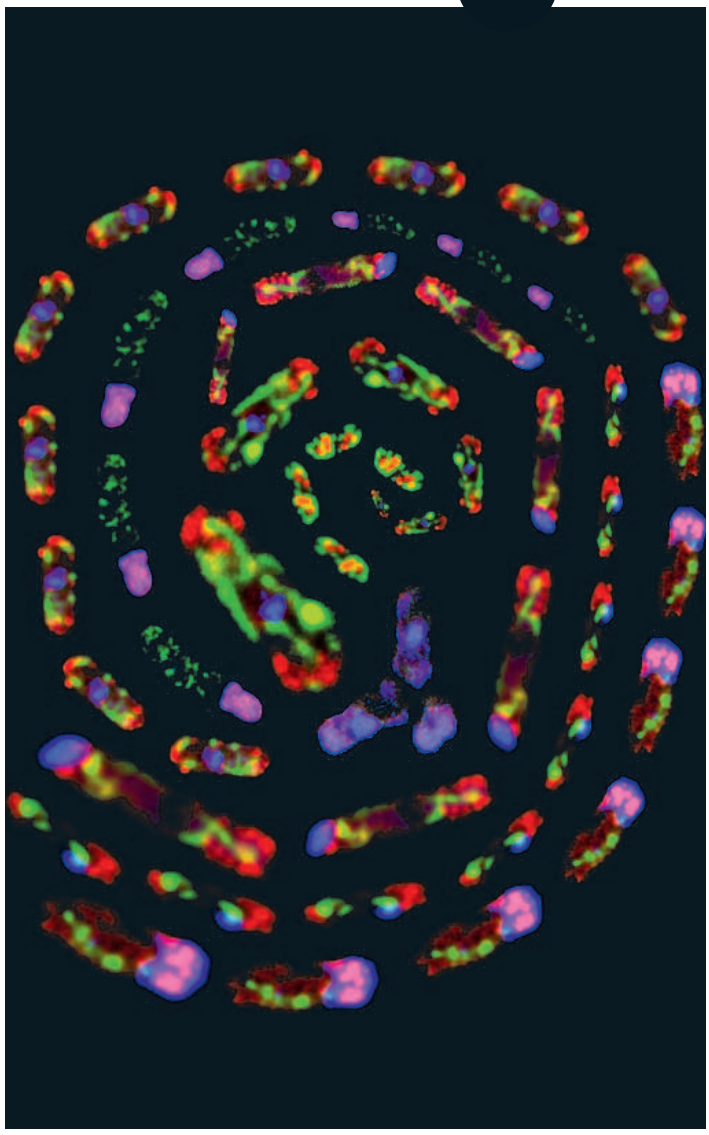
Microorganism collections in the Biology Resource Center

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, which 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 cells and tissues. By using oxygen-sensitive fluorescent sensors, oxygen distribution in cells and tissues will be 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 lifespan of the fluorescent marker.



Schizosaccharomyces pombe yeasts (LM)

2009

public health

The Institut Pasteur is committed to strengthening its clinical research and developing partnerships with hospitals, providing optimum conditions to ensure that academic research finds applications as quickly and easily as possible. With its specialized structures, it plays an essential, recognized role in monitoring and characterizing infectious diseases.

Clinical research and public health

The Institut Pasteur has always sought to turn its discoveries into applications for human health as quickly and effectively as possible.

The influenza A(H1N1) pandemic in April 2009 illustrates the Institut Pasteur's rapid response capability. It was able to develop a diagnostic test in a matter of days and make the test available for the medical community, while the Virology Department simultaneously launched research programs on the subject.
In 2009, the Institut Pasteur (i) pursued research projects in the fields of vaccines and gene therapy, (ii) contributed to the development of ethical research on campus and in the Institut Pasteur International Network, and (iii) strengthened its institutional links with the Paris Public Hospital Network (AP-HP).

WIDE-RANGING AND ETHICAL CLINICAL RESEARCH

In 2009, the Clinical Research Committee, which is placed under the responsibility of the Medical Department, examined the regulatory, legal and ethical compliance of 52 research projects related to human beings or products derived from humans and conducted by Institut Pasteur teams and external partner organizations (35 projects were investigated in 2008). The Institut Pasteur is the legal sponsor of 19 projects. Twenty per cent of the projects submitted come from the Institut Pasteur International Network. This committee has an Institutional Review Board (IRB) which grants approval for researchers; this is essential if they wish to lay claim to certain US funds and is a prerequisite for publication in some international journals.
The Clinical Research Center (PIRC) has continued to support large-scale projects sponsored by the Institut Pasteur:
– the development of vaccine candidates for HIV (F. Tangy), breast cancer (MagTn3: C. Leclerc), anthrax (M. Mock in association with the DGA) and shigellosis (Ph. Sansonetti, L. Mulard);
– a gene therapy project for Sanfilippo disease (J.-M. Heard).
Keen to conduct its research within an ethically sound framework, the Institut Pasteur, with the support of the Ethical Vigilance Committee, has drawn up an Ethics Charter for researchers on campus and in the Institut Pasteur International Network. In connection with this issue, a university qualification entitled "Research on Human Beings and Applied Ethics", coordinated by the research ethics adviser and the PIRC, is now available for Institut Pasteur and external researchers.
With its ranks of healthy and patient volunteers and its biobank activities, the Clinical Investigation and Access to Biological Resources platform (ICAReB) has been able to meet the growing needs of the campus with 26 research teams using the platform (compared with 10 in 2007), participation in 2 Transversal Research Programs, 11,500 samples generated in 2009 (compared with 2,500 in 2007 and 7,500 in 2008), management of the WHO biobank on African trypanosomiasis, etc. This platform has also conducted research on bioresources, with the aim of optimizing the processing and preservation of biological samples.

85,449 vaccinations

15,299 consultations for infectious and tropical diseases and travel medicine

7,908 consultations for allergies

2,249 consultations for rabies

Finally, in 2009 it completed its first series of declarations of human biological sample collections, with all the collections held by twenty Institut Pasteur units being declared to the French Ministry of Research.

INTERACTIONS WITH HOSPITALS THROUGH TWO TASK FORCES

The signing of a framework agreement between the Institut Pasteur and the Paris Public Hospital Network (AP-HP) in August 2009 formalized the already strong links between the Institut Pasteur and the hospital community. This agreement includes provisions on staff mobility (temporary posts, interface contracts and joint research programs).

The Medical Department has set up two task forces in this area, in association with clinicians and Pasteur researchers:

– the PATHODISC program, coordinated since January 2009 by M. Eloit and monitored by a medical committee, on the use of high throughput sequencing and complementary methods to identify pathogens that may be involved in particular pathological situations;

– the Sepsis group, coordinated since October 2009 by J.-M. Cavaillon, which will initially focus on "Genetics and sepsis" and "Viruses and sepsis".

THE MEDICAL CENTER

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

The CMIP's activities extended to pediatrics

A system of specific consultations for child travelers before they set off and upon their return (in particular if they have been expatriated) has been set up. This measure is part of an overall family monitoring strategy.

The certification procedure

The year 2009 has seen progress made in the CMIP's certification procedure thanks to the efforts of working groups involving all categories of CMIP staff. This procedure should come to fruition in 2010 with the certification being obtained. The involvement of the French Authority for Health (HAS) as an observer has been formalized.

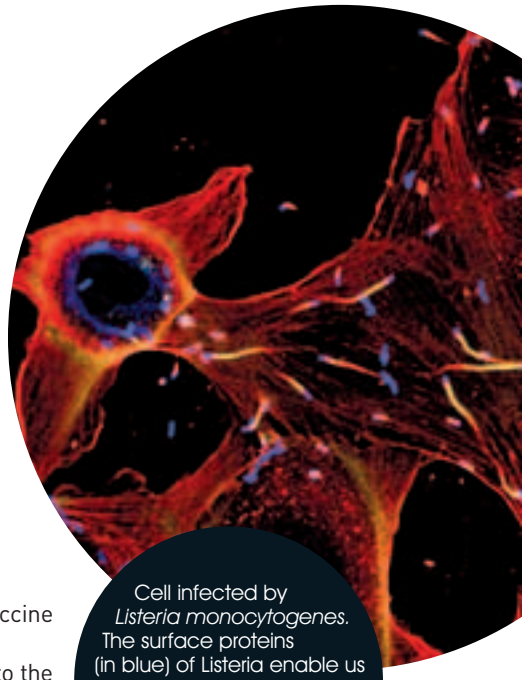
Continuous medical training

Four continuous medical training sessions were run in 2009 coordinated by the CMIP and the infectious diseases department of Necker Hospital, through the Necker-Pasteur Center for Infectious Diseases: "Guidelines for HIV post-exposure", "Guidelines for dealing with fever after returning from a tropical country", "Native parasites: clinical approach, diagnosis and treatment" and "Infections and pregnancy".

Clinical research

The Medical Center continued clinical research work in several areas, including HIV infection (in cooperation with the French National Agency for AIDS research (ANRS)), research into infectious agents in olfactory disorders, and malaria, etc.

National Reference Centers and WHO Collaborating Centers



Cell infected by *Listeria monocytogenes*. The surface proteins (in blue) of Listeria enable us to view the bacteria. Actin, a constituent protein of cells, is shown in red and green.

The National Reference Centers (CNR in French) and World Health Organization Collaborating Centers (WHOCCs) contribute to the Institut Pasteur's public health activities, acting as microbiological observatories for communicable diseases.

Twenty-three Institut Pasteur research units were accredited by the French Ministry of Health for five years (the 2006-2010 term); 21 as National Reference Centers and two as associated laboratories. They are partners of the French General Directorate of Health (DGS) and the French Institute for Public Health Surveillance (InVS).
Seven World Health Organization Collaborating Centers (WHOCCs) play 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 Genotyping of Pathogens and Public Health Platform and the Laboratory for Urgent Response to Biological Threats, to develop tools and conduct research for their given missions.

INFLUENZA VIRUS NATIONAL REFERENCE CENTER (NORTHERN-FRANCE)

This structure contributes to the national and international epidemiological monitoring effort for influenza viruses and monitors circulating influenza viruses, ensuring the suitability of vaccine strains and sensitivity to antiviral drugs.
After a moderate influenza epidemic linked to the A(H3N2) viruses, 2009 was marked by the emergence of the pandemic 2009 A(H1N1) virus at the end of April. In the light of this outbreak, the National Reference Center was in great demand throughout the year, both in an advisory capacity for various national and international authorities, and to conduct virological tests for the north of France as well as for French overseas territories and regions and some foreign countries.
Detection tests were rapidly developed and transferred to the "influenza A" laboratory network set up by the DGS and to the laboratories of the Institut Pasteur International Network. The characterization of the pandemic viruses, both for severe forms and as part of the population monitoring conducted by the network of regional influenza observation groups, enabled the identification of viruses resistant to oseltamivir, mainly in treated immunodeficient patients but also for one non-treated case in the general population.
A virus carrying a hemagglutinin mutation (D222G) that may favor viral multiplication in the lungs was also identified. Sequencing tests conducted in cooperation with the Genotyping of Pathogens and Public Health Platform, together with antigenic characterizations, confirmed the absence of major variations for the viruses circulating in France.

LISTERIA NATIONAL REFERENCE CENTER (AND WHOCC)

Since 2006, an increase in the number of cases of human listeriosis has been recorded. This trend continued in 2009, with over 300 cases reported; the increase has also been observed in other European countries.

The Mycology and Antifungals National Reference Center has contributed to the expertise of the Infectious Diseases Society of America to update the recommendations for treating patients with cryptococcosis.

The importance of monitoring this disease is underscored by the 25-30% mortality rate. The National Reference Center is working together with national and international health authorities in an effort to understand the reasons for this recent increase. In cooperation with the French Food Safety Agency (AFSSA) and French Institute for Public Health Surveillance, the National Reference Center contributed to a report on this subject (http://www.afssa.fr/Documents/ MIC-Ra-ListerioseAliments.pdf).

In this context, the French health authorities requested that the National Reference Center manage alerts on contaminated products in France and third countries, and it was also called on by the Austrian health authorities during an epidemic. It also gave its support for the establishment of monitoring systems in Portugal and Algeria.

The National Reference Center optimized the methods for diagnosing gastroenteritis caused by *Listeria monocytogenes* and improved understanding of this particular clinical form. It also demonstrated the role of *Listeria ivanovii* in cases of human listeriosis, and described a new species, *Listeria rocourtiae*. In cooperation with the Genotyping of Pathogens and Public Health Platform, the National Reference Center completed a strain characterization profile using MLVA (multilocus variable-number tandem repeat analysis). It also conducted a phylogenetic study using multilocus sequence typing (MLST) with strains from the five continents, which will provide researchers with in-depth knowledge of the biodiversity and evolution of the *Listeria monocytogenes* species.

MYCOLOGY AND ANTIFUNGALS NATIONAL REFERENCE CENTER

The National Reference Center has contributed to the expertise of the Infectious Diseases Society of America to update the recommendations for treating patients with cryptococcosis. Cooperation with the French Institute for Public Health Surveillance has also made it possible, for the first time at a country-wide level, to identify a rise in the incidence of mucormycosis in patients suffering from hematological malignancies or insulin-dependent diabetes. This finding should accelerate the taxonomic, physiopathological and therapeutic research on this invasive mycosis – still largely unknown but fatal in over 50% of cases – and on its causative agents.

MENINGOCOCCUS NATIONAL REFERENCE CENTER

In 2009, the National Reference Center alerted the public health authorities of the emergence of a new serogroup C clone exhibiting particular clinical severity. This was one of the main factors that led to a review of the meningococcal vaccine strategy in France. Another contributing factor was the spatio-temporal association between influenza and invasive meningococcal infections.

The National Reference Center analyzed this link and put forward the theory that the viral neuraminidase favors adhesion to the epithelial cells (and therefore colonization) by the meningococcus. In 2009, France's High Council for Public

21 National Reference Centers
2 associated laboratories
7 WHO Collaborating Centers

In 2009, the Meningococcus National Reference Center alerted the public health authorities of the emergence of a new serogroup C clone exhibiting particular clinical severity. This was one of the main factors that led to a review of the meningococcal vaccine strategy in France.

Health (HCSP) therefore recommended that the vaccination against meningococcus be generalized in France for infants aged between 12 and 24 months, with a single dose of meningococcal serogroup C conjugate vaccine. The HCSP also recommended extension of this vaccination in a catch-up campaign for people aged up to 24 years and over using the same single-dose strategy.

HUMAN PAPILLOMAVIRUSES (HPVS) NATIONAL REFERENCE CENTER

The National Reference Center focused its activities on establishing methods for detecting HPV infections and setting up programs to determine HPV distribution before introducing vaccination for HPV 16 and 18, responsible for 70% of cervical cancer cases.

The National Reference Center investigated the genotyping and cell preservation media used by 35 hospital-based and private virology laboratories. It assessed the performance of five commercially-available kits for HPV genotyping commonly used in virology laboratories. The National Reference Center is developing an aid for these laboratories which includes an HPV panel to assess the performance of genotyping methods. It is also working with the WHO to draw up recommendations for the use of molecular biology and serology methods to detect HPV infections.

The National Reference Center undertook a study on the distribution of HPVs in Pap tests showing normal cytology among the general population or among people infected by HIV. Finally, the HPV National Reference Center launched a website for the general public and contributed to the "Planet vaccination" exhibition organized by the French National Institute for Prevention and Health Education.

BUSINESS DEVELOPMENT

research applications

The Institut Pasteur has always strived for excellence in research to enable the development of new solutions for the diagnosis, prevention and treatment of diseases. The Research Applications and Industrial Relations Department (DARRI) contributes to the protection and application of these scientific discoveries to ensure that society can reap the benefits as soon as possible.

ACTIVE LINKS WITH INDUSTRIAL PARTNERS

Enjoying close relations with a range of industrial partners is the best guarantee that the Institut Pasteur's scientific innovations can be transferred to where the medical needs are greatest. This year, the DARRI has worked to follow up and secure the portfolio of 171 industrial contracts, including 71 license agreements. The contracts signed in 2009 particularly concerned 31 research and development or expertise agreements, and 27 biological material agreements.
To ensure the optimization and sustainability of industrial relations, the DARRI is constantly seeking to maintain a network of privileged partners.

In 2009, a new strategic partnership was concluded with Mérieux Alliance, which has recently become the Institut Mérieux. This new agreement aims to develop synergies between the respective talents of the Institut Pasteur and the Institut Mérieux to create the diagnostic tools of the future.

A STRONG INTELLECTUAL PROPERTY STRATEGY

Wide-ranging, high-quality scientific research is a valuable source of innovation which must be protected through patent applications before transfer to an industrial partner. This transfer takes place within the framework of a patent

4,150 active patents, including
535 priority patents
31 R&D or expertise agreements signed in 2009
171 industrial contracts, including
71 license agreements

license agreement. In 2009, 40 new patent applications were filed and 79 patents were granted. Seventy deposits of biological material were also made at the National Collection of Microorganism Cultures (CNCM). As of December 31, 2009, the Institut Pasteur had a portfolio of 535 priority patents and a total of 4,150 active patents. The total number of deposits of biological material with internationally recognized collections in terms of patent deposits was 1,602.
The diversity and complexity of this portfolio mean that it is vital to reassess its performance on a regular basis as further scientific progress is made. An optimization strategy for this portfolio was launched in the second half of 2009 and will continue in 2010.

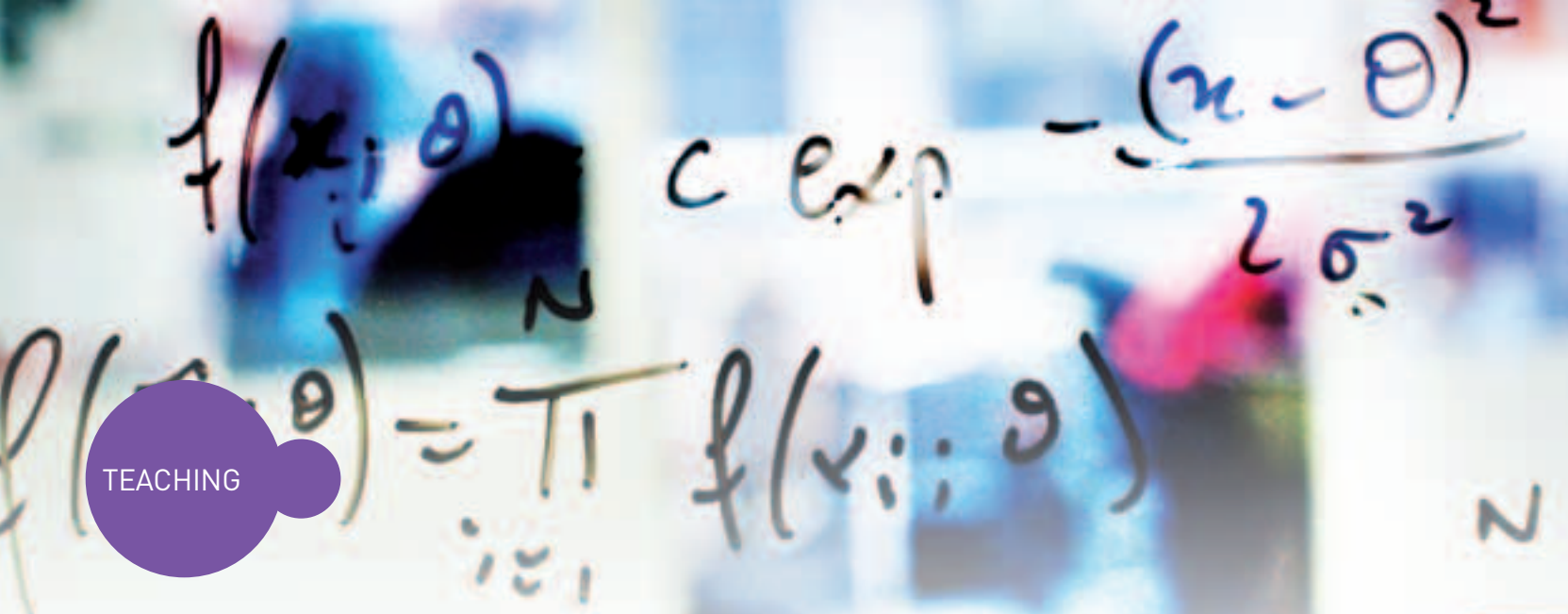
THE CARNOT PROGRAMS AT PASTEUR MI

This year, the Pasteur Infectious Diseases Carnot institute (Pasteur MI) was keen to make a strong commitment to nurture the valuable link between the high scientific quality of a research program and the transfer of research to an industrial partner. This commitment was formalized in 2009 with the issue of a call for tenders, offering 2 million euros in support of ambitious, innovative four-year programs. Pasteur MI will fund the first two years, with the funding for the third and fourth years coming from an industrial partnership. These innovative Carnot programs are based on making those involved in scientific research responsible for the transfer of their research to medical applications. Four Carnot programs began in 2009 in the area of therapeutic innovation applied to viral, fungal and parasitic infections, and to the development of integrated models capable of reconstituting a human immune response.

A number of other Institut Pasteur units are also involved in the Carnot institutes network, particularly the Genetics & Physiology of Hearing Unit, attached to the "Seeing and Hearing" Carnot institute, which brings together the world's leading laboratories specializing in sight and hearing. The activities of this Carnot institute are centered on neuroprotection, sensory rehabilitation, innovative investigation tools and disability management.

FRESH IMPETUS FOR START-UP COMPANIES

Setting up companies has been one of the research application and technology transfer methods most promoted by the Institut Pasteur during the last fifteen years. Despite many fine success stories, the upstream stages of the company start-up process needed to be given fresh impetus. 2009 saw the creation of the Kurma Biofund venture capital fund of 50 million euros, initially dedicated to the Institut Pasteur and the Institut Curie. This fund is unique in that it will enable scientific innovations to be financed within research units, with the aim of reaching proof-of-concept level within a period of three to five years. At the end of this period, the work can be handed over to a start-up company created at the Institut Pasteur or to an industrial partner.



TEACHING

the transfer of values

Ever since the introduction of the "Technical Microbiology" course – the world's first microbiology course – in 1889, teaching has been a priority at the Institut Pasteur. In 2009, 525 students took the courses run on campus. The courses are both theoretical and practical, organized by researchers from the Institut Pasteur and by external scientists from France and other countries.

The year 2009 was particularly marked by the arrival of the first PhD students for the Pasteur-Paris University International Doctoral Program and the oral defense of the first year of students taking the specialized Masters in Public Health. To meet the needs of young biology researchers and healthcare professionals, the Institut Pasteur is constantly updating the courses that it offers. A course entitled "Research on Human Beings and Applied Ethics" was introduced this year.

A DEDICATED ENVIRONMENT AND VARIED COURSES

The new teaching center based at the former Pasteur hospital, which still features its original façades, provides an environment where practical biology courses and theory courses are taught. Twenty-eight courses were run during the 2008-2009 academic year. These courses are divided into three main areas: Epidemiology and Public Health, Mechanisms of Living Organisms and Biology of Microorganisms. They cover a wide range of fields including microbiology, genomics, immunology, vaccinology, neuroscience, epidemiology, cell biology and public health disciplines. They are aimed at students, graduates from French and foreign universities, university teaching hospitals and French *grandes écoles,* as well as working professionals wishing to supplement their training.

A number of these courses can be counted as part of a Masters degree course, either as second year teaching units for the Masters offered at Paris Descartes, Pierre and Marie Curie, Paris Diderot, Paris-Sud 11 and Versailles universities,

28 courses

3 main areas of study:

– Epidemiology and Public Health
– Mechanisms of Living Organisms
– Biology of Microorganisms

or as part of the "Infectious Risk" specialization of the Masters in Public Health run by the Pasteur-CNAM School of Public Health. Outside these university programs, they can lead to the award of a university diploma by the partner universities. Most of the courses can be taken as doctoral school modules by PhD students.

TEACHING FOR STUDENTS FROM ALL OVER THE GLOBE

The Teaching Center welcomes scientists, doctors, pharmacists, engineers and veterinarians from all over the world. In 2009, there were 200 international students out of a total of 525, representing 55 nationalities. Teaching is generally in French, but in this international environment – both in terms of students and lecturers – some courses are taught exclusively in English and others are taught alternately in French and English from one year to the next.

The year 2009 saw the arrival of the first doctoral students for the Pasteur-Paris University International Doctoral Program. This program, which involves agreements with Paris Descartes, Pierre and Marie Curie, and Paris Diderot universities, is open to students who have completed studies at a foreign university. It is a three-year program leading to a PhD. The "Louis Pasteur" class of 2009 includes five students from Germany, Brazil, Italy and Mexico. In 2010, the "Jacques Monod" class will involve six or seven doctoral students.

The specialized Masters in Public Health, recognized by the French *Conférence des Grandes Ecoles,* is run in partnership with the French National Conservatory of Arts and Trades (CNAM) under the aegis of the Pasteur-CNAM School of Public Health.

After several months of theoretical training, the students carry out a six-month internship. In 2009, the first 13 students to take the course completed their oral defense. Some had completed their internships in institutes or centers affiliated to the Institut Pasteur International Network, including the Institut Pasteur in Madagascar, the Institut Pasteur in Dakar, the Institut Pasteur in Guadeloupe, the Pasteur Center in Cameroon, the Center for Health and Medical Research in Niamey, and the National Institute of Hygiene and Epidemiology in Hanoi. This course therefore helps develop partnerships with the institutes in the Institut Pasteur International Network for research projects in the area of infectious risk.

The Institut Pasteur Multimedia Library specializes in microbiology, virology, immunology, molecular biology and biochemistry. Since 1996, it has been associated with the National Library of France as a center for biology and microbiology. It has been a depository for the World Health Organization's publications since 2000.

INTERNATIONAL

the strength of a network

Whether setting up major projects in partnership with public or private international organizations, establishing a presence in numerous countries or promoting the development of regional centers throughout the world, the Institut Pasteur is recognized as the major partner for leading scientific programs.

The Institut Pasteur is developing a number of international partnerships through its relations with the scientific and medical research community.

Several agreements were signed in 2009, including a Memorandum of Understanding with the Centers for Disease Control and Prevention (CDC), two partnership agreements with Mexico and a new bilateral cooperation agreement with the Oswaldo Cruz Foundation (Fiocruz) in Brazil.

A scientific symposium on "The challenges facing biomedical science at the beginning of the 21st century" was jointly organized in late October by Fiocruz and the Institut Pasteur in Rio de Janeiro, to coincide with the Year of France in Brazil.

The Institut Pasteur International Network is a partnership of research and public health institutes spread over all five continents. It was created as a result of Louis Pasteur's determination to combat infectious diseases, and the International Network contributes to this effort with its high-quality international research and public health activities. The institutes in the Network are today mainly independent and strongly rooted in their national contexts. Their sustainability is ensured by the training of local researchers.

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

- major pandemic diseases;
- upstream research for new vaccines and therapies;
- emerging diseases;

80 grants awarded to international students (42 study grants and 38 internship grants)

8 International Network grants (5 PhD grants and 3 conference grants)

10 AmSud-Pasteur grants

9 grants co-funded with the Pierre Ledoux-International Youth Foundation

• health safety;
• monitoring and research for resistance to anti-infection treatments;
• neglected diseases.

For each of these areas, the Institut Pasteur and the Institut Pasteur International Network are recognized as key partners by the Health Ministries in France and abroad, by the World Health Organization (WHO) and the European Union, by private foundations and by the major national and international research and public health organizations (IRD, INSERM, CNRS, CIRAD and InVS).

Some examples of the major partnership projects developed within the Institut Pasteur International Network are as follows:

• a program focusing on bacterial meningitis in Africa and a program on influenza in Asia and Africa are being supported respectively by the French Ministry of Foreign Affairs and the French Ministry of Health;
• the US Department of Health and the Institut Pasteur have signed a cooperation agreement for support, consolidation of expertise and training in connection with influenza monitoring in South East Asia and Africa;
• the French Development Agency is financing the SISEA regional project for the monitoring and investigation of epidemic situations in South East Asia;
• the Total Foundation is funding projects on infant diarrhea in Madagascar and the Central African Republic.

A BSL3 laboratory was inaugurated at the Institut Pasteur in Madagascar in early February 2009. The Institut Pasteur in Korea moved to its new premises which were officially opened on May 8, 2009. Since September 2009, the Tuberculosis and Mycobacteria Unit from the Institut Pasteur in Guadeloupe has been part of the WHO's TB Supranational Reference Laboratory Network (SRLN). The status of the Institut Pasteur in Dakar has changed; it has now become a foundation under Senegalese law. Regional meetings of the International Network for the North Africa-Iran region and the Americas region have been held, providing an opportunity to compile a list of major scientific projects. The first Institut Pasteur International Network scientific report was published in French and English.

With its presence on all five continents, the Institut Pasteur is a strategic ally of the World Health Organization in the area of infectious diseases. In addition to the seven WHO Collaborating Centers (WHOCCs) housed at the Institut Pasteur in Paris and the 11 WHOCCs hosted within the Institut Pasteur International Network, the Institut Pasteur was called on to submit its application for the establishment of a global WHOCC for influenza. The International Network also houses 30 National Reference Centers recognized by the WHO.

International teaching

Each year, more than 100 scientists from the Institut Pasteur International Network complete their training with courses or internships in Paris.
In 2009, 13 courses funded by the International Network were taught in nine countries – four in Africa, five in Asia, two in Latin America, one in Europe and one in the Middle East. Other courses supported by the Institut Pasteur are held across the world, including the AmSud-Pasteur courses, the courses on salmonellosis monitoring organized jointly with the WHO, and the course on ticks taught at the Research Center for the Monitoring of Emerging Diseases in the Indian Ocean, on Reunion Island.

expertise and resources

human resources

Recruitment, labor relations, welfare – the Institut Pasteur's employment policy in 2009 focused on improving recruitment practices for young researchers and employment and career development of its senior staff members.

RECRUITMENT

Overall, the number of Institut Pasteur staff members remained stable, with around 1,900 employees, although the number of permanent staff fell slightly (- 31 at the end of 2009) and the number of fixed-term staff increased (+ 25).
This rise in fixed-term contracts is due to the recruitment, as regular employees, of young researchers, doctoral students and postdoctoral fellows who were previously taken on as trainees.
These young researchers, who numbered 281 as of December 31 (compared with 249 in January), were mainly employed by means of individual research training grants or under international agreements or agreements for young foreign researchers living in France on a temporary basis.
2009 was marked by a policy to control workforce numbers, mainly achieved by the non-systematic replacement of departing permanent employees, mostly those taking retirement. This policy will be continued in 2010.

LABOR RELATIONS

2009 saw a general rise in salaries of 1.3%, taking effect on March 1, along with a wage increase for the lowest salaries. In addition to these general measures, a budget representing 2% of the indexed salary of all employees was set aside for individual pay rises. On average, one in two Pasteurians receives an individual annual pay rise.
In the area of labor relations, several major initiatives, some of which were launched in 2008, were completed this year, including the agreement on the employment of senior staff, signed by all the Institut Pasteur's trade unions. Given the demographic profile of the Institut Pasteur, which represents a balanced age pyramid, this agreement aims to maintain a proportion of at least 20% of employees aged 55 and above up to December 31, 2012.
The agreement is based on four areas: anticipating career development, enhancing skills, implementing measures for staff approaching retirement age, and ensuring transfer of knowledge. Emphasis is particularly placed on professional training, by means of various initiatives.
In terms of working arrangements, the Institut Pasteur has concluded an agreement to promote telecommuting on an experimental basis for two years. This system will be tested in departments that rely heavily on IT, such as the computing resources and "dry" biology sectors. Around a hundred Pasteurians are potentially eligible for this scheme.
Finally, the Institut Pasteur has adopted an agreement making it possible to employ staff under a fixed-term contract for specific assignments. This agreement, concluded pursuant to the 2008 law on modernization of the labor market, will enable the institute to offer contracts of 18 to 36 months for research projects, if justified, independently of its permanent contract recruitment policy.

Each year,

over **60** nationalities
are represented on campus

On December 31, 2009, the Institut Pasteur workforce totaled

2,526 people

1,909 Institut Pasteur employees (81% on permanent contracts)
514 employees from external research organizations,
87% of whom are researchers
103 trainees

WELFARE

In 2009, the five-yearly review of the Institut Pasteur's choice of welfare organization took place. This review, carried out with staff representatives, also involved an audit of the guarantees offered and the rates applied. A new insurance organization and a new contract manager were selected following a call for tenders.
Several guarantees were improved and others were offered or consolidated within the framework of an optional package funded entirely by the employee on a voluntary basis.
Moreover, the Institut Pasteur and all the trade union organizations were in favor of the immediate application of the National Interprofessional Agreement, under which guarantees for Pasteurians who leave the institute are maintained for a maximum of nine months.

1,909 Institut Pasteur employees, including:

1,178 women (61.7%)
731 men (38.3%)

Women hold **53.4%** of manager positions, and represent:

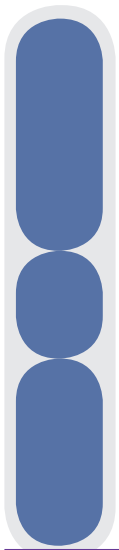
55.2% of administrative and technical managers/doctors
48.3% of researchers
68.3% of research engineers

diverse income sources

current income in 2009 €232.6 M

€88.4 M
revenue from own activities

41.4%(1)



€39.2 M Research contracts

€17.8 M Sales and services

€31.4 M Industrial royalties

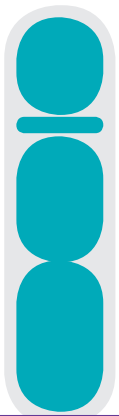
Industrial royalties (€31.4 M and 14.7% of income) are essential for the Institut Pasteur. They are a direct result of the research carried out on campus. They have decreased because some patents have expired.

Sales and services (€17.8 M and 8.3% of income) comprise activities linked to business development (expert assessments, advice for industrialists, etc.), public health activities carried out at the Medical Center, and services provided particularly to network institutes. This income remains stable.

Research contracts (€39.3 M and 18.3% of income) have risen again this year; this increase applies to public contracts, with the growing importance of the French National Research Agency (ANR), to major programs aimed at network institutes, and also to European and foreign funding.

€67.2 M
fundraising and patrimony incomes

31.4%



€16.3 M Donations

€1.4 M Apprenticeship tax

€24 M Legacies

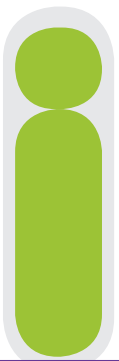
€25.5 M Patrimony incomes

PATRIMONY INCOMES (€25.5 M) include current financial revenue, rent from income property and agricultural revenue from estates registered among the Institut Pasteur's assets.

Fundraising (€41.7 M) includes all donations and legacies, and apprenticeship tax. Donations in 2009, including those for investments, totaled €19.8 M (+ 10.6% compared with 2008), resulting both from an increase in fundraising campaigns targeted at individuals and from communications initiatives that have been under way for several years. Apprenticeship tax stands at €1.4 M (an increase of 13% compared with 2008). Legacies (€24 M), as regards the share allocated to current revenue, have risen slightly. The amounts recorded in 2009 correspond to completed legacies, the majority of which were bequeathed in previous years.

€58.1 M
government contributions

27.2%



€6 M French Institute for Public Health Surveillance (InVS)

€52.1 M French Ministry of Research

These are mostly made up of the grant from the French Ministry of Research (€52.1 M), which increased by €4.7 m in 2009 (+ 9.8%).

They also include the **annual grant from the French Institute for Public Health Surveillance,** which covers some of the costs of the activities carried out by the National Reference Centers (€6 M).

€18.9 M
non-allocated

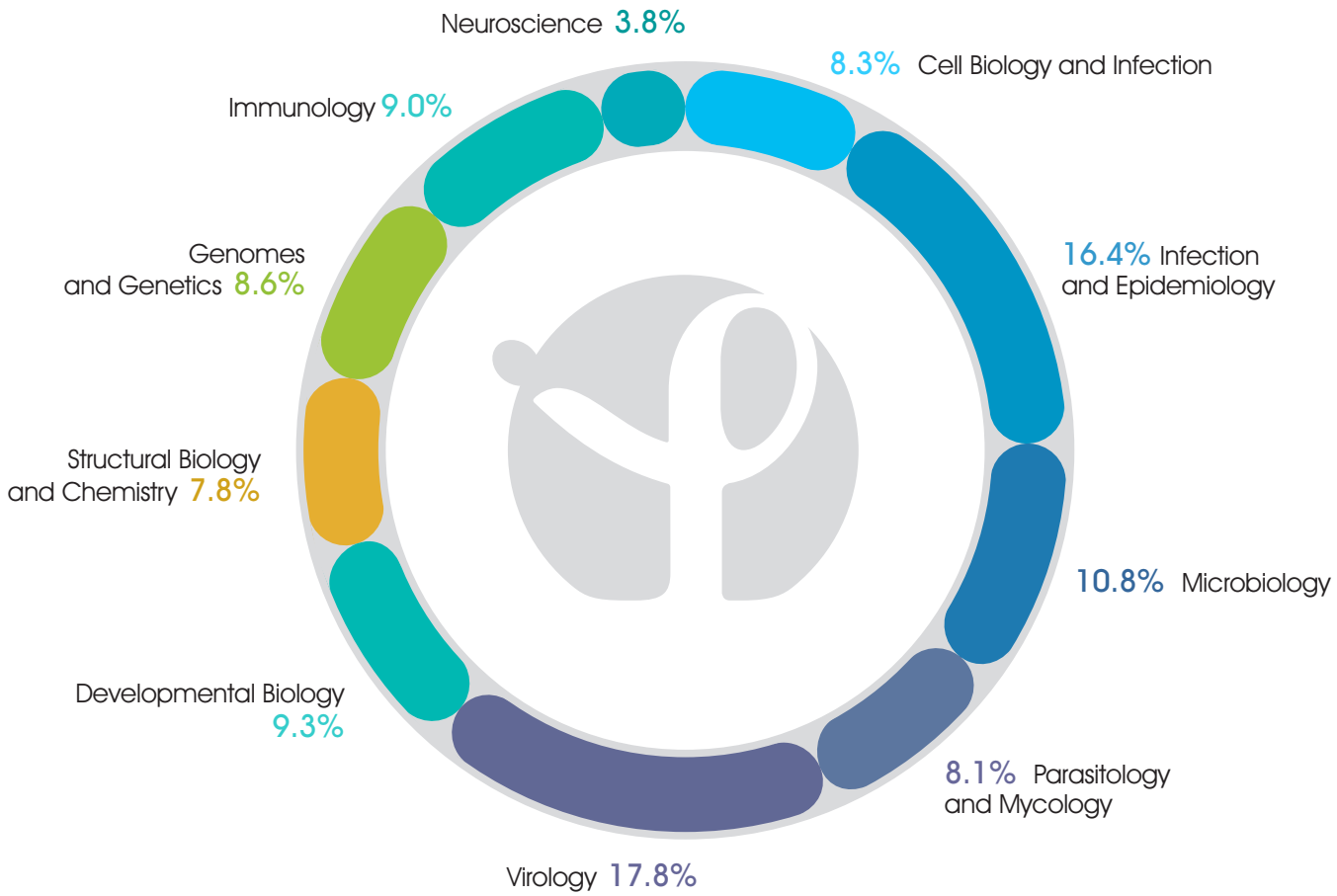
€18.9 M Carry-over income

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

(1) Percentages calculated excluding carry-over of unused income from previous years and recovery of provisions.

current expenditure in 2009 €230.6 M

- €111 M
  personnel expenditure
- €80.7 M
  operating costs
- €11.3 M
  depreciation
- €27.6 M
  provisions and future commitments



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

financial situation

In 2009, the operating result totaled €1.2 M, a slight fall of €0.6 M compared with the previous fiscal year. It comprises €232.6 M of current revenue (public grants, fundraising and patrimony incomes, and revenue from own activities), and €230.6 M of current expenditure (operating and personnel expenditure).

CURRENT OPERATIONS

Current revenue increased by 1.4% on average in relation to 2008, with contrasting developments for the various items: government contributions and research contracts were up this year, industrial royalties fell sharply and income from fundraising was on a par with 2008. These developments clearly show the fragile nature of the Institut Pasteur's financial resources.
Current expenditure rose by 0.9% in relation to 2008. Personnel expenditure was generally similar to 2008, and operating expenditure fell as a result of the decrease in resources allocated and non-recurring operations of the previous year.
In terms of the Institut Pasteur's activities, research accounts for the majority of this expenditure, while the rest is allocated to public health and teaching.

NON-RECURRING OPERATIONS

In 2009, non-recurring operations recorded a surplus of €75.4 M (compared with a deficit of €112.8 M in 2008). 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 (€6 M in 2009)). In 2009, the total recorded in the accounts as non-recurring income was €16.6 M (compared with €18.5 M in 2008).
In total, legacies recorded in the accounts in 2009, as both recurrent and non-recurring income, amounted to €40.5 M, compared with €41.7 M in 2008.
The Institut Pasteur's assets are managed by several specialist financial institutions on the basis of management agreements. The long-term allocation of assets corresponds to a balance between shares and bonds. In 2009, the overall growth of the global financial markets meant that €58.9 M of non-recurring income was able to be recorded in the long-term investment portfolio. The overall return on our portfolio for 2009 was 17.9%.
The net surplus this year is €76.6 M. This is mainly attributed to non-recurring income recorded for our long-term investments and to legacies recorded as non-recurring income.
These results show that funding for the Institut Pasteur's current operations remains a challenge and that the conditions required to develop the foundation's activities depend on maintaining a high level of income from industrial royalties, increasing fundraising efforts and receiving continued support from the French government.

donations and legacies

The generous donations, legacies and sponsorship provided by individuals and companies have always been vital for the Institut Pasteur, guaranteeing its independence and enabling its research teams to offer a rapid response in emergency situations such as disease outbreaks. 2009 was a landmark year in terms of fundraising: with donations totaling €19.8 M, it was the best year in the Institut Pasteur's history.

DONATIONS

Donations from individuals rose sharply, with €11.5 M as against €9.15 M in 2008. This increase of over 25% was particularly due to the many generous donors who agreed to set up a direct debit – the number of direct debits has virtually doubled over the past year.
Major contributions include a high level of support for the program to develop a cancer vaccine candidate, MAG-Tn3; the clinical stages of this program are entirely funded by the generosity of donors.
2009 again provided opportunities for donors to meet Institut Pasteur researchers at the many conferences and evening events, and also at the "Pasteurdon" events held in several French towns and cities, which brought the institute's research to a wider audience.

COMPANY SPONSORSHIP

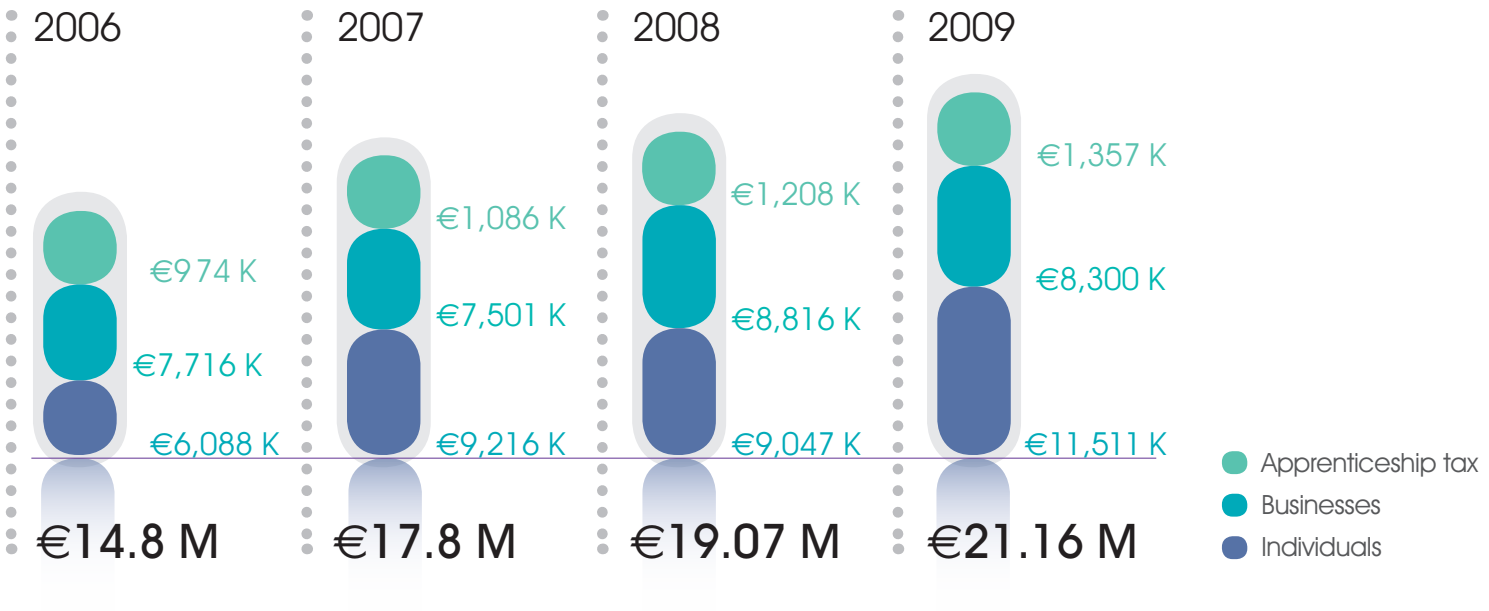
Company support also played a crucial role, totaling €8.3 M in 2009, over 85% of which was allocated by companies to a specific research program. In 2009, the Institut Pasteur was pleased to welcome on board a number of new company sponsors, including OdysseyRe and Idéal.

APPRENTICESHIP TAX

Companies can also contribute to the Institut Pasteur's educational mission by allocating part of their apprenticeship tax to the institute, money which is then used to train future researchers. A total of €1.35 M in apprenticeship tax was collected in 2009, a 12% increase that will greatly benefit the work of the Teaching Center.

The *Variétés Club de France* were pitted against a celebrity team in a charity soccer match held in Jean Bouin Stadium on June 3, 2009, with funds going to the Institut Pasteur.

Development of fundraising in €M



ETHICS

The Institut Pasteur makes every effort to maintain complete transparency in its fundraising operations. The accounts are published each year and are issued to each donor. They are inspected by a statutory auditor and are subject to the approval of the Institut Pasteur's Board of Directors.
The Institut Pasteur's activities are also subject to the control of the *Comité de la Charte*, which verifies the rigor and transparency of our management.

LEGACIES

Despite a difficult economic context in 2009, the number of legacies increased (114, as against 106 in 2008), with a rise in the number of specific legacies compared with the number of general legacies. This trend reflects the fact that legators are increasingly keen to support a range of causes by sharing their assets between a number of different organizations. However, the average amount bequeathed fell slightly in 2009. Among the major legacies received were the general legacy of Miss Anita Semail (€3.5 M), heiress to three generations of antique dealers and specialist in works by Compigné; an auction of her prestigious collection of paintings, gouaches, sculptures, fine art objects and furniture from the 18th century was held in Drouot in March 2009.
Contributions from life insurance policies were down compared with 2008 but nevertheless represented over €3 M in 2009.
The Institut Pasteur is a member of the *Comité de la Charte* and abides by a code of scientific ethics. It has also recently introduced procedure guidelines certified by the quality department to optimize legacy management.
To support endowment fund projects set up to provide financial assistance for the Institut Pasteur's research, some of the institute's departments, which together have a wealth of expertise on the subject, have established an "endowment fund unit" to provide information and advice about setting up an endowment fund.
The aim of this unit is to support the administrative side of the project: drafting articles of association, preparing the contractual documents required subject to forthcoming regulatory provisions (articles of association, identity of founder(s)), and filing and monitoring the application to set up the endowment fund with the local authorities.
In general, this unit is there to offer individual assistance and expertise for the creation of endowment funds, with the same rigorous approach and control frameworks as the Institut Pasteur itself.

communications and fundraising

After the 120th anniversary celebrations in 2008, how could the Institut Pasteur continue to maintain the same level of public confidence and awareness and the same outstanding reputation in 2009? How could the institute continue to nurture relations with the public? These were important questions to answer as the Institut Pasteur pursued its fundraising efforts.

To promote the Institut Pasteur's reputation and image while encouraging people to continue giving, our communications efforts needed to be focused on a single slogan that sums up the institute's activities and acts as a call for donations. This slogan would be used for all the initiatives launched by the Institut Pasteur and would give it a modern image that was crucial for the success of its communications campaigns. Researchers, donors, partners, together with the Institut Pasteur: "Let's strike a blow to sickness" (*Rendons malades les maladies*). This slogan offered great potential for use in a wide range of contexts, enabling the institute to develop its own specific style. A campaign focusing on four major research areas was launched in spring 2009 in the French daily press and with a series of posters in Greater Paris. This initiative received the backing of industry professionals, winning the Empreintes 2009 prize in the Corporate Health category. It is the second year running that the Institut Pasteur's communications strategies have received such an award. This campaign also went down well with both donors and non-donors, according to a public opinion survey carried out in September 2009. The new slogan enhances the institute's image by making it more accessible, and it also stimulates curiosity. The slogan will continue to be used in 2010.

MAJOR MEDIA COVERAGE FOR PASTEURDON

The third Pasteurdon enjoyed the support of major French companies and for the first time was broadcast on all the French digital terrestrial channels, creating a major media impact. As well as the twelve digital terrestrial channels that agreed to broadcast short programs, this edition was supported by two national radio stations, long-standing partners of the event. This year's Pasteurdon also featured an unprecedented street party organized by the Institut Pasteur at Place de l'Hôtel de Ville in Paris.

All the researchers gathered at Place de l'Hôtel de Ville in Paris on Sunday October 11, 2009, for Pasteurdon.

This event was a wonderful opportunity to raise public awareness of science and biomedical research, and to emphasize the Institut Pasteur's reliance on public support. The next edition of Pasteurdon will take place in October 2010.

NEW SUSTAINABLE PARTNERSHIPS

Increasing numbers of partner companies and donor institutions are supporting the Institut Pasteur, a recognized leader in its areas of expertise. Alongside loyal partners such as Sanofi-Aventis, Danone, the Total Foundation and the AREVA Foundation, in 2009 new supporters joined the cause, including MGEN and OdysseyRe.

THE FIRST CONFERENCE ON PHILANTHROPIC TRUSTS

In 2009, to consolidate its position in the charity world and in line with the strategy pursued over the last four years, the Institut Pasteur launched the first conference on philanthropic trusts, with 350 delegates. The event, held on November 18, was attended by Christine Lagarde, French Minister for the Economy and Finance, and led by François de Witt, President of Finansol and a journalist known by all the specialists in the field; it brought together the leading professionals and experts in this new developing sector, including notaries, assets managers, specialist bank departments, tax lawyers, academics and researchers, representatives of public authorities and major institutions, and directors of charities and foundations with first-hand knowledge of the new products developed as a result of legislative, regulatory and fiscal innovations. And, of course, the event would not have been complete without the presence of major donors and founders, whether in the traditional sense or "new philanthropists".

The *Rendons malades les maladies* communications campaign was awarded the Empreintes Corporate Health prize

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A WEB PLATFORM FOR OPTIMIZED COMMUNICATION

With over 10,500 visits every day, the Institut Pasteur's websites attract a wide variety of Internet users. From the institute's site, pasteur.fr, to the site for specific events and the general public, aiderpasteur.fr, a huge amount of information is available about the Institut Pasteur, totaling over 42,000 pages! In 2009, the dedicated Pasteurdon site (pasteurdon.fr) was given a complete graphical and technical overhaul. A range of tools were provided to make it easy for users to spread information about the campaign on the web – social networks, RSS feeds, videos, blog counters, personal fundraising pages, pasteurmail, etc.
On the aiderpasteur.fr site, donors can now view their donation history and manage their generous contributions online.

A SCIENTIFIC INFORMATION CAMPAIGN

The Institut Pasteur continued to promote and explain its research to the public. Of the 35 press releases published this year, 24 focused on advances in research work. Many talks were also organized for the general public in Paris and throughout France. The "Mysteries of Science" and "Mr Pasteur's Way" lectures, in particular, met with great success.

Sylvain Coudon,
Vice-President
Communications
and Fundraising

"I am always impressed at the generosity of the public and our sponsors – thanks to them, our donations have increased by 127% in five years!"

The science of communication

He has a gift for public interest work. He chose communications so that he would feel like he was making a difference, and the Institut Pasteur so that he could promote its ideas and its humanist vision of the world. He is also a "researcher" – one who searches for funds. The quote by the famous geneticist Albert Jacquard is particularly apt in his case: *"To communicate is to share; and sharing is what makes us who we are."* Sylvain Coudon chose to combine his gift for communication with his commitment to public interest work. He has been involved in charitable organizations for almost twenty years – the National Union for Maladjusted Children, the French Muscular Dystrophy Association, the French Institute for Public Health Surveillance (InVS), the Agence Verte and the MFP Group.

This public communications specialist is proud to help raise the public's awareness of the Institut Pasteur: *"I am always impressed at the generosity of the public and our sponsors – thanks to them, our donations have increased by 127% in five years!"* His strategy involves campaigning to change public habits. But every Thursday evening he is happy to stick to his old habit of reading the major French weeklies. *"It took me a long time to decide between public interest communication and sports journalism."* Anyone would think that communication is also a sport! Sylvain Coudon also remembers why he has a particular interest in science. He tells the story of his grandfather, from the Berry region, who, suffering from stomach cancer, chose to place his trust in his clock. *"He suffered terribly before he died. I always wondered how it was possible to be so narrow-minded and hold such superstitions. It made me think about our relationship with medicine and science."*

He goes on to talk about Clara, his daughter, who wants to become a lecturer and prefers history to the virtual world. *"At 15, she knows all there is to know about the life of Anne Boleyn, the second wife of Henry VIII, who was beheaded for adultery, incest and high treason."* His own interests are many and varied. He tells us about the North American Indians – in particular the Sioux – before moving on to Björn Borg and Swedish tennis players. *"For even if we are surrounded by mass communications, it is vital that we find the time to communicate with ourselves."*

Ever more generous **sponsors**

By lending their support to the Institut Pasteur's various programs and campaigns, its sponsors are constantly demonstrating their commitment to the institute's research teams and efforts to combat diseases.

TOTAL, A RENEWED COMMITMENT

On October 13, 2005, Total and the Institut Pasteur signed a five-year sponsorship agreement under which Total agreed to contribute €500,000 each year to research programs led by the institute's multidisciplinary, international teams based in Paris. The programs focused on hepatitis C, emergency diarrhea diagnosis, a dengue vaccine candidate, apoptosis (or programmed cell death) in response to infections, detection of emerging viral agents, malaria transmission by the mosquito vector, and the role of the genetic variability of viral quasispecies in pathogenesis and its implications for vaccinology.

This partnership also involved the contribution of Pasteurian scientific expertise in selecting and supporting programs to combat major pandemics (HIV, hepatitis, malaria and infant diarrhea) financed by Total in the countries of the Institut Pasteur International Network, as well as operations coordinated by the Institut Pasteur in other world regions.

To further strengthen the scientific and human resources available to fight infectious diseases, the Total Foundation has decided to renew its commitment for the period 2010-2014. The new agreement will provide for the establishment of a research and training chair, directed by Professor Françoise Barré-Sinoussi, winner of the 2008 Nobel Prize in Medicine, to develop research and training through research on protective mechanisms against HIV/AIDS. A second section will focus on the continued funding of field programs in southern countries.

ACTIMEL, A LOYAL SUPPORTER

A partner of Pasteurdon since its first edition in 2007, Actimel once again supported the Institut Pasteur's charity appeal in 2009. In addition to supporting Pasteurdon on all Actimel packaging, the famous Danone Group brand publicized the event in advertisements on terrestrial and digital terrestrial channels and on several websites. Following the success of Pasteurdon 2009, Actimel has already announced that it will take part in the 2010 edition.

The Institut Pasteur and Actimel are also working on a campaign to raise awareness of the institute's research in other European countries. The campaign was launched in Spain in May 2010.

TWO QUESTIONS FOR **CHRISTOPHER A. VIEHBACHER,** CEO OF SANOFI-AVENTIS

Beyond the standard industrial agreements, how have you provided sponsorship support for the Institut Pasteur?

The Institut Pasteur is a long-standing partner of the Group, particularly through its Sanofi Pasteur vaccine division. In 2009, our support focused on two main areas – the Institut Pasteur's research on parasitic diseases, and sharing knowledge through the vaccinology course, of which we are a partner.

How do you see your future alongside the Institut Pasteur?

The global population is approaching 7 billion, and everyone potentially needs our help to lead a better life. If we are to meet this challenge, innovation in research and development is essential. Today, adopting a single approach is no longer enough; we need to consider a wide range of solutions to target all aspects of disease, for the benefit of patients. Being open to external innovations is crucial in this holistic approach. This is a major part of the sanofi-aventis Group strategy and is fundamental to our partnership with the Institut Pasteur.

Gilles Pélisson,
Chairman and CEO
of the ACCOR
Group

"I was struck by the sharing of knowledge among all these global networks of researchers, by the passion and mutual respect demonstrated by these people…"

ACCOR – true to its values…

All glass and greenery, the gleaming new international headquarters of ACCOR at the Odyssey building in Paris' 13th district were designed by famous British architect Norman Foster. The office of Gilles Pélisson, the Group's Chairman and CEO, is bathed in natural light. *"From a sociological viewpoint, our profession of hotelier goes way beyond just greeting clients who are looking for a room. A hotel is also a dynamic place where people meet and exchange ideas in a town or city; it is something which has a lasting impact. This is why we launched the Earth Guest program in 2006, to contribute to the fight against epidemics, particularly the spread of the AIDS virus and malaria, and to offer a response in terms of prevention and protection for our clients and our staff."*

From Abidjan to Dakar, from Phuket to Bangkok, the societal and environmental commitment of the Group's 4,000 hotels and 150,000 staff can be expressed through this slogan: *"As guests of the Earth, we welcome the world." "We were easily able to identify with the humanist values embodied by the Institut Pasteur, and so came up with the idea of a partnership agreement to assist the institute in its research. As part of our series of initiatives on the theme 'from small streams big rivers will flow', our clients now have the option of converting points obtained through the loyalty scheme into donations for the Institut Pasteur. At the same time, the Group is furthering its involvement in the prevention of emerging diseases through the funding of an information and prevention website for travelers – pasteurtravel.com."*

On a visit to the Institut Pasteur, he was impressed by the teams' fast response to health emergencies: *"I was struck by the sharing of knowledge among all these global networks of researchers, by the passion and mutual respect demonstrated by these people… As I'm a big fan of detective novels, where the stories are sometimes about the spread of viruses, I was aware of the importance of laboratory security."*

At 53, Gilles Pélisson is a committed manager who has also chosen to become a donor and a driving force behind the work of the Institut Pasteur's researchers. *"We are happy to be able to help the Institut Pasteur move forward in its research, and in the process to help offer ever better levels of protection for our clients and staff worldwide."*

general organization

general organization of the Institut Pasteur

board of directors

May 2010

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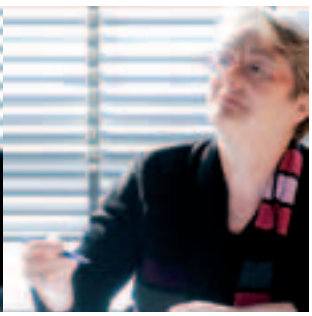

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Head of the Viral Genomics and Vaccination Laboratory

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