ANNUAL REPORT

FOR OUR FUTURE





AT THE HEART OF **GLOBAL CHALLENGES**

The Institut Pasteur is internationally renowned for its work on infectious diseases, striving daily to combat the microorganisms that cause them. In addition, teams focus their efforts on neuroscience, developmental biology, genetics, and genomics, while 130 research units apply their expertise to serve human health and development. Its truly international outlook has resulted in partnerships with many of the field's leading players from around the globe.

PROFILE



AT THE FOREFRONT OF **BIOMEDICAL RESEARCH**

The Institut Pasteur's scientific strategy focuses on developing new topics for biomedical research, enhancing multidisciplinarity, and improving the transfer of scientific discoveries to applications. By providing its teams with the technological resources they need, the Institut Pasteur renews its commitment to making progress in biomedical research and expertise and winning new victories against disease.

SETTING THE INTERNATIONAL STANDARD

In addition to the many partnerships and projects developed in cooperation with major international scientific bodies, such as the World Health Organization and universities and research institutes from around the world, the Institut Pasteur is at the heart of an international network of 32 institutes located worldwide. These member institutes have declared their commitment to Pasteurian values and are united in the fight against infectious diseases.

INSTITUTES

WORLDWIDE



TEACHING STUDENTS FROM AROUND THE WORLD

Each year, the Institut Pasteur Teaching Center welcomes students from all over the world who come to further their knowledge or supplement their degree programs. Thirty courses are offered which can be divided into three categories: Mechanisms of Living Organisms, Biology of Microorganisms, and Epidemiology and Public Health. These courses emphasize practical work and can be taken as part of Masters degree programs at various universities or as part of the specialized Masters run by the Pasteur-CNAM School of Public Health.

A UNIQUE Economic model

The Institut Pasteur's budget is based on four sources of funding – public generosity, government contributions, the development of business based on Pasteurian research and research grants – a feature that guarantees the independence of the research policy pursued by this private state-approved foundation.

MILLION EURO BUDGET IN 2011

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BOARD OF DIRECTORS

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SCIENTIFIC COUNCIL

Chairman of the Board of Directors

INTERVIEW WITH **JEAN-PIERRE JOUYET**

You took over as Chairman of the Institut Pasteur Board of Directors on July 7, 2011. How did you feel about taking up this post?

I was delighted to take up this role. Joining the Institut Pasteur is like becoming part of a big, happy family, with a true "Pasteurian" spirit and ethic that you won't find anywhere else. It is a family that is generous, courageous, hard-working, and open to all, regardless of location or nationality.

Working at the Institut Pasteur is about sharing a sense of open-mindedness, about valuing others, whoever they might be. It's about discussing and exchanging ideas – and not just about science, I must admit! The Institut Pasteur fosters a truly democratic spirit: it is rare to find a foundation with so many committees and assemblies where each individual can be heard.

What events have stood out for you over the past six months?

As well as the serious economic and financial crisis that marked the year 2011, four events in particular caught my attention.

The first was the Institut Pasteur's success in the calls for tender issued by the French government under the "Investing in the Future" program. The funding secured by the Institut Pasteur and its partners through this program will enable us to improve our technical expertise in key research areas, as well as strengthen our relations with the scientific community in France. We are particularly pleased about the official accreditation awarded to three Institut Pasteur "laboratories of excellence" projects, and that the Institut Pasteur was selected to set up one of the six Technology Research Institutes in collaboration with Lyonbiopôle.

Working at the Institut Pasteur is about sharing a sense of open-mindedness, about valuing others, whoever they might be. It's about discussing and exchanging ideas. I am absolutely convinced that the Institut Pasteur has the talents and resources necessary to maintain its high standards across the board.

The second event was the meeting held in Paris last November for the directors of institutes in the International Network, I would also like to highlight the scientific vitality of this network, its ever increasing efforts towards modernization and collaboration, and its fundamental role in addressing the challenges facing public health - all of which are driven by research, training, and infectious disease monitoring, particularly in the countries and regions where the institutes are based.

The third event that stood out for me would have to be Pasteurdon. I was especially touched by the display of commitment to Pasteurdon, with Institut Pasteur staff getting together to create a life-size Pasteurdon logo to mark the launch of the event.

Finally, the fourth event that I feel marked the year 2011 was the completion of work on the new building, which will be officially inaugurated in November 2012.

What are your thoughts on the Institut Pasteur's financial situation?

Despite economic difficulties, the Pasteurian community has shown a united front and worked hard to maintain the Institut Pasteur's high standards, in all respects. Unfortunately, in terms of the financial crisis, we're not out of the woods yet and the coming months will be challenging for France and for Europe.

The Institut Pasteur is in a strong position to keep on track, but it will have to maintain its efforts and, most of all, remain vigilant in the face of the current economic climate.

At its recent meeting, the Board of Directors and the general management discussed at length about how well the Institut Pasteur would be able to cope with an economic slowdown, a situation that would impact public resources and resources from business development, as well as donations and fundraising.

The Institut Pasteur must be aware of its strenaths but must also understand the importance of adjusting to changing contexts. It must be able to react to unpredictable events. These matters, I am happy to say, have been at the heart of many fruitful discussions held throughout the year between the Board and the management.

The reforms carried out by the Institut Pasteur management over the last few months are a step in the right direction and should be continued in 2012 so that our institution can maintain the level of resources it needs to match the ambitious tasks it has set itself.

Finally, I am absolutely convinced that the Institut Pasteur has the talents and resources necessary to maintain its high standards across the board.

What are the major challenges facing the Institut Pasteur in 2012?

Firstly, let me emphasize my wholehearted commitment to the Institut Pasteur. Since the beginning of my term, I have visited laboratories and talked to various people working at the Institut Pasteur. I have met researchers from different scientific departments and was delighted to have the opportunity to speak to the eminent Prof. François Jacob. In 2012, the Board will be working hard to ensure that the Institut Pasteur secures the resources required to match its ambitions, despite the economic difficulties it may face. The Board will continue to work with the management to enable our institution to pursue its missions and to meet the scientific challenges of the 21st century, while upholding the humanist values that constitute the foundation of all its work.

INTERVIEW WITH **ALICE DAUTRY**

What do you take away from the year 2011?

President

2011 was a watershed year in many respects for the international community. The Arab Spring, the earthquake and tsunami in Japan, and the ongoing economic and financial crisis profoundly altered our world and the way we view it. The Institut Pasteur, firmly positioned at the heart of society since its very early days, felt the impact of these events. This historic context has only made us more determined to pursue our missions – particularly in our International Network – to develop new partnerships, and to step up our efforts to ensure that the Institut Pasteur will continue to have the resources it needs to match its ambitions.

What were this year's most memorable moments?

International events had quite an impact on the activity of the Institut Pasteur in 2011. Several countries with institutes in the International Network or with whom we have developed long-term partnerships were shaken by severe political crises. My colleagues who have been so courageous and have continued to carry out their work despite difficult and sometimes tragic conditions have nothing but my utmost admiration and respect. Some of them have suffered incredibly trying circumstances and I would like to assure them that the whole Pasteurian community is with them in spirit.

In spite of this difficult climate, the Institut Pasteur has maintained an active role internationally. The creation of the "Pasteur International Network" Association, for example, which aims to carry out large-scale scientific projects that encourage collaboration and expertise in the fight against infectious diseases. In addition, the US Department of Health and Human Services has renewed its agreement with the Institut Pasteur and the institutes in the International Network. Finally, we were pleased to organize

The coming year will see the inauguration of our new building for emerging diseases. This is a grand-scale project. a conference for young researchers from the International Network in November. During this event we were particularly struck by the development of young talent in countries that have their own Institut Pasteur.

Various new industrial agreements were concluded in 2011, but I was particularly touched by the signing of an agreement with the Japanese firm Meiji Feed Company just a few months after the terrible natural disaster that struck Japan. We were all very moved at the signing of this agreement and the prospect of developing new projects together.

In terms of fundraising, we created the Sanofi-Institut Pasteur Awards to encourage scientific excellence for health applications. These awards will provide support for four innovative research projects that have the potential to make some real advances in the life sciences and offer responses to major global health problems. We also signed an agreement with the AREVA Foundation for HIV/AIDS projects. Furthermore, despite the economic difficulties, the support of our donors has remained as strong as ever. One example that I might mention is the sale of two paintings by Claude Monet and August Renoir, with the proceeds going to the Institut Pasteur. Of course one of the major highlights has been the success of the Institut Pasteur in the calls for tender issued by the French government under the "Investing in the Future" program.

Could you tell us a little about the projects that have been selected?

Under this program set up by the French government, the Institut Pasteur bid for the tenders for which it was eligible, either as a coordinator, co-promoter, or partner. This process required a major joint effort and real commitment from a huge number of Institut Pasteur employees. I would particularly like to emphasize their remarkable level of dedication and focus. The funding secured will enable us to improve our technical expertise in key areas and also to develop completely new lines of research and new technologies, as well as strengthen our relations with the scientific community in France. Three "laboratories of excellence" (LabEx) projects led by the Institut Pasteur received official accreditation, as did one EquipEx project. The Institut Pasteur is also a partner in seven other LabEx projects and two EquipEx projects.

The Technology Research Institute project put forward by the Institut Pasteur and Lyonbiopôle, in collaboration with major industry players such as Sanofi, Danone, and the Institut Mérieux, around 50 SMEs and research organizations (CNRS, Inserm and CEA), also received official accreditation. This project will enable us to develop new approaches in our relations with industry players and SMEs, in addition to the close links that we have already forged in this area.

In scientific terms, what have the Institut Pasteur's main achievements been in 2011?

Over the past year, the Institut Pasteur has achieved significant results in all its departments. Let me give you some examples: researchers discovered a new strategy used by Listeria bacteria to reprogram gene expression in the cells they infect (to their own advantage); progress has been made in the use of iPS cells for gene therapy; scientists have discovered a new group of mosquitoes that are particularly adept at spreading malaria; new results have emphasized the importance of synaptic genes in autism; a study has demonstrated the importance of the order in which treatments are administered to patients co-infected by HIV/ AIDS and tuberculosis; and an antibody against dengue has been characterized.

However, maintaining the quality of the scientific research of the Institut Pasteur requires the ongoing recruitment of toplevel researchers - whether young researchers or those with more experience - from across the world. With this in mind, the Institut Pasteur created four new five-year groups - known as "G5s" – in 2011. These research groups are directed by young scientists with outstanding potential, who are given funding for five years to build a team and carry out their research. Several new units have also been created with the aim of developing new fields and exploring new avenues of research. The international doctoral program launched three years ago to train young researchers has been very successful. The number of talented candidates has gone up each vear. The students, selected from across the world, work towards their PhD in one of the 130 laboratories of the Institut Pasteur.

Finally, the quality of the research of the Institut Pasteur was once again recognized this year with many researchers receiving prestigious awards. Seven researchers in particular won a contract from the European Research Council (ERC): four were awarded a Starting Grant and three an Advanced Grant.

What major events are coming up for the Institut Pasteur in 2012?

The coming year will see the inauguration of our new building for emerging diseases. The facility will be fitted with the latest technological equipment and will aim to encourage a multidisciplinary approach. This is a grand-scale project that has involved several people over the past few years, and one that has been carried out despite various bumps in the road, particularly the unfavorable economic climate. The modernization of the campus will also be stepped up, with buildings being renovated and departments reorganized to optimize efficiency. There will be more recruitments, particularly for G5s.

At an international level, we were pleased to be able to inaugurate the Institut Pasteur in Laos in January 2012. This new research center for infectious and parasitic diseases will help reduce the risks of pandemic outbreaks in South-East Asia. where such diseases are rife.

As you can see, the Institut Pasteur will pursue its missions in 2012, despite the difficult times, staying united and true to its humanist values.



SCIENTIFIC DISCOVERY FOR SUSTAINABLE HEALTH

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The Institut Pasteur is committed to providing researchers with the resources they need for the implementation and realization of ambitious, varied scientific projects. This, as well as ongoing investment in cutting-edge technologies, regular cooperation with the Institut Pasteur International Network, application of discoveries from Pasteurian research, and dissemination of knowledge and expertise, all help foster quality research.



EFFECTIVE MULTIDISCIPLINARY RESEARCH

- CELL BIOLOGY AND INFECTION
 - DEVELOPMENTAL BIOLOGY
- STRUCTURAL BIOLOGY AND CHEMISTRY
 - GENOMES AND GENETICS 🔅
 - IMMUNOLOGY 🛄
 - INFECTION AND EPIDEMIOLOGY
 - MICROBIOLOGY 🜅
 - NEUROSCIENCE
 - PARASITOLOGY AND MYCOLOGY
 - VIROLOGY 斗
 - TECHNOLOGICAL PLATFORMS
- - CNRs and WHOCCs

CELL BIOLOGY AND INFECTION

Two neurons connected by a tunneling nanotube exchanging prion aggregates (in green). This department analyzes interactions between infectious agents and their targets – cells and tissues – at all stages of infection. Several teams carry out research on specific infectious agents while others work towards an in-depth knowledge of cells in a non-infectious context.

Understanding infectious mechanisms requires extensive research into how cells function both during infection and in balanced conditions between the commensal flora and the host. This is where the Cell Biology and Infection Department comes in, to develop analysis of the interface between microorganisms and cells/tissues. In order to achieve this, three priorities stand out:

• step up efforts to integrate cell biology, cell microbiology, genomics and imaging to enable more effective analysis of bacterial, viral, parasitic and prion infections;

• gain expertise in tissue microbiology by using increasingly sophisticated *in vivo* imaging technologies, improving understanding of infection at the whole-animal scale;

• 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.

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TECHNOLOGICAL PLATFORMS

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

3D CELLS FROM EVERY ANGLE!

Researchers from the Quantitative Image Analysis Unit have developed a new tool for the analysis of 3D biological images based on the 3D deformable models used in video games and animated films, known as active meshes.

This new, fully automated calculation method involves creating meshes that deform and mold perfectly to the surface of each object of study (the nucleus or cell, etc.). Identifying the precise contours of these objects enables scientists to pinpoint them and monitor them from one image to the next. This makes it possible to observe cell deformations and interactions in detail over time and to quantitatively study the influence of various factors such as drugs, mutations and disruptions on cell dynamics (mobility, deformation, morphological changes, etc.). This new tool is an invaluable addition to the previous work of this unit, directed by Jean-Christophe Olivo-Marin, in the field of image analysis. This research has applications in areas such as cell biology, host-pathogen interactions and morphogenesis.



PASTEUR-WEIZMANN FUNDING FOR PRION RESEARCH

Each year, the Pasteur-Weizmann Association provides funding for several research projects carried out in collaboration between the Institut Pasteur and the Weizmann Institute. In 2011, the grant awarded to Chiara Zurzolo (Institut Pasteur) and Zvulun Elazar (Weizmann Institute) for a project to tackle prions using autophagy was doubled by the annual Hugo and Valérie Ramniceanu Prize.

A prion, or PrPsc protein, is an abnormally folded form of the PrPc protein that occurs naturally in mammal cells, although we don't know its role. When PrPsc infects a healthy cell, it induces abnormal folding in PrPc. This change in form leads to an accumulation of prion aggregates, which block several cell functions. In the long term, these aggregates spread from one neuron to the next in the brain and lead to incurable neurodegenerative diseases such as Creutzfeldt-Jakob disease.

The two prize-winning teams are trying to find out whether these aggregates can be destroyed using autophagy, a process activated in the event of cell stress that involves the degradation of certain cell components that have become useless or harmful. By artificially stimulating autophagy, and therefore increasing the presence of degradation organelles (autophagosomes) in the cell, scientists hope to be able to destroy prion aggregates and reverse the symptoms of disease.

SUMOSTRESS

All newly produced proteins undergo changes that determine how they will act and develop. In the majority of cases, these proteins are modified by the attachment of small chemical groups of sugars, lipids, inorganic residue or even proteins to specific amino acids in the protein.

SUMOylation, where one or more SUMO proteins bind to the protein being modified, is a good example of this. SUMOylation plays a vital role in many cell functions including gene expression, DNA repair, cell division and cell architecture. Although we are now fairly familiar with the SUMOylation process, its regulation mechanisms remain largely unknown. That is why the SUMOSTRESS project, led by Anne Dejean and funded by an ERC* Advanced Grant, aims to identify the stress signals that induce or inhibit it and to shed light on its mechanisms. By using a combination of cutting-edge technologies (biochemistry, proteomics and genomics), Anne Dejean's research unit, Nuclear Organization and Oncogenesis, is attempting to reveal how SUMOylation modifies gene expression and, conversely, how different states of gene expression (and therefore different cell states) influence the SUMOylation process.

Improving our understanding of SUMOylation in normal and pathological conditions could open up therapeutic possibilities for diseases linked to cell stress such as inflammation and cancer.

* European Research Council.

Protein identification

In developing countries, infection by *Chlamydia trachomatis* is responsible for trachoma, the leading infectious cause of blindness. Bacteria from this species are also agents for widespread sexually transmitted diseases, a primary cause of female infertility. The Biology of Cell Interactions Unit is focusing on the interactions between *C. trachomatis* and its host. In 2011, an ERC* Starting Grant was awarded to Agathe Subtil, a researcher in this unit, to identify all the *Chlamydia* proteins that are secreted in the nucleus of the host cell and impair cell function. "*This project will shed light on many unknown aspects* of the host-pathogen relationship as well as the nuclear functions of eukaryotic cells," explains the grant recipient.



DEVELOPMENTAL BIOLOGY

The work conducted by the Developmental Biology Department covers a broad spectrum of multidisciplinary research that focuses on everything from individual cells to the organism as a whole. This includes several projects on the study of stem cells and their potential in biomedicine.

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.

Four main research objectives have been defined:

• identify embryo cell movements and migrations that are required for organ and tissue formation and the information exchanges used during this process;

• determine how the identity of each cell is established and maintained through specific programming mechanisms;

• establish the role of stem cells, which play a dominant part not only in embryogenesis but also in the regulation and maintenance mechanisms of adult tissues;

• clarify the respective roles of innate and non-genetic factors in the phenotype developed by the individual, and their genetic contributions to the host's resistance to infectious diseases and/or congenital and metabolic diseases.

The Department successively submitted the REVIVE laboratories of excellence (LabEx) project to the French government's prestigious Investing in the Future program. The ten-year funding obtained will make possible the development and coordination of this key project which aims to build a world class network of stem cell experts from the Institut Pasteur and Paris region that will ultimately become a globally recognized hub for regenerative medicine.

MOUSE GENETICS ENGINEERING CENTER

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

CHROMATIN AND ITS USE IN ALTERNATIVE RNA SPLICING

Histones, which act as the spool around which DNA is wound do more than just structure DNA: scientists from the Epigenetic Regulation Unit directed by Christian Muchardt have now demonstrated that they can also influence alternative RNA splicing, thereby altering the length of the proteins produced by an individual gene.

Under certain conditions, histone H3 undergoes modifications. If a histone modification occurs in the CD44 gene – a gene often associated with cancer and used as a model – scientists observed that the mature CD44 RNA was longer and coded for a longer protein. This demonstrates that modifications of histone H3 can help control the cell's RNA splicing decisions, influencing the nature and function of the proteins produced by genes.

Although alternative splicing, a form of RNA modification that can result in the synthesis of different proteins, was discovered several years ago its regulatory basis has remained largely unknown. The finding represents a crucial step forward towards a better understanding of the mechanisms that lead from gene to protein, and may enable us to correct problems occurring during this process that lead to disease.

The cells in the intestine are produced by stem cells. Here, the groups of cells shown in red, yellow or green are derived from a single stem cell.

RESEARCH UNITS

STEM CELLS - A DELICATE BALANCING ACT

In a healthy body, tissue integrity depends on a series of delicate judgment calls on the part of stem cells. These cells must strike a balance between their differentiation into tissue specific cells allowing maintenance and repair, and their proliferation allowing maintenance of a sufficient stock of stem cells. A team led by François Schweisguth, Director of the Drosophila Developmental Genetics Unit, has identified part of the mechanism responsible for this tricky balancing act in the epithelial tissue of the fly intestine. Given that these mechanisms have been well preserved in most species, it is highly likely that the situation is similar in humans.

The scientists showed that the activation level of a signaling pathway, the Notch pathway, regulates the future development

of stem cells. High Notch activation results in stem cells differentiating into epithelial tissue cells in the intestine, whilst Notch inhibition preserves stem cell identity.

As the Notch pathway is involved in several other cell functions its activity level can vary, so it is important that the activation threshold for stem cell differentiation is high enough to avoid accidental differentiation. This previously unknown protective role of the Notch activation threshold adds an important dimension to our understanding of stem cells and of the vital role played by Notch in cell life.

REVIVE

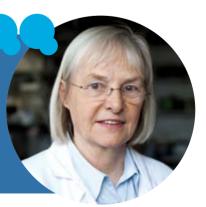
The Developmental Biology Department recently received substantial funding from the French government initiative Investing in the Future to develop and coordinate the REVIVE laboratory of excellence (LabEx).

This project has huge scientific and medical potential. It will initially aim to coordinate stem cell research groups at the Institut Pasteur (where 14 units are currently involved) and in the greater Paris region* to create a dynamic interactive network. This core of high-level experts will stimulate information exchange and knowledge creation, while attracting other international researchers.

Recruitment will be one of the major focuses and key areas for this LabEx. The funds allocated to the project will be used to support four new research teams at the Institut Pasteur – two five-year groups and two units for experienced researchers – as well as to recruit PhD students and post-doctoral researchers.

REVIVE's long-term ambition is to establish the Institut Pasteur and the greater Paris region as key international reference centers for research into stem cells, regenerative medicine and aging. These research areas are increasingly important and are seen as essential for biomedicine where they are opening up innovative possibilities for tissue regeneration and the identification of drug candidates that are expected to lead to new therapies in the years ahead.

* Partner research centers: CNRS, Inserm, ENVA, INRA, Pierre and Marie Curie University (Paris VI). Partner hospitals: Necker Hospital, Georges Pompidou Hospital, Pitié-Salpêtrière Hospital. Industry partners: Axenis, Cellectis, Diagenode, Roche, Sanofi.



Distinction

The research carried out by Margaret Buckingham from the Molecular Genetics of Development Unit has shed new light on the genetic regulation underlying the behavior of muscle stem cells and the origin of the cells that form the heart. In 2011, her research contributions were acknowledged by her nomination as a Foreign Associate of the US National Academy of Sciences. "This distinction is good news as it reflects the appreciation of the international scientific community for all the work carried out at the Institut Pasteur," commented modestly Margaret Buckingham.

STRUCTURAL BIOLOGY AND CHEMISTRY

β² R546 V0 K587 K531 Clun2A16

> Structures of a complex formed by an enzyme domain (in light blue) and a peptide (in dark blue) that may inhibit its anti-apoptotic activity.

This department primarily studies the structure and properties of molecules of biological interest, particularly when it comes to human disease. Identifying links between the structure and function of these molecules is essential for developing new therapeutic strategies.

The Structural Biology and Chemistry Department studies the three-dimensional structure of molecules in order 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. The department uses and develops cutting-edge technologies such as:

• molecular modeling, which plays a key role in determining and manipulating structures;

• crystallography, which displays the 3D structure of a molecule and is used to carry out drug-design studies on potential targets;

• nuclear magnetic resonance (NMR), which provides access to the structure of smaller molecules and reveals information about their movements and the molecular interactions being studied;

• ultrastructural microscopy, which is used to obtain highly detailed images of complex biological structures.

The department combines structural approaches with 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.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

MOLECULAR AND STRUCTURAL BIOLOGY OF BACTERIAL TRANSFORMATION

Europe is constantly seeking to encourage its young researchers. In 2011, it rewarded the excellent work of Rémi Fronzes and his five-year group Structural Biology of Bacterial Secretion with an ERC* Starting Grant of \in 1.4 million over five years.

This funding will make it possible for the group to decipher the transformation mechanism that some bacteria use to acquire new genes by "importing" DNA from their environment. The exogenous DNA fragment binds to a multiprotein complex on the bacterial surface before crossing the bacterial cell wall. Once inside the cell, it is incorporated into the cell's DNA and is expressed, thereby giving the bacteria new characteristics. These can represent an advantage for the bacteria, such as genes that confer resistance to antibiotics, or a disadvantage, leading to cell death.

The protein complex that binds the DNA and enables it to cross the wall is highly conserved between bacteria, but we still know little about how it works. The researchers will use highresolution electron microscopy and X-ray crystallography techniques to determine its precise structure and function at the molecular level. A series of complex steps is required for a large hydrophilic molecule such as DNA to pass through a lipid membrane.

This research will shed light on lesser known aspects of microbiology and could pave the way for longer-term applications.

* European Research Council.

A BAYESIAN FRAMEWORK FOR STRUCTURAL CELL BIOLOGY

Structural analysis technologies for molecules or larger complexes are on the rise, bringing with them a range of results that vary in terms of relevance and reliability. Although it is very difficult to compare the results of an analysis using crystallography with those using spectrometry or electron microscopy, the different sources of information can be complementary and mutually informative.

Michael Nilges has been awarded an ERC* Advanced Grant to develop software used to link the data from these different structural analysis techniques. This project, conducted within the Structural Bioinformatics Unit, chiefly aims to aggregate the assorted results to identify the precise structure of large protein complexes, while also devising reliability indexes for the various data used and for the overall structure pieced together from this data. These indexes are very important since each method of analysis has its own degree of bias. Individual reliability must therefore be ascertained to determine to what degree the overall structure is realistic.

This project meets the demands associated with the rapid growth of structural biology, and its results will find a wide range of applications in many areas of the life sciences.

* European Research Council.

CENTER FOR THE ANALYSIS OF COMPLEX SYSTEMS IN COMPLEX ENVIRONMENTS

The Institut Pasteur* is coordinating the CACSICE project, the Center for the Analysis of Complex Systems in Complex Environments, in cooperation with the Institut de Biologie Physico-Chimique (Physical and Chemical Biology Institute), Paris V and Paris VI Universities. This enigmatic title conceals a truly innovative project that has received 7.5 million of EquipEx funding under the 2011 Investing in the Future program.

The project aims to create a structural biology analysis platform that will include a vast range of equipment such as electron microscopy, X-ray crystallography, liquid- and solid-state nuclear magnetic resonance (NMR), small-angle X-ray scattering and structural mass spectrometry.

Researchers are increasingly coming across complexes containing several molecules whose complete structures are

very difficult or impossible to determine using just one analysis method. It is therefore crucial for scientists to have access to a wide range of analysis methods in order to compare data and reconstruct the 3D image of all the parts of a complex. This platform will also be used to observe molecular mechanisms in their natural environment, in other words in the cell or in a complex constructed environment.

This cutting-edge facility will provide French laboratories with the possibility of performing research that currently has to be carried out abroad, and will firmly position the Institut Pasteur and the Paris region as major centers for structural biology.

* Five Institut Pasteur departments are involved in the establishment of CACSICE.



GENOMES AND GENETICS

With the continual discovery of new genes revealing new biological functions, genetics raises numerous issues 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 body and microorganisms such as yeast and bacteria. The genomes of the tuberculosis bacilli, *Streptococci, Vibrio, Legionella* and other pathogenic bacteria and models are studied in depth with the aim of understanding how they live and what determines their pathogenic nature. Yeasts are also studied, both for their own properties and as models to help us understand human genetics.

The department is also investigating the evolution of infectious agents and the selective pressures they have exerted on human genes over time. The progress of these research programs benefits greatly from developments in new sequencing and genotyping techniques.

TECHNOLOGICAL PLATFORMS

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

GENETIC DIVERSITY AND PHARMACOPEIA

Mycobacterium

image).

tuberculosis, the tuberculosis agent, in scanning electron microscopy (colored

Interferons (IFNs) are proteins that help stimulate our natural defenses. There are three types that differ according to function and genetic variability. A team of researchers led by Lluis Quintana-Murci, Director of the Human Evolutionary Genetics Unit*, used population genetics to identify the interferons that appear to be essential for our survival and those that play a secondary role.

The members of the type I IFN family are genetically heterogeneous. Some are highly conserved, demonstrating the essential role they play in our survival, while the genetic diversity of others reveals considerable immunological redundancy.

The single type II IFN, on the other hand, does not contain mutations from one individual to another. This high degree of stability indicates an extremely specific, irreplaceable function, particularly in the immune response to mycobacteria. The type III IFN family harbors specific characteristics depending on geographical origin: populations with European and Asian origins have various mutations that have made them more adaptable, probably as a result of selective pressures exerted by viruses.

These results strengthen the case for a more precise, targeted medical use of interferons. For example, IFN-alpha2, which is used in the treatment of chronic hepatitis C and some cancers, has side effects. Identifying a subtype of type I IFN with a more targeted action mechanism might avoid this problem. These results need to be confirmed before clinical application but should help to expand the therapeutic arsenal against an array of diseases such as hepatitis C, multiple sclerosis and various cancers.

* Joint Institut Pasteur-CNRS unit.



RESEARCH UNITS

TUBERCULOSIS AND VIRULENCE FACTORS

Mycobacterium tuberculosis is the pathogenic bacterium responsible for tuberculosis. The bacillus is still responsible for more than 1.5 million deaths every year across the world and for the emergence of 8 million new cases. This virulence intrigues scientists, who are comparing the different members of the *Mycobacterium* genus to identify the factors behind such extreme pathogenicity.

Roland Brosch, Director of the Integrated Mycobacterial Pathogenomics Unit, is studying protein secretion systems in this bacterium, focusing on one in particular, known as ESX-1, whose proteins appear to play a role in this virulence. The researchers in his team have demonstrated that suppressing the genes of this secretion system reduces the virulence of the bacillus. It even appears that the absence of this system in the attenuated Calmette-Guérin strain of the bacillus (more commonly known as BCG), used to vaccinate children against tuberculosis, is what makes it innocuous.

The unit is now working to elucidate the true role of the proteins produced by this secretion mechanism, how they interact with each other and how they stimulate the action of the immune system, particularly T lymphocytes. This research will help further our understanding of the weaknesses of the BCG and improve the quality of tuberculosis vaccine candidates.

NEW UNITS

Two new teams were created in the Genomes and Genetics Department in 2011. The first, the Functional Genetics of Infectious Diseases Unit, directed by Anavaj Sakuntabhai, is focusing on the genetic bases of susceptibility to two major human infectious diseases transmitted by mosquitoes: malaria and dengue. The aim is to identify new genes that control different aspects of these diseases (clinical manifestations, transmissibility, etc.) in infected patients, and also to understand the role these genes play in the development of the diseases. The five-year group Spatial Regulation of Genomes, directed by Romain Koszul, is studying the organization of chromosomes in the nucleus, how this spatial arrangement influences the metabolic processes of DNA (replication, repair, etc.) and what the consequences are for genome stability. This team is mainly working on *Saccharomyces cerevisiae* (baker's yeast) and related species. Their approach involves the expertise of mathematicians and physicists and uses two genetic methods, high-throughput sequencing and quantitative imaging. The mechanisms observed, correlated with those observed in mammals, should shed new light on various processes in tumorigenesis.

Bioinformatics

The Institut Pasteur organized the 12th edition of the JOBIM conference (*Journées* ouvertes en biologie, informatique et mathématiques), the annual event for the French-speaking bioinformatics community, held under the auspices of the French Bioinformatics Society (SFBI). The 2011 edition had 450 delegates. "*JOBIM covers themes* relating to the entire bioinformatics spectrum in a broad sense. This includes upstream aspects relating to methodology – mathematical modeling, computing, statistics and physics –, software tools and more applied contributions, and the achievement of new results in the field of biology," explains Ivan Moszer, Director of the Genomic Bioanalysis Platform at the Institut Pasteur.





The Immunology Department's research focuses on the development and regulation of the immune system, as well as protective and pathological immune responses.

The work of the Immunology Department can be divided into three main research areas:

• Immune system development: 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. Research teams are studying these responses, the cells responsible and their interactions;

• Immune response and pathology: Some teams are studying ways to enhance protective, anti-infectious and anti-cancer immunity; others are focusing on ways to fight immune disorders such as allergy or autoimmune diseases.

The laboratories of excellence (LabEx) project submitted by the department, and funded as part of the French government's Investing in the Future program was awarded this past academic year. This ten-year project aims to define the Milieu Intérieur ("Environment Within"), by identifying the genetic and environmental factors that influence variability of the immune response among human populations.



RESEARCH UNITS

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

LYMPHOCYTE DEVELOPMENT AND ONCOGENESIS

The fragmentation <u>of the nucleus</u> (in blue)

and the deterioration

red) reflect the effects of mycolactone produced by Mycobacterium ulcerans (in green) in infected

of the cell skeleton (in

cells.

Ludovic Deriano officially joined the Institut Pasteur from the United States in autumn 2011, to create the five-year group Lymphocyte Development and Oncogenesis. His research project aims to define the mechanisms involved in genome stability and oncogenesis.

Lymphocytes, cells in our immune system, naturally rearrange some sections of their DNA to produce suitable receptors or antibodies to tackle the many pathogens they defend us against. This recombination or "cut and paste" process, which is normally so beneficial to us, can sometimes go wrong and create potentially cancerous genomic abnormalities. Ludovic Deriano and his team will use genetically modified mouse models to study the mechanisms at work in these genetic recombinations, whether beneficial or harmful. The results will then be used to determine the stages through which lymphocytes acquire genomic abnormalities and then become cancerous. The team hopes to identify markers that could pinpoint this risk at an early stage so that early diagnostic tests can be developed and potentially promising therapeutic targets can be explored.

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TECHNOLOGICAL PLATFORMS

TOXINS - DR. JEKYLL AND MR. HYDE

The toxin mycolactone, secreted by the bacterium *Mycobacterium ulcerans*, causes debilitating cutaneous ulcers that are difficult to treat. This feature represents its Mr. Hyde side. Researchers in the Immunobiology of Infection Unit led by Caroline Demangel have successfully described a highly original mechanism used by this molecule to enable the bacterium to escape the immune system.

Mycolactone inhibits the expression of L-selectin, a receptor normally found on the surface of T lymphocytes – those cells in the immune system that play a key role in eliminating pathogens. This receptor normally guides T lymphocytes as they circulate in the body, particularly pointing them towards the lymph nodes, where they come into contact with sentinel cells, sounding the alert that pathogens are present. By preventing this meeting of T lymphocytes and sentinel cells, mycolactone stops the immune system from recognizing and combating the invader.

This immunosuppressive mechanism developed by *M. ulcerans* makes mycolactone an extremely dangerous Mr. Hyde. But it can potentially turn into Dr. Jekyll and be a powerful therapeutic ally. Recent research carried out in the same unit shows that synthetic molecules inspired by mycolactone could help control excessive responses of the immune system, such as observed in autoimmune diseases.

"HUMANIZED" MICE

In a bid to overcome the limitations of conventional mouse models, researchers in the Innate Immunity Unit directed by James Di Santo have "humanized" their mice by transplanting them with human cells. Using mutant mice created in the laboratory, they obtained animals that can host a human immune system, and more recently they created a strain whose liver can be partly made up of human cells. These "humanized" mice represent much more than simply an ingenious feat of science: they offer vast potential for therapeutic research.

They were used in an innovative collaborative research project published in October 2011 in *Nature*. Researchers from the University of Cambridge and the Sanger Institute first took samples of skin cells from patients suffering from a genetic liver disease; they then placed the cells in culture to remove their specificity and give them the properties of pluripotent stem cells. Next they used genetic engineering to correct the mutation responsible for the disease, and finally they programmed these now "healthy" stem cells to differentiate into human liver cells again.

Institut Pasteur researchers tested these human liver cells on their animal model, obtaining chimeric mice with a humanized liver and thereby proving that the human cells were perfectly functional.

"Humanized" mice could also play an invaluable role in other research projects. Researchers have developed models that combine an immune system with a humanized liver to test new therapies for liver diseases such as hepatitis B and C.

Allergies

Allergies are paradoxical reactions of the immune system to substances as harmless as pollen, cat fur or even food, which make sufferers ill rather than protect them. In their attempts to explain the workings of allergies, immunologists have looked beyond the protective immune reaction to other mechanisms. But the work of Marc Daëron, Director of the Molecular and Cellular Allergology Unit, and his team have shown that this is the wrong approach. Their research demonstrates that the same antibodies and cells are involved but they are tightly controlled, and it is the efficacy of this control that determines whether the response is protective or pathogenic. These results suggest new treatments for these conditions, which are becoming increasingly common and severe.



INFECTION AND EPIDEMIOLOGY

In 2011, the Infection and Epidemiology Department was actively involved in efforts to tackle the *E. coli* crisis that hit Europe, via its *E. coli* CNR*. This event illustrates the wide range of activities and research carried out by the department.

The Infection and Epidemiology Department studies all aspects of infectious diseases: reservoirs and transmission mechanisms of pathogens, virulence factors, physiopathological processes of the host, the innate immune response and the role of vaccines. Its work involves several disciplines, including immunology, epidemiology, bacteriology and virology. The department recognizes the importance of staying in touch with clinical reality; it conducts a number of clinical and epidemiological studies with hospitals so that its research can be successfully applied to humans. The department is also closely involved in public health: it has several units specializing in epidemiological risks and hosts nine National Reference Centers and three WHO Collaborating Centers. The Laboratory for Urgent Response to Biological Threats (CIBU), in collaboration with the Genotyping of Pathogens and Public Health Platform, provides an emergency response to potential epidemics.

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

MULTI-ANTIBIOTIC RESISTANT SALMONELLA

T. vivax parasite during its non-infectious stage. fl: flagellum. k: kinet<u>oplast.</u>

n: nucleus.

Salmonella bacteria represent one of the primary causes of foodborne infections in humans. As early as 2002 the Salmonella CNR* at the Institut Pasteur, in collaboration with the InVS**, detected the emergence of a type of salmonella affecting a small number of travelers returning from Egypt, Kenya and Tanzania. The bacteria, known as Kentucky Salmonella, showed resistance to numerous antibiotics, notably fluoroquinolones, currently one of the key treatments in severe Salmonella infections.

As part of a large-scale international study, researchers at the Institut Pasteur, INRA and the InVS, under the supervision of François-Xavier Weill, traced the evolution of the bacteria over the last 50 years. This has enabled them to establish a timeline of the emergence of the different forms of resistance and to unravel the various resistance mechanisms. They have identified poultry as the main vector of the strain. Their observations indicate that Egypt could be the geographical birthplace of antibiotic resistance. But today in over 10% of cases the patients have not traveled abroad. This suggests that the bacteria are beginning to take root in Europe.

The results of this study underline the importance of microbiological monitoring at international level, in particular for countries in the southern hemisphere. They are a reminder of the public health risks of non-regulated use of antibiotics in the farming industry, which promotes the emergence and spread of resistant genes in bacteria responsible for foodborne infections.

* National Reference Center.

** French Institute for Public Health Surveillance.

DECIPHERING CRYPTOCOCCOSIS

Cryptococcosis is a severe infection caused by the yeast Cryptococcus neoformans. It mainly affects immunodeficient patients such as patients with AIDS. France remains relatively unaffected because it offers access to triple therapy for HIV patients, but there are an estimated one million cases of cryptococcosis in the world each year and around 600,000 deaths, mostly in sub-Saharan Africa and Southeast Asia.

Most studies on immunity to C. neoformans are based on reference strains rather than clinical isolates of the fungus. The Molecular Mycology Unit directed by Francoise Dromer, however, based its research on clinical data and strains collected in a national multicenter study set up in 1997. This decision was based on the hypothesis that the diversity of clinical strains is partly responsible for the diversity in clinical presentation and in the evolution of disease observed in patients. By developing a model for the interactions between a macrophage cell line and clinical isolates, researchers were able to demonstrate that strains from patients whose infection had evolved unfavorably behaved differently within the macrophages from those from patients whose treatment had proved successful.

These findings are the first proof that the infection's evolution is influenced by factors related to the fungus and not just the patient. The scientists now hope to find other prognostic markers that could help target treatment more effectively.

TOOLBOX

Sleeping sickness, spread by the famous tsetse fly, is not exclusive to humans; pets and livestock are also at risk. In the African and Latin American countries where it is rife, this disease, known as nagana, is at the root of major economic and food-related problems - depriving farmers of traction power and decimating animal holdings.

The disease is caused by a parasite, *Trypanosoma vivax*, from the same genus as the parasite responsible for the human form.

But unlike its human counterpart, research into T. vivax is limited, due to the lack of specific molecular biology and genetic engineering analysis tools.

That is, until now. The team led by Paola Minoprio from the Trypanosoma Infectious Processes Laboratory has developed an innovative protocol enabling researchers to study the parasite

from all angles. Using the field strain, the scientists created an experimental in vivo model where the immune response and pathology induced in the host were similar to those of infected animals. This was followed by an *in vitro* study protocol allowing them to culture all the forms of the parasite and differentiate between infectious and non-infectious strains, a key step in understanding the parasite's life cycle and how the disease develops and progresses. They also designed the first suitable vector for genetically modifying the parasite which will enable them to analyze its genome and characteristics.

Researchers are now able to focus on a very specific protein in the parasite, proline racemase, which seems to play a key role in the parasite's differentiation into an infectious form and its ability to escape immune responses.





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

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

Archaea are a third domain of life, distinct from bacteria and eukaryotes. Here we see a single-celled microorganism from this domain infected by a virus.

BIOLOGICAL RESOURCE CENTER

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

A NICKEL A DAY...

Helicobacter pylori is a bacterium responsible for 10% of all peptic ulcers and 1 to 3% of gastric cancers. While it is more prevalent in poorer areas and generally remains asymptomatic, it still infects half the world's population. Found in the stomach, *H. pylori* relies on urease, a specific enzyme requiring nickel to function, to resist the acidic environment.

For this reason, the bacterium has a highly sensitive regulator, known as NikR, to ensure sufficient nickel uptake to meet requirements but not so much that it becomes toxic. By detecting concentrations of nickel in the cell the regulator then activates or represses the cell's uptake, transport, storage, distribution and assimilation of nickel. However, under the direction of Hilde de Reuse, researchers in the *Helicobacter* Pathogenesis Unit have now demonstrated that there are different degrees of regulation. For example, as the concentration of nickel increases, and without becoming toxic, the bacteria are able to store reserves for use at a later date. If the concentration increases still further and exceeds a given toxicity level, the bacteria reduce their synthesis of transporter proteins, thereby reducing the uptake of nickel in the cell.

This study reveals a gradual, temporal regulation that is dependent on the concentration of nickel and provides a response tailored to the needs of the cell. It will help improve understanding of the action mechanisms in bismuth based treatments for *H. pylori*. This work also unveils new possibilities for therapeutic targets, namely the nickel storage and transport mechanisms vital for the bacteria's survival.



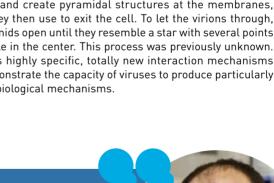
A WHIFF OF FRESH AMMONIA

While we already know a great deal about bacteria's production of volatile, sometimes odorous compounds, the biological role of these molecules in interactions between bacteria remains relatively unexplored. Although several studies have demonstrated the influence of bacterial volatile compounds on organisms ranging from plants, to fungi, to nematode worms, only one study focusing on the Escherichia coli bacterium suggests that an unknown volatile compound emitted by this bacterium could alter the resistance of organisms to ampicillin and tetracycline. The Genetics of Biofilms Unit directed by Jean-Marc Ghigo went even further, demonstrating that the ammonia released by E. coli is responsible for modifying antibiotic resistance in all bacteria exposed to it, including Pseudomonas

aeruginosa, Staphylococcus aureus and Bacillus subtilis. The researchers demonstrated in *E. coli* that ammonia released by the degradation of an amino acid, aspartate, alters the permeability of the membrane wall in bacteria exposed to it. leading to increased resistance to some antibiotics. This study therefore demonstrates one of the first volatile chemical signals to remotely alter the physiology of recipient bacteria. The authors suggest that other bacterial volatile compounds could also play an important biological role in complex environments (such as soils, intestines or biofilms) where volatile molecules appear to represent excellent communication signals between physically separate bacteria.

UNPRECEDENTED

Unlike bacteria and eukaryotes (organisms including human beings whose genome is protected by a nucleus), archaea, microorganisms that represent a third domain of life, remain relatively unexplored. The same is true of the viruses that infect them as so far their characteristics have undergone very little analysis. Yet studying these microorganisms in terms of their evolution or their role in the biosphere can help us understand the biological laws that govern some ecosystems. Some archaea and their viruses thrive in volcanic ecosystems and can live at temperatures higher than those withstood by bacteria and eukaryotes. These atypical viruses whose forms and genomes are guite unlike anything scientists had previously encountered. have been the focus of David Prangishvili's team in the Molecular Biology of the Gene in Extremophiles Unit. The researchers discovered that they have a very unusual means of exiting the infected cell: after they enter the cell, the virus particles (virions) multiply and create pyramidal structures at the membranes. which they then use to exit the cell. To let the virions through, the pyramids open until they resemble a star with several points and a hole in the center. This process was previously unknown. It reveals highly specific, totally new interaction mechanisms that demonstrate the capacity of viruses to produce particularly original biological mechanisms.



The Biology and Genetics of the Bacterial Cell Wall Group run by Ivo G. Boneca studies the bacterial cell wall, whose role is essential to bacterial survival. Research focuses on the molecular mechanisms involved in its biosynthesis and its role in the interactions between bacteria and hosts (particularly humans). Several antibiotics specifically target the bacterial cell wall. "Today, given the increase in resistance to these drugs and the difficulties in developing new molecules, other therapeutic strategies are needed," explains lvo G. Boneca. "In view of this, we are using the Helicobacter pylori bacterium, responsible for stomach ulcers and cancers, as a research model for the bacterial cell wall biosynthesis pathway." In 2011, this work earned Ivo G. Boneca the Pasteur Vallery-Radot Prize, awarded by the National Library of France. This prize was shared with Philippe Bousso, Director of the Dynamics of Immune Responses Unit.



The Neuroscience Department is committed to unraveling the mechanisms of the nervous system in molecules, cells, synapses and neuronal circuits. This fundamental research has been at the core of numerous significant therapeutic breakthroughs.

Several of the department's teams defined their research areas while carrying out genetic studies of poorly understood human pathologies such as deafness, autism and addictions. The molecules identified today provide a starting point for understanding the intricate workings of the molecular assemblies responsible for complex functions in nerve cells or sensory cells, as well as the development of these assemblies over time to ensure the plasticity of the nervous system and its adaptation to the environment.

Better understanding adaptability is one of the department's main objectives. This may be the physical adaptability of a chemical receptor, the cell skeleton, a synapse or neural network or a newly formed neuronal population, or the adaptability of a child's behavior towards the environment.

In recent years, the department has benefited from a dynamic imaging platform which enables researchers to view neuronal structures and mechanisms and study the links between structure and function in more detail.

RESEARCH UNITS

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

THE FIRST HUMAN MODEL FOR STUDYING SANFILIPPO SYNDROME

A team of researchers directed by Delphine Bohl from the Retrovirus and Genetic Transfer Unit has developed the first human neuron model for studying Sanfilippo syndrome. This discovery opens up highly innovative possibilities for fundamental and therapeutic research.

The structure of

a bacterial receptor

GABAA receptor (in very light blue) to which a general anesthetic is bound (the green molecule in the center).

homologous to the

This two-part technology begins with scientists reprogramming patient skin cells to obtain what are known as "induced pluripotent" stem cells, these same cells are then programmed to differentiate into neurons. Analyses have shown that neurons obtained using this method develop cellular defects characteristic of Sanfilippo syndrome and are therefore excellent research models. Sanfilippo syndrome is caused by a genetic mutation that results in the abnormal accumulation of mucopolysaccharides in several tissues in the body. There is currently no treatment for patients with this disease which leads to serious mental retardation and has a life expectancy of less than 30 years.

The new model will help unveil the mechanisms of this devastating disease and could lead to identifying potential therapeutic targets. The technology may also be used to create models for studying other neurodegenerative diseases, thereby furthering research in other fields.

3D STRUCTURE FOR THE ACTION SITES OF TWO GENERAL ANESTHETICS IDENTIFIED

Researchers from the Channel Receptors Group and the Structural Dynamics of Macromolecules Unit, directed respectively by Pierre-Jean Corringer and Marc Delarue, have determined the 3D structure of two general anesthetics, propofol and desflurane, in complex with a bacterial receptor homologous to the GABAA receptor.

The GABAA receptor relays most inhibitory nerve impulses in humans and is the main target of general anesthetics, forming a channel across the cell membrane. By analyzing receptor/ anesthetic complexes using X-ray diffraction, scientists were able to determine their structure with atomic resolution, and even identify the precise binding sites for the anesthetic in the receptor. This demonstrated that propofol and desflurane bind precisely to the external surface of the receptor channel. The scientists also observed how binding site structure changes could alter the anesthetic's effect.

This study is the first to demonstrate exactly how general anesthetics work by using structural elements in high resolution. Although these molecules have revolutionized medicine over the last two centuries, their action mechanism remains unclear. These findings help improve our understanding while paving the way for the design and development of new, more specific molecules with fewer side effects.

A NEW HEARING-RELATED MECHANISM

How does the ear transform the acoustic – mechanical – waves that it picks up into an electric current that can be interpreted by the brain? The search for an answer to this all-important question continues, but researchers from the Genetics & Physiology of Hearing Unit, directed by Christine Petit, have solved a large piece of the puzzle.

The mechanoelectrical transduction of the signal takes place in the ear's sensory cells within structures that resemble cilia and are known as stereocilia. These are organized into three rows, each one bigger than the next. The stereocilia are linked to the larger stereocilia in the next row by filamentous "tip links". The tension exerted on these filaments when the acoustic wave passes through generates an electric current, which is then transformed into a nerve impulse relayed by the auditory nerve to the auditory centers.

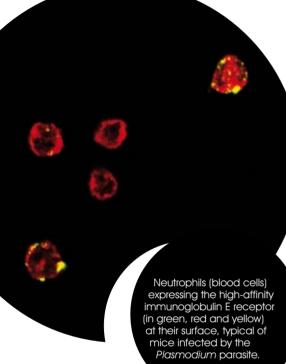
The researchers demonstrated that the intracellular protein known as Sans forms a complex with the constitutive proteins of tip links. By inhibiting the gene that codes for Sans in mice, researchers found that the amplitude of the transduced electrical signal was reduced, the characteristic oblong form of the stereocilia tips was lost and the stereocilia were smaller in size. Identifying this link between mechanoelectrical transduction and the architecture of stereocilia paves the way to further research on the relationship between these two functions, a key step towards the development of reparative strategies for stereocilia, the main target of hearing disorders.



Imaging

The dynamic two-photon imaging and photostimulation platform became fully operational in 2011, enabling researchers to observe living neurons in their natural environment. "*This cutting-edge facility will enable us to conduct more detailed research into synaptic communication in a neural network*," explains David DiGregorio, the platform director. Impaired communication between neurons is believed to be responsible for diseases associated with memory loss such as Alzheimer's disease or autism. The dynamic study of these processes is therefore vital to help us shed light on how the brain functions in both its normal and pathological states.

PARASITOLOGY AND MYCOLOGY



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

The department focuses its research on three key eukaryotic parasites responsible for severe diseases of major burden in developing countries, in terms of both health and economic impact: *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 that can be fatal in immunodeficient 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 vaccine trials. Novel experimental models and tools are developed to help understand the dynamic interactions between these microorganisms and their hosts, identify the fundamental bases of parasitism and transmission by vectors, reveal host invasion mechanisms, and determine the virulence factors and survival strategies of these organisms.



RESEARCH UNITS

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

CEREBRAL MALARIA

Cerebral malaria is an extremely severe form of malaria primarily affecting children under five years of age. The disease causes high fever and convulsions followed by coma and, in nonfatal cases, severe neurological sequelae.

A team led by Salah Mécheri from the Biology of Host-Parasite Interactions Unit* examined how cerebral malaria occurs in brains with poorly controlled immune responses. The researchers demonstrated that the development of cerebral malaria is not directly caused by the parasite developing inside the red blood cell but rather originates from an allergy-like mechanism causing inflammation. In mice models that mimic the human disease, researchers showed that the parasite induced the production of an antibody receptor for immunoglobulin E (IgE), essential for the allergic reaction, on specific types of white blood cells called neutrophils. Neutrophils are immune system cells that generally lack this receptor. The induced IgE/receptor complex triggers a series of inflammatory reactions that cause cerebral malaria.

This study sheds new light on the way experimental cerebral malaria is understood. Researchers are now focusing on identifying whether or not these neutrophils and the described mechanisms are present in humans, a finding that would be an important step towards a potential therapeutic target. Antiallergy treatments directed against IgE receptors to prevent allergic reactions in certain individuals could then be used as a preventive treatment against cerebral malaria.

* A study by the Institut Pasteur and the CNRS, in collaboration with Inserm and Paris Diderot University.



UNEXPECTED BEHAVIOR

Field studies examining how *Anopheles gambiae* mosquitoes spread malaria had previously been based on the theory that people are mainly bitten in their homes at night. So the insect vectors were collected in villages, inside houses. Kenneth Vernick, Director of the Genetics and Genomics of Insect Vectors Unit*, and his teams worked on the basis that the mosquitoes collected represented only part of all *A. gambiae* populations. Previously collected samples only contained mosquitoes that remained inside after biting their prey, and not those that entered homes in search of a meal and left once they had finished or those that never entered homes at all.

As part of a vast project in Burkina Faso to map the genes controlling susceptibility to the malaria parasite in *A. gambiae*, scientists worked for four years over a stretch of more than 400km across the country, taking samples of adult insects and larvae in domestic and peridomestic areas, both inside and outside homes. The researchers discovered a new subpopulation of *A. gambiae*, never previously described, that represents over half the mosquito samples taken. These mosquitoes, termed *A. gambiae Goundry*, have proven to be highly susceptible to malaria, that is, the disease develops effectively in them and they are particularly good at spreading it.

This surprising discovery may partly explain why the current vector control strategies, applied in homes, are not successfully reducing the spread of malaria to humans. It emphasizes how important it is to rethink the strategies adopted to control this disease, taking into account mosquito behavior so that all vector insects can be effectively targeted.

* Institut Pasteur-CNRS Unit URA 3012, in cooperation with the National Center for Research and Training on Malaria (Ouagadougou, Burkina Faso), the University of Minnesota (United States) and Harvard University (United States).

DIFFERENTIATION

Human African trypanosomiasis, better known as sleeping sickness, is a parasitic disease spread to humans through the bite of the tsetse fly. This disease, which is fatal if left untreated, threatens almost a million people in Sub-Saharan Africa, mainly in rural populations. To shed light on the different stages by which the parasite is transmitted to humans, the team from the Trypanosome Cell Biology Unit, directed by Philippe Bastin, focuses on how it develops in infected flies. In these insect vectors, the parasite moves from the mid-intestine to the salivary glands, where it can be transmitted to humans through the insect's bite when it takes its blood meal. This means that the parasite must adapt to different environments and undergoes morphological and biochemical changes. Philippe Bastin's team identified a new family of proteins known as ALBA that plays a key role in all stages of development. The scientists observed that inhibiting these proteins at the mid-intestine stage results in only partial differentiation to the following stage, in the anterior intestine, and that forced expression at the anterior intestine stage considerably slows down the parasite's ability to reach the salivary glands. This important discovery sheds light on the parasite's development until it reaches the fly's salivary glands, and will help researchers identify the mechanism that transforms it from a non-infectious form (in the intestine) to an infectious form (in the salivary glands).



Leishmaniasis

The department is also involved in studying so-called neglected parasite diseases such as leishmaniasis, which affects some 12 million people across the world, according to WHO. A group known as LeishRIIP has been set up, coordinated by the new Molecular Parasitology and Signaling Unit directed by Gerald Späth, to improve dialog between the different institutes of the Institut Pasteur International Network (RIIP). "LeishRIIP aims to identify synergies and complementarities between individual projects and to improve competitiveness in terms of national and international funding," explains Gerald Späth. LeishRIIP currently covers nine institutes and involves 16 laboratories.



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

The department's 19 units focus their research on viruses, examining their molecular organization, interactions with their host and pathogenicity determinants. The viruses studied include arboviruses, transmitted by insects and responsible for severe diseases such as dengue ("tropical flu"), yellow fever and Rift Valley fever; retroviruses such as HIV and HTLV; respiratory (flu), enteric (polio), neurotropic (rabies) viruses; and viruses that cause cancer such as human papillomavirus or hepatitis B or C.

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 Virology Department also hosts four of the 15 National Reference Centers and WHO Collaborating Centers, thereby playing a major role in the epidemiological monitoring of infectious diseases.

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RESEARCH UNITS

FOCUS ON 3 SIGNIFICANT HIGHLIGHTS

NO PARKING

Those rare individuals infected by HIV-1 (fewer than 1% of HIVpositive patients) have been controlling the virus for years. These patients, known as "HIV controllers", are HIV positive and were infected over 10 years ago but have no detectable virus in their plasma. They are able to contain the infection naturally without treatment and don't go on to develop clinical AIDS.

AIDS virus particles at the surface of a lymphocyte.

The team led by Gianfranco Pancino in the Regulation of Retroviral Infections Unit focuses on understanding the mechanisms that enable these patients to keep the virus under strict control. This team had already shown in previous research that these patients' T8 killer cells are capable of effectively eliminating infected T4 cells. Recently, researchers have demonstrated another viral control mechanism. They have shown that in these patients, T4 cells and macrophages – immunity cells that are the main targets of HIV-1 – block the virus as soon as it enters the cell and before it can inject its genetic material there. This effect limits the viral reservoirs that therapies are unable to eliminate. This is a major breakthrough in our understanding of HIV infection mechanisms, offering new possibilities for the development of preventive or vaccine-based therapies.

UNDER THE SPOTLIGHT

Understanding how viral proteins interact with host proteins is vital as it helps to identify the molecular mechanisms behind the pathogenicity of a virus and answers crucial questions, such as: How does the virus hijack the cell network? Which cell proteins are targeted? How is the network's spatial arrangement disrupted?

The current high-throughput analysis methods that can provide answers to these questions remain fairly unwieldy in experimental terms and their results face their own set of challenges. These genetic tests are performed on baker's yeast (*Saccharomyces cerevisiae*); in other words, in a cell model that is far removed from the infectious context. This methodology also generates a considerable number of false positives that may compromise the reliability of results.

The team led by Yves Jacob from the Genetics, Papillomavirus and Human Cancer Unit has developed a new method that can be used to test and directly validate interactions between viral and cell proteins in a human cell. Molecular interaction is indicated by the emission of blue light (480nm), and measured by quantifying the emitted photons.

In addition to offering practical benefits for researchers, this technique should help identify potential new targets for the development of therapeutic molecules that are capable of destabilizing or disabling pathogenic interactions.

THE RETURN OF THE INTERFERON

Interferons (IFNs) are essential proteins in the immune response. They are naturally produced by our body in response to viral infections. The hepatitis C virus (HCV) has developed different strategies to prevent production of these proteins, which is why the current therapy for HCV requires an exogenous source of IFN (combined with ribavirin, an antiviral molecule that stimulates both the immune response and, more recently, direct antiviral agents). Unfortunately there are major side effects including flu-like symptoms and hallucinations.

The team led by Eliane Meurs in the Hepacivirus and Innate Immunity Unit has recently discovered a new signaling pathway that is activated by HCV at the very early stages of infection (two hours after it enters the cell) to prevent IFN synthesis. To achieve this, HCV recruits the cell protein PKR to divert various elements of the IFN induction pathway to its own advantage. The researchers observed that by neutralizing a PKR domain they were able to relaunch interferon production.

This discovery opens up new therapeutic possibilities for hepatitis C treatment that could preserve a patient's intrinsic production of IFN by targeting PKR rather than using a combination of IFN treatments with significant adverse effects.

Pathodisc

Since 2009, the Pathodisc (Pathogen Discovery) program has focused on identifying pathogens responsible for diseases of unknown etiology but thought to be of infectious origin. "This program makes use of new very high-throughput sequencing methods that have vastly increased detection capabilities for new viruses directly from biological samples. It has made it possible to identify new viruses or viral genera in humans, such as the polyomavirus and the gyrovirus, and in animals, such as the pasivirus in pigs," explains program director Marc Eloit. Pathodisc is working in close collaboration with French hospitals and the Institut Pasteur International Network, particularly the Institut Pasteur and the recent start-up Pathoquest.



TECHNOLOGICAL PLATFORMS

With 13 technological platforms in three clusters, as well as the Central Animal Facility, the Mouse Genetics Engineering Center, and the Center for the Production and Infection of Anopheles, the Institut Pasteur ensures that its teams have all of the resources they need to perform cutting-edge research.

GENOPOLE

When it comes to microorganisms, humans, or anything in between, high-throughput sequencing has revolutionized the analysis of genetic information. Its capacity for large-scale genome sequencing and polymorphism characterization provides data for population genomics studies, sheds light on evolution, and enables epidemiological monitoring of pathogenic strains. Applications include characterizing microorganisms at specific stages to identify virulence factors and antibiotic resistance, and revealing the dynamics and 3D structures of genomes. Metagenomic and metatranscriptomic data mining paves the way for discovering new pathogens, particularly viruses, and helping prevent their emergence. Large-scale transcriptional analysis, which combines sequencing and DNA microarrays, has improved our understanding of how organisms function in a normal or pathological state. Researchers use it to address fundamental questions in microbiology and in the study of genetic and epigenetic programming during embryo development, in the generation and development of cancers, and during stem cell differentiation. A Eukaryote Genotyping Platform has also been set up to meet the needs of human and mouse geneticists. Another major part of this research focuses on analyzing data generated using computing techniques. The new Genomic Bioanalysis Platform works with the Center of Informatics for Biology and the other Genopole platforms to develop and implement computing methods that can be used to analyze and manage genomic and post-genomic data. At the Genopole, 34 researchers, engineers, and technicians with a wide variety of skills are involved in fundamental research and public health projects. All five Genopole platforms have received official accreditation from the GIS IBiSA (Scientific Interest Group–Infrastructure for Biology, Health and Agronomy) and are partners of France Génomique, the national infrastructure for biology and health.

PROTEOPOLE

The Proteopole (IBiSA-accredited since 2008) focuses its combination of high-level technological and methodological expertise on the analysis of macromolecules, and more specifically, proteins. Their wide range of work includes:

• protein production in microorganisms (prokaryotes/ eukaryotes), insect and mammal cells;

• production of monoclonal recombinant antibodies;

• protein identification and analysis using mass spectrometry and analytical chemistry;

• biophysical characterization at the molecular level: spectroscopy and hydrodynamics, surface plasmon resonance, and microcalorimetry;

• structural characterization at the atomic level, particularly using X-ray crystallography.

By leveraging synergies between different methods of analysis, the Proteopole can provide research teams with answers to vital questions as well as pinpoint new areas for analysis.

Its 32-member staff working in the four platforms provides a wide range of services. They are closely involved in a number of fundamental and methodological research projects in cooperation with Institut Pasteur units and other French or

foreign institutions, particularly in the field of structural biology of infectious diseases.

IMAGOPOLE

The Imagopole is a center dedicated to imaging research in the life sciences. Its four technological platforms (Dynamic Imaging, Ultrastructural Microscopy, Flow Cytometry, and the Center for Human Immunology) were officially accredited by IBiSA in 2009, and, together, have around forty imaging systems that are used 40,000 hours a year by around 500 scientists. The Imagopole is used by several hundred researchers at the Institut Pasteur and throughout France and, building on its international reputation, the center has fostered many close collaborations with research groups outside of France. The Imagopole has recently renewed its ISO 9001:2008 certification, which guarantees commitment to constantly improving quality of service and relations with its users.

The Imagopole mission is to provide conventional and sophisticated qualitative and quantitative imaging technologies, particularly in the study of infectious, systemic, and tumoral diseases, at both molecular and functional levels. The 35 research engineers at the Imagopole work with everything from individual cells to whole animals. Their specialties include ultrastructural microscopy, optical microscopy, cytometry, cell culture, molecular biology, and imaging.

To ensure that biology researchers have access to the latest techniques, the Imagopole has adopted an approach encouraging correlative microscopy and acquired imaging systems for highthroughput screening.





Infection imaging

The Imagopole works to develop and apply methods for hostpathogen interaction research at the molecular and cellular levels, as well as for tissues and entire organisms. The portfolio includes *in situ* analysis of sub-cellular dynamics, such as spatio-temporal parameters based on the observation of fluorescent and/or bioluminescent tracers. The development and management of mathematical, bioinformatic, and statistical approaches facilitate data analysis.

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), and viruses such as the AIDS virus (HIV), the hepatitis C virus, and human papillomaviruses.

Researchers also focus on bacteria such as *Listeria, Shigella* and *Mycobacterium tuberculosis.* Lastly, imaging technologies are used to research emerging diseases such as SARS, avian influenza, and chikungunya.

In 2011, the Imagopole worked to secure several grants from the French National Research Agency (ANR). In the second quarter of 2012 the Dynamic Imaging and Ultrastructural Microscopy Platforms will be moving to the Integrative Biology of Emerging Diseases building to meet better the needs of researchers and to develop new experimental approaches.

MOUSE GENETICS ENGINEERING CENTER (CIGM)

The discovery of new genes, new promoters, or new regulatory regions opens up the possibility of generating new transgenic mice. These tools are highly effective research aids that can improve understanding of biological functions and confirm expression profiles and genetic regulatory mechanisms in an overall genomic context.

Since it was set up in 2003, the center has generated very many genetically modified mice using "traditional" and "targeted" transgenesis techniques. "Traditional" transgenesis involves microinjecting transgenes (DNA fragments) into mouse embryos so that they can be integrated into the mouse genome. Another form of "traditional" transgenesis performed at the platform, "traditional" lentiviral additive transgenesis, has been optimized to modify rat embryos genetically. Genetic modification via "targeted" transgenesis involves homologous recombination in embryonic stem cells and has enabled the precise manipulation of the mouse genome, thus providing a large number of KO/KI mutant mice for the desired genes. The four members of the CIGM team have wide-ranging and highly specific skills in embryonic stem cell biology and culture, microsurgery and embryo microinjection, and can boast expertise in handling mice at all stages of development. The platform is involved in fundamental and applied research projects conducted by various Institut Pasteur units as well as other research institutions in France and worldwide.

CENTRAL ANIMAL FACILITY

The use of animal models remains a necessity for Institut Pasteur research programs and the Central Animal Facility houses almost all the resources deployed for working on small rodents. Its total capacity is 15,000 cages, 1,200 of which are used for rodents infected with class 2 and 3 biological agents so that research can be performed on the diseases caused by these agents. Three veterinarians supervise the 47-strong team. The Central Animal Facility also handles technical operations such as cryopreservation and the decontamination of strains, the development of genetically modified strains, and the production of mice strains with defined microbial flora.

The new animal facility at the Integrative Biology of Emerging Diseases Building began operation in May 2012. It will feature state-of-the-art, sophisticated equipment (including an automated washroom) as well as comprise a large high health status breeding and testing area for rodents and an adjoining A3 area of BSL3 laboratories (total capacity of around 11,000 cages). This is the first stage in a vast reorganization program for the animal facility that aims to offer a better quality of service and at compliance with new regulations.

CEPIA

The activities and organization of the Center for the Production and Infection of Anopheles (CEPIA) are geared towards researching interactions of the Plasmodium parasite (malaria agent) with its mammalian and insect hosts (mice or cell lines and mosquitoes of the Anopheles genus, respectively). The platform mass-produces two species of Anopheles: An. gambiae, the African vector, and An. stephensi, the Asian vector. It is the only French structure specialized in the experimental infection of mosquitoes with the human parasite P. falciparum. A range of equipment and facilities is provided for studying interactions between Anopheles and Plasmodium (cell biology and functional genomics) and for the production of sporozoites, the infectious stages of the parasite for the mammal host. More than 15 researchers and technicians from the Institut Pasteur use the platform each week. Funding from the Greater Paris region (DIM Malinf) has enabled CEPIA to strengthen its logistics capabilities for research into the mosquito stages of P. falciparum.

The platform is a partner in several collaborative programs on and off the campus, including a European project called INFRAVEC. CEPIA also responds to external requests from the Greater Paris region, elsewhere in France, and abroad, and



regularly hosts foreign interns. The platform has adopted a quality approach with the aim of being awarded ISO 9001 certification in July 2012. Alongside its mosquito and *P. falciparum* production activities, CEPIA is working to improve and develop new tools such as gametocyte purification and the *in vitro* production of *P. falciparum* ookinetes. The platform is also involved in the creation of *An. gambiae* transgenic lines, in cooperation with the Genetics and Genomics of Insect Vectors Unit.

CLINICAL RESEARCH AND THE MEDICAL CENTER

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

The year 2011 was particularly marked by:

• the French Institute for Public Health Surveillance and the General Directorate of Health's call for nominations for the renewal of National Reference Centers (CNRs) in microbiology for 2012-2016. The Institut Pasteur currently hosts 15 CNRs and four associated laboratories;

• the first productions of vaccine batches for clinical trials of breast cancer and anthrax vaccines, and the gene therapy trial for Sanfilippo B disease;

• responses to increasing demands from the European Commission to provide ethical guidelines for projects submitted under European calls for tender;

• the launch of two new joint calls for tender, one with the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) and the other with the Paris Public Hospital Network (AP-HP), and the creation of two guest researcher posts between the AP-HP and the Institut Pasteur. This will help foster long-term partnerships with these public healthcare and research organizations.

FROM SCIENTIFIC TO CLINICAL RESEARCH: AN INCREASINGLY PROFESSIONAL APPROACH

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

The Institut Pasteur as promoter

In promoting research on humans, the Institut Pasteur helps bridge the gap between the fundamental research carried out in its units and clinical research. The role of the Clinical Research Center is to represent the Institut Pasteur as a promoter. In 2011, the Clinical Research Committee examined the regulatory, legal, and ethical compliance of 52 new research projects on human beings or healthcare products.





VACCINATIONS (84,197 VACCINES ADMINISTERED)

Twenty-nine percent of these projects involved the Institut Pasteur International Network. The Institut Pasteur was the promoter/legal sponsor for 62% of these projects. This growing role as institutional promoter demonstrates the Institut Pasteur's desire to commit to translational and clinical research and to accept the responsibilities that come with this type of research as regards the human subjects involved. Since 2008, the Clinical Research Committee has examined 169 projects: in 2011, 64 were monitored pending start-up authorization and 23 actually began (the others were in progress, closed, or abandoned).

In 2011, the Clinical Research Center was also involved in two major projects: (i) laboratories of excellence – the Milieu Intérieur ("Environment Within") project (genetic and environmental factors controlling the variability of the immune response, laying the foundation for personalized healthcare), and (ii) the ERC Evoimmunopop project (Human Evolutionary Immunogenomics: Population Genetic Variation in Immune Responses).

Developing innovative therapies: from preclinical to clinical

The year 2011 also saw significant progress made on several large-scale projects led by the Clinical Research Center:

• RMV-HIV: phase I clinical trial of an HIV vaccine candidate; the results are currently being analyzed;

• Anthrax: entry into the preclinical operational phase of a vaccine candidate against anthrax, in partnership with the DGA

(the French defense procurement agency);

• MAG-Tn3: development of the final formulation of the breast cancer vaccine candidate;

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

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

Clinical Investigation and Access to Biological Resources Platform

The Clinical Investigation and Access to Biological Resources Platform (ICAReB) strengthened its partnerships with research teams from the Institut Pasteur and external institutions in 2011. It also continued its research on bioresources. A dedicated website was launched in 2011.

Training... and informing

For the third year running, the "Research on Human Beings and Applied Ethics" program trained researchers in regulations for research on human beings. Targeted educational measures have been implemented to train PhD students and researchers in ethics.

CONSULTATIONS FOR INFECTIOUS AND TROPICAL DISEASES AND TRAVEL MEDICINE



CONSULTATIONS FOR RABIES CONSULTATIONS FOR ALLERGIES

The second season of Clinical Research Center Workshops met with great success. This new series of six twice-monthly training and information sessions is designed to help scientists improve their understanding of the regulations behind the development of clinical research protocols and to meet the growing demands that govern the submission of publications and access to national and international funding.

THE INSTITUT PASTEUR MEDICAL CENTER

The Institut Pasteur Medical Center is the only Institut Pasteur unit to be in direct contact with patients, through its vaccination center and consultations for rabies, infectious and tropical diseases, travel medicine, and allergology. As well as vaccinations and advice to travelers, particularly for fragile patients (i.e. those with HIV or organ transplants), and the treatment of imported diseases on their return, a major part of the Medical Center's work is dedicated to HIV infection, infectious diseases such as Lyme disease, treatment for rabies, and dermatology, particularly through the treatment of hidradenitis suppurativa. Some of these diseases are monitored in cooperation with Necker-Enfants Malades University Hospital. In France, the Institut Pasteur Medical Center performs more allergy consultations for adults than anywhere else in the

country, with some 7,500 patients tested each year. It also provides treatment for the largest national hereditary angioedema cohort.

In addition, the Medical Center carries out clinical research directly related to its medical focus areas: cohorts and therapeutic studies on HIV infection; the physiopathology of hidradenitis suppurativa (in cooperation with Necker Hospital and the ICAReB Platform); vaccinology (interaction of yellow fever and measles vaccines in children); treatment of imported malaria; and the physiopathology of post-infectious anosmia.

NATIONAL REFERENCE CENTERS AND WHO COLLABORATING CENTERS

As microbiological observatories for communicable diseases, National Reference Centers (CNRs) and World Health Organization Collaborating Centers (WHOCCs) play an important part in the Institut Pasteur's public health activities.

Results are in after the 2011 call for nominations for the renewal of National Reference Centers (CNRs) in microbiology, issued by the French Institute for Public Health Surveillance (InVS) and the Health Ministry. For the 2012-2016 period, 15 on-campus research units were officially appointed as CNRs and two research units at the Institut Pasteur in French Guiana were appointed as laboratories (four in total) associated with the CNRs in mainland France (by ministerial decree of 12/30/2012). These CNRs support health authorities in the areas of diagnosis, epidemiological monitoring, and research into communicable infectious diseases. They are expert laboratories that serve as microbiological observatories for communicable diseases in France. Seven of these 15 CNRs are also WHO Collaborating Centers (WHOCCs), and one CNR/WHOCC has been designated as a reference laboratory for the OIE (World Organization for Animal Health). The CNRs also draw on the scientific environment of their host units and the various support structures, including

the Genotyping of Pathogens and Public Health Platform (PF8) and the Laboratory for Urgent Response to Biological Threats (CIBU).

NATIONAL REFERENCE CENTER FOR E. COLI AND SHIGELLA

Three hemorrhagic *Escherichia coli* (EHEC) epidemics occurred from May to late June 2011, first in Germany and then in Lille and Bordeaux, in France. This resulted in a major workload increase for the National Reference Center for *E. coli* and *Shigella*, with a huge number of stool and serum samples and bacterial strains being sent for testing. Between January 1 and October 1, 2011, the number of stool specimens tested for *E. coli* increased fourfold, the number of strains tested doubled, and the number of serological tests increased by 59% compared with the same period in 2010 (benchmark year).



These epidemics resulted in the urgent development of new molecular methods to detect the *E. coli* 0104:H4 strain, and the use of highly discriminatory molecular typing techniques (optical mapping and whole genome sequencing) to monitor the epidemic strains. The analysis of all the samples and strains received led to cases being confirmed and new cases being identified. Various cutting-edge molecular methods were used to shed light on the origins and circulation of the different epidemic strains, contributing to the rapid identification of the 0104:H4 strain in the Bordeaux outbreak. This helped narrow down the food questionnaire and pinpoint the source as quickly as possible. The CNR's directors were courted by the national media – they gave over 100 interviews to the written press, radio, and television – to outline methods that could be used to prevent EHEC.

NATIONAL REFERENCE CENTER FOR SALMONELLA

This center identified a worrisome increase in salmonellosis cases caused by a monophasic variant of serotype *Typhimurium* (antigenic formula 4,5,12:i:). In 2011, this population became the most common serotype of salmonellosis in humans in France (over 2,000 confirmed cases in 2011, compared with around 50 each year before 2005), overtaking the traditional prevalent serotypes such as *Typhimurium* and *Enteritidis*. It was also responsible for the two major national epidemics investigated in 2011, one of unknown origin with over 1,000 cases, and the other

with over 300 cases caused by consumption of dried pork sausage. Salmonellosis is relatively homogeneous in genetic terms, meaning that if an epidemic occurs, extensive molecular analysis (PFGE, MLVA, CRISPOL, etc.) is required to distinguish between epidemics and sporadic cases.

NATIONAL REFERENCE CENTER FOR MENINGOCOCCUS

This National Reference Center is involved in the epidemiological monitoring of invasive meningococcal infections in France and Europe and the development of France's meningococcal vaccine policy. Strain typing results indicate that the invasive meningococcal infections that occur as sporadic cases in Europe are caused by heterogeneous strains. In France, the 2011 surveillance data indicates that the annual incidence is stable (less than 1 in 100,000).

Serogroup B remains the most common (69%), followed by serogroup C (17%), serogroup Y (10%), and serogroup W135 (2%). One notable trend is that cases of meningococcal C have continued to fall. This phenomenon has become more marked since the meningococcal C vaccine was recommended. The increase in the number of cases of meningococcal Y was confirmed in 2011.

In 2011, the laboratory became a WHO Collaborating Center and contributed to the typing of isolated strains in Africa. In Sub-Saharan Africa, invasive meningococcal infections are prevalent



in the form of seasonal epidemics caused by homogeneous genotypes, which determine the severity of the infection in immunologically naive populations.

NATIONAL REFERENCE CENTER FOR LISTERIA

Continuing in its microbiological monitoring activities, this center characterized and typed the strains of several cases of listeria similar to those seen in recent years. It has also described a new PCR serogrouping profile.

In addition to its monitoring activities, the center is involved in public health and research. Work continued on the prospective case-control study Monalisa (clinical trial NCT01520597), which aims to prospectively analyze the clinical, radiological, biological, and genetic characteristics of this infection. This study included over 200 cases of septicemia, 100 cases of central nervous system infection, and 60 cases of maternal-fetal infection. The center also published the first series of osteoarticular listeriosis, a rare form of this infection. At the same time, the CNR published its biodiversity study of the species *Listeria monocytogenes* and used a global sample of strains collected as part of its WHOCC activities to demonstrate the major clones' ubiquitous distribution.

NATIONAL REFERENCE CENTER FOR ANAEROBIC BACTERIA AND BOTULISM

In 2011, this National Reference Center carried out a biological diagnosis of human botulism: a total of nine botulism foci covering 15 cases were identified. The center diagnosed two type A botulism foci, which occurred in Avignon and Amiens (France) and were responsible for seven severe forms, caused by the consumption of a store-bought olive-based product. Foodborne botulism was the most frequent form (eight out of nine foci, through the ingestion of preformed toxins in food), and one case of infant botulism (type A botulism) was identified. Although rare, this disease has been

reported more regularly in recent years. Unlike in previous years, type A botulism was the most frequent (five foci and 10 cases), while two foci (two cases) were type B, one focus (one case) was type E, and for another focus (two cases) the type was not determined.

NATIONAL REFERENCE CENTER FOR PERTUSSIS AND OTHER BORDETELLA

The National Reference Center pursued its research on the evolution of species of the Bordetella genus following the replacement of the whole-cell pertussis vaccine with an acellular vaccine containing only a few proteins of Bordetella pertussis, the primary agent of pertussis, or whooping cough. However, once just a theory, it seems that vaccine-induced immunity coupled with the population's high vaccine coverage is resulting in the increased circulation of Bordetella pertussis and Bordetella parapertussis (isolates that do not express one of the vaccine antigens). In recent years the proportion of such isolates has increased regularly. The antigen whose expression is inhibited is pertactin (an adhesin). This data demonstrates the importance of monitoring microbial species targeted by vaccination and closely-related species that can be modified depending on population immunity. With regard to whooping cough diagnosis, the Bordetella RT-PCR, recommended by the 2005 European Consensus on Development, is 50 times more sensitive than previous PCRs but is not specific to Bordetella pertussis, the whooping cough agent. The center therefore carried out a retrospective study and demonstrated that 20% of samples from adults and adolescents who had been diagnosed as having whooping cough were actually carriers of B. holmesii and not B. pertussis. The acellular vaccine containing four B. pertussis antigens does not offer protection against B. holmesii. Current biological diagnosis using RT-PCR (IS 481 target) is therefore a diagnosis of the Bordetella genus. Confirmation of whooping cough, particularly in adolescents or adults, is based on a series of clinical, microbiological and epidemiological arguments, including vaccination status.

RESEARCH APPLICATIONS

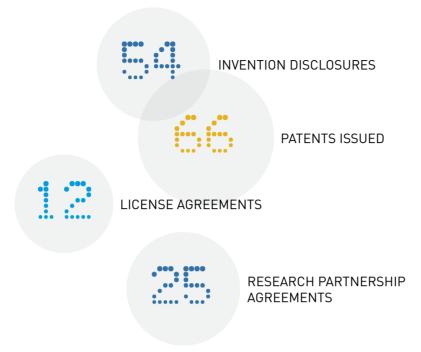
The Research Applications and Industrial Relationships Department (DARRI) has been highly involved in preparing bids in response to calls issued through the Investing in the Future national program. Significant actions have also been put into place to foster the innovation process and optimize management of the patent portfolio.

The year 2011 was dominated by the French Investing in the Future national program. The Research Applications and Industrial Relationships Department, working on its own or in collaboration with other bodies, has been very much involved preparing tender submissions geared towards business development and industrial partnership projects. As a matter of fact, the hard work paid off: all the bids submitted were selected by the various juries. Under the Carnot institute call, both the Pasteur Infectious Diseases Carnot institute bid (led by the Institut Pasteur) and the "Seeing and Hearing" Carnot institute joint bid were successful. The Global Care project led by the Institut Pasteur was selected under the international Carnot institutes call. The CVT-Sud project, in partnership with IRD and CIRAD, was successful under the "business development consortium" call. The Île-de-France Innov project, which the

Institut Pasteur supports as a strategic partner, was selected under the "technology transfer acceleration organizations" call. Last, the Bioaster project, jointly run with Lyonbiopole, was selected under the "technological research institutes" call. For each of the many other projects submitted by the Institut Pasteur, the DARRI helped identify potential industrial partners for the laboratories on campus and built a business development strategy for the innovations expected to be generated through the projects.

FOSTERING INNOVATION

Following a detailed analysis of the mapping of invention disclosures submitted by Institut Pasteur units over the past ten



years, the DARRI has implemented a new program for regular meetings with all the unit directors (around 100 meetings in total). The aim is to raise researchers' awareness regarding the different aspects involved in business development, and to establish a dialog to help identify new opportunities. Starting in 2012, this action should lead to a 10 to 20% rise in the number of invention disclosures submitted.

RATIONALIZING THE PATENT PORTFOLIO

Analysis of the patent portfolio continued aiming at eliminating patents with no business development potential. This has led to substantial savings on the patent fee budget.

BRINGING HIGH-POTENTIAL PROJECTS TO MATURITY

The DARRI is helping bring around 15 projects stemming from the Institut Pasteur campus up to maturity, via the Pasteur Infectious Diseases Carnot institute and its own calls for tender. This is a way to validate the approaches used and significantly boost the potential value of these projects.

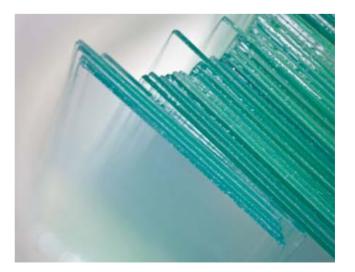
SUPPORTING YOUNG COMPANIES

Four young companies have joined the BioTop incubator. One new company was set up in 2011 and two projects reached maturity, paving the way for possible new start-up creation in 2012. The Institut Pasteur is represented on the boards of eight young companies and is keen to be actively involved in its capacity as shareholder. To this end, it has renewed its representatives and stakeholder engagement process.

STRENGTHENING RESEARCH PARTNERSHIPS

Several important partnership contracts have been signed with major industrial partners (including Sanofi, the Institut Mérieux, Danone, Roche, and Meiji) or emerging partners such as the US gene therapy firm BlueBird Bio, which is leading two gene therapy trials (adrenoleukodystrophy and beta thalassemia) based on a technology developed at the Institut Pasteur.

Revenue from research partnerships more than doubled between 2010 and 2011. Three patents on new pathogenic viruses have been filed as a result of collaborative research with Pathoquest, a young company originating from the Institut Pasteur Campus.



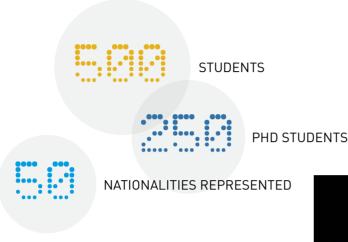
THE TRANSFER OF VALUES

The theoretical and practical courses offered at the Institut Pasteur Teaching Center are organized and taught by French and international researchers from the Institut Pasteur or other scientific organizations. The content of the courses and training programs is constantly being updated to meet the needs of scientists and healthcare professionals.

In 1889 the Institut Pasteur offered the world's first microbiology course, "Technical Microbiology", and it has made teaching one of its core missions ever since. Today the Institut Pasteur is truly a higher-education hotspot. Every year, around 500 students take courses at the Teaching Center, 50 students complete their Masters internships, and 250 PhD students conduct research projects in Institut Pasteur laboratories.

A DEDICATED ENVIRONMENT AND VARIED COURSE SELECTION

The Teaching Center, based at the former Pasteur hospital, offers both practical biology and theory courses. These courses are separated into three main areas of study: Epidemiology and Public Health, Mechanisms of Living Organisms, and Biology of Microorganisms. They cover a wide range of public health topics including microbiology, genomics, immunology, vaccinology, neuroscience, epidemiology, and cell biology. They are aimed at students from French and foreign universities, university teaching hospitals, and French grandes écoles, as well as working professionals – scientists, doctors, and veterinarians – wishing to supplement their training. Around 30 courses, lasting from one to 12 weeks, are offered each year. Many of these courses can be counted as part of a Masters degree program, either as second year teaching units for the Masters offered at Paris Descartes, Pierre and Marie Curie, Paris Diderot, Paris-Sud 11, and Versailles Saint-Quentin-en-Yvelines universities, or as part of the specialized Masters in Public Health run by the Pasteur-CNAM School of Public



Health. Outside these university programs, they can be taken as part of degree programs from partner universities. Most courses can also be taken by PhD students as part of their doctoral studies.

TEACHING STUDENTS FROM AROUND THE WORLD

The Teaching Center welcomes students, scientists, doctors, pharmacists, engineers, and veterinarians from all over the world. Each year, 150 students from around 50 different countries come to take courses at the Institut Pasteur. With the growing number of foreign students and lecturers, an increasing number of courses are taught in English.

The year 2011 welcomed the third class of 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 "Georges Canetti" class of 2011 includes seven students from Germany, the United Kingdom, the United States, Portugal, and Singapore.

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) at the Pasteur-CNAM School of Public Health. A partnership agreement was also signed in 2011 between this school and the



French School of Public Health (EHESP). After six months of theoretical training, students complete a six- to eight-month internship researching infectious diseases, either in France or abroad at one of the Institut Pasteur International Network member institutes.

A GLOBAL PRESENCE

The Institut Pasteur is at the heart of a unique international network for public health, teaching, and research. The Institut Pasteur International Network includes 32 research and public health institutes on the five continents.

The Institut Pasteur International Network (RIIP), born of Louis Pasteur's will, has become a key global player in fighting infectious diseases. Its 32 research and public health institutes, spread over the five continents, are well integrated in the national health systems and work in close collaboration with the medical and research communities in their countries. Their work is carried out by a vast network of qualified researchers, trained in the member institutes.

The activities of the International Network cover the three Pasteurian missions – scientific research, public health, and teaching – which primarily target infectious and emerging diseases, resistance to anti-infectious treatments, neglected tropical diseases, and the evaluation of diagnostic and therapeutic strategies. In each of these areas, the RIIP institutes are key partners for national health ministries in France and abroad, top national and international research institutes, universities, and international organizations.

The network is a major partner of the World Health Organization (WHO) for the diagnosis of infectious diseases among the most vulnerable populations as evidenced by the eight WHO Collaborating Centers (WHOCCs) hosted in Paris, as well as the 10 WHOCCs, and more than 45 National Reference Centers recognized by the WHO within the Institut Pasteur International Network.

Several international agreements were signed in 2011, including two in Niger, the first with AREVA for a project on malaria and



the second with the Principality of Monaco for a meningitis project.

THE INSTITUT PASTEUR INTERNATIONAL NETWORK IS CURRENTLY INVOLVED IN SEVERAL AMBITIOUS PROGRAMS:

• monitoring influenza and severe respiratory infections in South-East Asia and Africa with the support of the US Department of Health (HHS-ASPR);

• setting up a network of reference laboratories to monitor infectious diseases, involving 13 Mediterranean countries (the European EpiSouth project);

• monitoring bacterial meningitis in Niger and Northern Cameroon;

• strengthening medical research capabilities in French Guiana to provide a better response to the infectious health risks faced by the country's population through the three-year STRonGer* program,

GRANTS FUNDED BY THE INSTITUT PASTEUR INTERNATIONAL DIVISION:



GRANTS TO STUDY IN PARIS INCLUDING 10 AMSUD-PASTEUR GRANTS

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INTERNSHIP GRANTS INCLUDING 2 TRAINEE GRANTS, 1 3-YEAR PHD GRANT IN SHANGHAI AND 1 2-YEAR POSTDOCTORAL GRANT IN CAMBODIA

CONFERENCE GRANTS

funded by the European Commission and coordinated by the

Institut Pasteur in French Guiana; • developing a network of laboratories that use modern molecular biology techniques to detect multiple-antibiotic-resistant tuberculosis with the Upgrade Laboratory Network for Tuberculosis Diagnosis and Drug Testing in Africa project led by Brigitte Gicquel from the Mycobacterial Genetics Unit. This two-year project involves the national reference laboratories from eight countries in Sub-Saharan Africa (Benin, Burkina Faso, Cameroon, Ivory Coast, Central African Republic, Guinea-Bissau, Niger, and Togo) and four reference countries from Northern Europe (France - the Institut Pasteur and the International Union Against Tuberculosis -, Italy, Belgium, and Denmark). This project, supported by OFID (the OPEC Fund for International Development), will provide training, equipment, and the latest molecular techniques to develop a South-South network of expertise and know-how to fight the emergence of multiple-resistant tuberculosis in these regions.

EVENTS

Several institutes of the Institut Pasteur International Network reached important milestones in 2011:

the Institut Pasteur in Ho Chi Minh City, created by Albert Calmette on November 18, 1891, celebrated its 120th anniversary;
the Institut Pasteur in Bangui, inaugurated on February 25, 1961,

celebrated its 50th anniversary;

 \bullet the Institut Pasteur in Montevideo, created in 2006, celebrated its $5^{\rm th}$ anniversary.

The Scientific International Meeting of the Young Researchers from the Institut Pasteur International Network, held at the Institut Pasteur in Paris during the 44th Board of Directors, was attended by more than 250 international scientists and saw three Young Researchers Prizes awarded.

Two regional meetings of the Institut Pasteur International Network were held in 2011:

• the Asia-Pacific regional meeting in Phnom Penh, Cambodia, which included an international symposium on 'Surveillance and Discovery in Respiratory and Other Emerging Infectious Diseases', marking the conclusion of the SISEA project (Surveillance and Investigation of Epidemics in South-East Asia);

• the European regional meeting at the Institut Pasteur – Cenci Bolognetti Foundation, Rome, which included three workshops on hepatitis, neurological infections, and respiratory infections.

Prof. Mireille Dosso, Director of the Institut Pasteur in Côte d'Ivoire, received the African Union Kwame Nkrumah Scientific Award for her work in the field of medical science.

TO FIND OUT MORE

The 2010 edition of the Institut Pasteur International Network Report is available on the website www.pasteur-international. org.

The open access archive HAL-RIIP allows the submission of scientific publications from the Institut Pasteur International Network and their consultation by theme, author, institute...: http://hal-riip.archives-ouvertes.fr/

* Strengthening Transdisciplinary Research on Infectious and Emerging Diseases in French Guiana: linking fieldwork, benchside and bedside.

GRANTS COFUNDED BY THE INSTITUT PASTEUR INTERNATIONAL DIVISION AND PARTNERS:



GRANTS FROM THE PIERRE LEDOUX – JEUNESSE INTERNATIONALE FOUNDATION

GRANTS FOM THE PRINCIPALITY OF MONACO

International teaching and training

Each year, more than 100 scientists from the Institut Pasteur International Network complete their training with courses or internships in Paris. In 2011, 20 courses and workshops funded by the RIIP were run in nine countries – two in Africa, four in Asia, two in Latin America, and one in Europe. Three courses and workshops were also given as part of the Amsud-Pasteur partnership.



EXPERTISE AND RESOURCES

- **HUMAN RESOURCES**
- 56 SUSTAINABLE DEVELOPMENT
- **FINANCING STRUCTURE**
- **FINANCIAL SITUATION**
- **DONATIONS AND LEGACIES TO SUPPORT RESEARCH**
- **63** COMMUNICATIONS AND FUNDRAISING

HUMAN RESOURCES

In 2011, the Human Resources Department concluded a number of important labor relations agreements and focused its efforts on change management, skills development, and recruitment.

In labor relations, an agreement was reached in 2011 on harmonizing the regulations governing contributions to welfare and medical expenses. The unions and management drew up a new agreement on the contribution scheme.

Another important agreement was reached on psychosocial risk prevention. The efforts of the working group set up in 2010 – comprising representatives from the Workplace Health, Hygiene and Safety Department, the CHSCT (Committee for Health, Safety, and Working Conditions), the Environment, Safety and Logistics Department, and the Human Resources Department – resulted in a memorandum of understanding. Three main areas for action were identified: training and raising awareness for those involved; identifying problem situations; and prevention with the help of a prevention unit. These will be gradually introduced during 2012.

The annual negotiations for the year 2012 were also concluded with the signing of a memorandum of understanding on various

payroll measures. These include both general measures, such as an overall wage increase and one-time bonuses, and also category-based measures, with a new method for calculating half-yearly bonuses for scientists which involves a two-phased approach, bringing the scientists' bonuses on a par with those of other staff categories.

ORGANIZATION AND DEVELOPMENT

The measures launched at the end of 2010 to restructure various support services were finalized in 2011. These changes targeted purchasing, logistics, management, technical services, and IT resources. An Information Systems Department, serving as an umbrella structure for all the IT activities on the campus, was set up at the beginning of the year. Training programs in job and



STAFF (INSTITUT PASTEUR WORKFORCE AS OF DECEMBER 31, 2011), INCLUDING:

EMPLOYEES FRO AND HIGHER EDU ORGANIZATIONS

EMPLOYEES FROM RESEARCH

INTERNS

INSTITUT PASTEUR EMPLOYEES (78% ON PERMANENT CONTRACTS)

skills management have been developed to facilitate these changes. Career development possibilities are also regularly offered to employees in relevant sectors.

All these developments are part of a broader modernization program designed to keep the Institut Pasteur in step with the changing requirements of research and to optimize the quality of its services. Wide-ranging discussions have been held with support and operational departments on developing the Institut Pasteur's information systems. The aim is to introduce an ERP system incorporating all the features required for effective management and also allowing the pooling of information and data.

Discussions were also held on the future of preparation laboratories in view of the new integrative biology of emerging diseases building, due to open in 2012. The building's innovative work spaces will provide an opportunity to review the organization of support activities. The Institut Pasteur will work with change management specialists to ensure that these structural changes go without a hitch.

RECRUITMENT

The policy to control workforce numbers continued in 2011. This policy, based on the fact that many Pasteurians are nearing retirement age, stipulates that departing employees are not systematically replaced. As of December 31, the Institut Pasteur had 1,867 staff members, 78% of them on permanent contracts (this figure has fallen). The number of employees on fixed-term contracts is increasing on a regular basis. 73% of these fixed-term employees are young researchers, mainly PhD students and postdocs, either recipients of research training grants or employed under an international agreement, or young foreign researchers living temporarily in France. One figure that particularly stands out in the Institut Pasteur's workforce is its high proportion of female employees (over 60%).



SUSTAINABLE DEVELOPMENT

The Institut Pasteur takes its corporate responsibilities seriously, and is constantly striving to optimize its efforts by focusing on the three main pillars of sustainable development: economy, society and environment.

The Institut Pasteur's commitment to social and environmental responsibility is based on two internationally recognized standards for corporate sustainable development: the UN Global Compact and ISO 26000. This year, the Institut Pasteur has pursued the Green Campus program launched by the general management in 2010. This environmental commitment led to the publication of two guides promoting responsible practices in 2011.

MEMBERSHIP OF THE UN GLOBAL COMPACT

The Institut Pasteur has been a member of the United Nations Global Compact since 2010. The Global Compact aims to promote corporate civic responsibility by inviting companies to adopt, support and apply a series of fundamental values, within



http://www.unglobalcompact.org/

their sphere of influence, relating to human rights, labor and environmental standards, and anti-corruption measures. The Institut Pasteur reports annually on its progress in these areas on the UN website.

SUSTAINABLE DEVELOPMENT IN NON-PROFIT ORGANIZATIONS GUIDE

In 2011, the Institut Pasteur took part in a working group set up to study sustainable development in non-profit organizations. This working group included representatives of various organizations and foundations including the Institut Pasteur, Ideas*, the French Center for Endowment Funds and Foundations, and a sustainable development consultant. The aim was to facilitate the integration of sustainable development in non-profit organizations and foundations. The idea of this group was first mooted at the sustainable development conference organized by the French Association of Treasurers and Managers of Non-Profit Organizations (AFTA) at the French Senate in 2010. The Institut Pasteur gave valuable feedback on its sustainable development initiatives, including the carbon footprint initiative, ISO 26000 certification, and its general strategy. The work of this group resulted in the online publication of a guide entitled Sustainable development in non-profit organizations (in French Le Développement durable au coeur des organismes sans but lucratif), which outlines the challenges, opportunities and best practices involved in sustainable



development for foundations and charities, and sets out the various possibilities available.

* Ideas is a non-profit organization that helps charities optimize their appeals for donations by developing a framework that encourages donors to give.



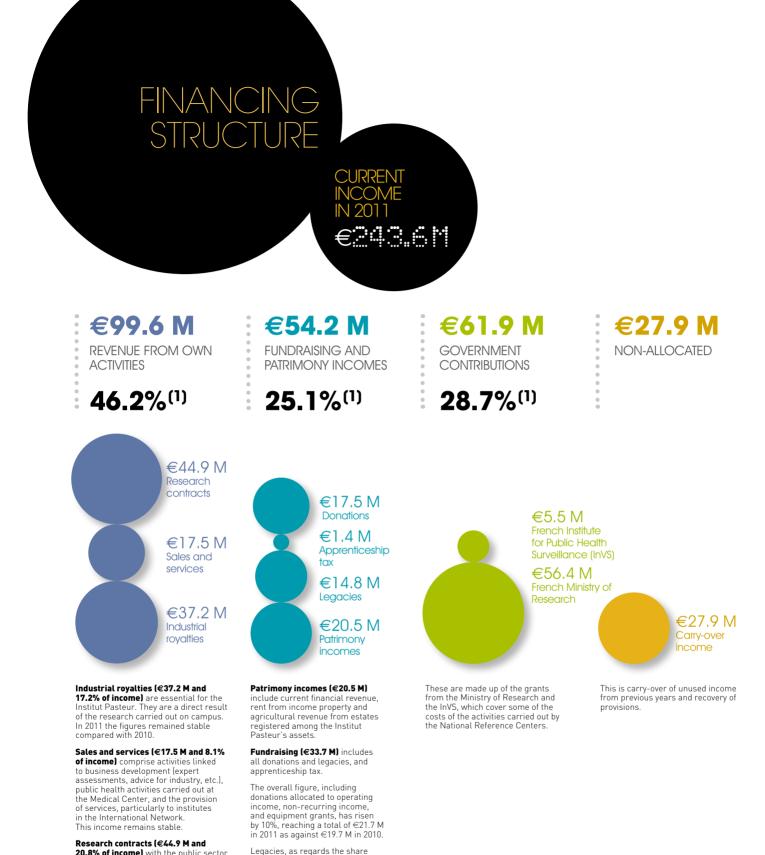
THE FIRST GUIDE TO ENVIRONMENTALLY RESPONSIBLE LABORATORIES

In 2011, the Institut Pasteur pursued the Green Campus program launched in 2010 by carrying out a range of initiatives, including setting up a working group of representatives from the Institut Pasteur's research units to study sustainable development in laboratories. This group worked together to draft the Institut Pasteur's first *Guide to environmentally responsible laboratories* (in French *Guide du laboratoire éco-responsable*), to be distributed to the Institut Pasteur's research laboratories in an effort to promote environmentally responsible practices in research activities. This guide is due to be published on an internal basis in early 2012.

AFAQ 26000 SOCIAL RESPONSIBILITY ASSESSMENT



"All progress must be measurable." Companies must know where they stand and where they are headed if they wish to make real progress. This is why the Institut Pasteur requested that AFNOR Certification carry out an AFAQ 26000 assessment to measure its progress in social responsibility and set relevant, realistic targets. This audit took place in March 2011. It looked at the Institut Pasteur's strategic, managerial and operational practices and analyzed its economic, social and environmental indicators. The assessment is based on ISO 26000 - the first international standard to give guidelines on social responsibility, published on November 1, 2010. It was a means of gauging how the Institut Pasteur measures up to the requirements of this standard. The Institut Pasteur was awarded the second rating on a scale of four: "progress". The Institut Pasteur is the first foundation to have requested this audit. The results show that the basic approach of the Institut Pasteur in terms of social responsibility is sound, but there are encouraging prospects for progress.



allocated to current revenue, have

correspond to completed legacies, the majority of which were bequeathed in previous years.

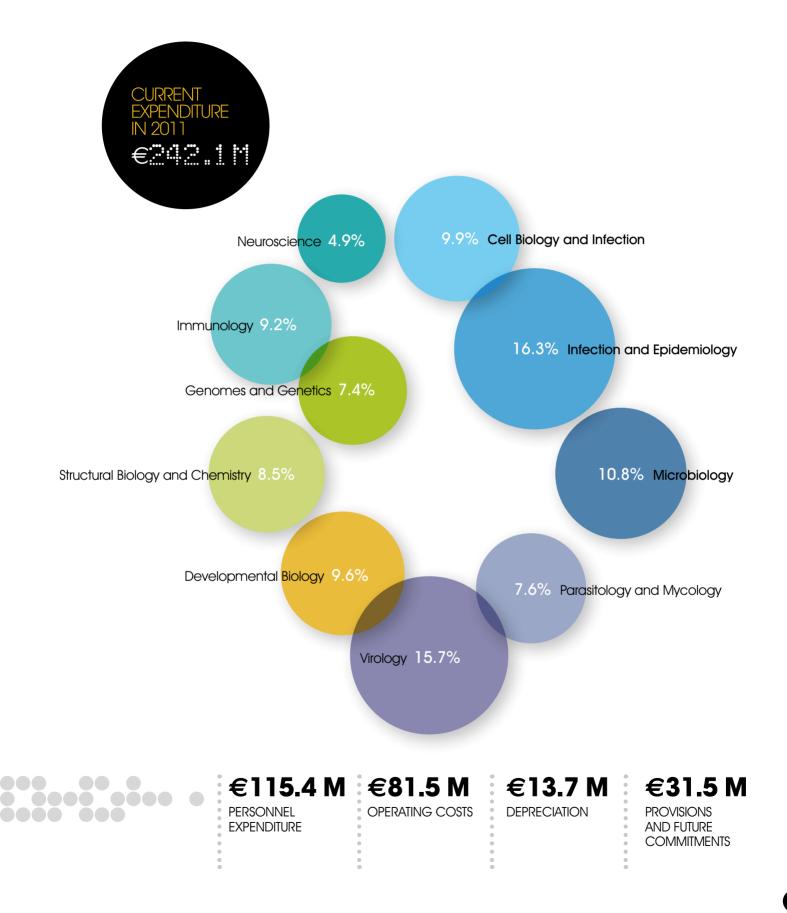
fallen compared with 2010. The amounts recorded as income

20.8% of income) with the public sector have increased this year. This is mainly due to the signing of three major contracts for laboratories of excellence with the French National Research Agency, under the Investing in the Future program. R&D contracts

with industry have increased in 2011 with the signing of new framework agreements with industry for diagnosis

and therapeutic research.

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





In 2011, the current-account surplus totaled \in 1.4 M, more or less on a par with 2010. This can be broken down into the operating result (- \in 11 M), structurally loss-making, and the financial result, comprising income from investments (\in 12.4 M).

CURRENT OPERATIONS

Current revenue fell by 2.5% in relation to 2010, with contrasting developments for various items. One significant difference is the absence of the non-recurring income received in 2010 from the settlement of various major industrial disputes.

This year, income from research agreements and contracts has risen considerably with the selection of three laboratories of excellence under the Investing in the Future program. Financial support from public authorities, particularly the French Ministry of Research, has generally remained at the same level as in previous years.

The operating result, structurally loss-making, shows that the balance of the Institut Pasteur's operating result is linked with the optimization of movable and immovable assets management. Current expenditure fell by 3.1% compared with 2010; this can largely be explained by various non-recurring events that took place in 2010. 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

The deficit in non-recurring operations, composed partly of legacies and gains or losses from the management of long-term

investments, stands at \in 26.9 M and structurally comprises the largest share of the annual net deficit.

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. In 2011, the total recorded in the accounts as non-recurring income was €15.7 M (compared with €12.2 M in 2010). In total, legacies recorded in the accounts in 2011 as both current income and non-recurring income amounted to €30.4 M, compared with €35.9 M in 2010.

The overall situation of the global financial markets meant that net non-recurring expenditure was recorded in the long-term investment portfolio (\in 42.7 M). 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. The performance of the portfolio stands at -6.4% in 2011.

The overall net deficit this year is \in 25.5 M. This is mainly attributed to non-recurring expenditure recorded for long-term investments, given the sharp losses sustained this year on the global financial markets.

DONATIONS AND LEGACIES TO SUPPORT RESEARCH

More than a hundred years ago, the generous public response to Louis Pasteur's international appeal for funds enabled him to set up the Institut Pasteur. The support of individuals and companies, as demonstrated through donations, legacies, and sponsorship, is now one of the four pillars of the Institut Pasteur's budget, giving its researchers the independence and freedom they need to carry out their work as effectively as possible.

In February 2011, the Institut Pasteur was awarded ISO 9001 certification by AFNOR for its advice and management concerning gifts and its real estate assets management. This is the culmination of several years of efforts to implement a structured working method and framework that would satisfy the needs of all its partners, including individuals looking for information about legacies and donations, and notaries, who have an important role to play in this quality policy. The Institut Pasteur is the only state-approved organization in France to have received AFNOR certification in this area.

DONATIONS - SUPPORT KEEPS GROWING

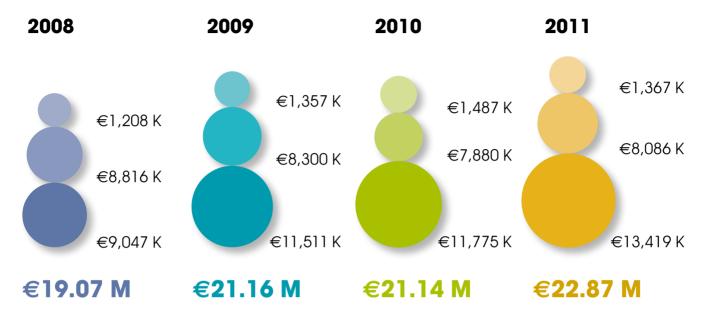
In 2011, our fundraising reached a new level, with a 10% increase and a total of ${\textcircled{\sc e}21.7}$ million raised from donations and

apprenticeship tax. This was particularly down to the success of the campaign aimed at taxpayers liable to the solidarity tax on wealth (ISF), which alone raised &2 million.

Support from individuals, whatever their level of donation, brought in €13.4 million. The fifth Pasteurdon held in October was the highlight of 2011. This was a chance for the public to learn more about the work of the Institut Pasteur's researchers and to show their support. The commitment of companies is just as important: 2011 saw the conclusion of an agreement with Sanofi to set up the Sanofi-Institut Pasteur Award in recognition of leading scientists, as well as the launch of the innovative BPE Altruis bank card scheme which offers BPE clients a new way to support Pasteurian research.

Several hundred SMEs have also contributed to the Institut Pasteur's work through gifts or by donating their apprenticeship

DEVELOPMENT OF FUNDRAISING IN €M (FROM TOP TO BOTTOM: APPRENTICESHIP TAX, BUSINESSES, INDIVIDUALS)



tax. The Fondation Pasteur Suisse and the Pasteur Foundation in New York have opened the way for Swiss and American donors to support the Institut Pasteur's researchers. In France, several sponsors have chosen to support work involving the institutes in the International Network. These include the Total Foundation, AREVA, BNP Paribas Corporate Investment Banking, Natixis, and Rotary International.

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 certified by a statutory auditor and are subject to the approval of the 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 its management.

LEGACIES BOOSTED BY IMPRESSIONIST MASTERPIECES

On March 16, 2011, an important collection of paintings from the estate of Mrs. Haegel (a member of the family that founded the Grands Moulins de Pantin) was sold at the Hôtel Drouot by auctioneer Christophe Joron Derem. Two major works by Claude Monet (La Promenade d'Argenteuil, un soir d'hiver) and Auguste Renoir (Portrait de jeune femme au chapeau fleuri) came under the hammer, the first fetching €2,250,000 and the second €500,000, excluding fees.

Following a widespread publicity campaign and press conference, interested buyers came from all over the world to the packed auction hall or made their bids by telephone. This outstanding legacy, worth some €14 million, demonstrates the relationship of trust between the legators and the Institut

Pasteur, who had been in close contact for almost twenty years. The year 2011 saw a return to previous levels after a marked fall in new legacies in 2010. Some 120 new legacies worth over €40 million were submitted to the bureau of the Board of Directors in 2011. The year also saw an 89% rise in life insurance policies received. These totaled €8.6 M in 2011.

CONFERENCE ON PHILANTHROPIC TRUSTS

The second edition of the conference on philanthropic trusts, organized jointly by the newspaper Le Monde and the Institut Pasteur, was an opportunity for several leading specialists to debate the issues involved in international philanthropy before an audience of over 400 people. This event is unique in that it draws professionals from all sectors of assets management (lawyers, independent assets management consultants, private bankers, notaries, and academics). It is now a firm fixture in the calendar for those involved in philanthropy, representing a great opportunity for these professionals to discuss and compare their approaches and methods, and to apply this shared expertise to philanthropic ventures. The conference also serves as a forum where participants can raise any problems encountered in a group setting and try to identify immediate solutions or suggest legal or fiscal amendments that should be introduced.

COMMUNICATIONS AND FUNDRAISING

The aim of the Department of Communications and Fundraising is to strengthen the Institut Pasteur's position in the landscape of biomedical research. In 2011, the department focused on highlighting the Institut Pasteur's achievements and successes and helped raise public awareness, while improving conditions to promote fundraising.

In 2011, the Department of Communications and Fundraising pursued its efforts among all sectors of the public to raise awareness of the action and values of the Institut Pasteur, to publicize its achievements, and to further emphasize its need for donations by developing Pasteurdon. The aim of improving the Institut Pasteur's visibility is particularly to encourage fundraising, a vital activity which has its own specific strategy. The corporate communications campaign launched in 2010 was repeated in 2011 to reinforce this message and to inform the public about the Institut Pasteur's missions. The department also adopted a new institute-wide slogan: "For research, for health, for our future". At the same time it introduced an internal and external communications strategy on the Institut Pasteur's major achievements in the Investing in the Future program, which included the selection of three LabEx proposals and the creation of the Bioaster Technology Research Institute. For the first time, the Department of Communications and

Fundraising also published a collection of all the 2010 reports, including the annual report, the financial report, the corporate and environmental responsibility report, and the international report. Finally, a major project was launched to revitalize the Institut Pasteur's digital presence, particularly focusing on the pasteur.fr site. The new version of this site will be launched at the end of 2012.

PASTEURDON INSPIRES THE PUBLIC

INSTITUT PASTEUR

Pasteurdon 2011 enjoyed the support of major French companies and was organized in partnership with all French digital terrestrial network channels, making a major media splash. As well as the short programs broadcast free of charge by 12 digital terrestrial channels, a specific campaign was launched for this fifth edition of Pasteurdon with the slogan "Vaccinate our researchers against a lack of funds".



Left to right: Karine Ferri (Direct 8), Sandra Lou (TMC), Joan Faggianelli (Gulli), Sonia Mabrouk (Public Sénat), Cyril Hanouna (France 4), Ruth Elkrief (BFM TV), Alexandra Lamy,

The Institut Pasteur opened its doors to the public for the event over the weekend of October 15, inviting people to come and meet its scientists. This helped raise public awareness of science and biomedical research, and emphasized the importance of donations for the Institut Pasteur's public health activities. Several Institut Pasteur employees were involved in the event, along with volunteers from the "AXA Atout Coeur" foundation.

MORE COMMITTED SPONSORS

Large numbers of partner companies and corporate donors are continuing to support the Institut Pasteur, a recognized leader in its areas of expertise. Alongside loyal partners such as the Total Foundation, the Le Roch-Les Mousquetaires Foundation and Danone, new sponsors have rallied to the Institut Pasteur's cause, including Gaumont-Pathé cinemas (for Pasteurdon) and insurance broker Gras Savoye, with the Gras Savoye Grand Steeple Chase de Paris. Major support has come from our partner Sanofi this year in setting up a series of four international science awards, to be awarded for the first time in 2012.





the face of Pasteurdon 2011, Maya Lauqué (i-Télé), Patrick Chêne (LCP), Rebecca Fitoussi (NT1), Matthieu Delormeau (NRJ12), Ayden (DirectStar), Faustine Bollaert (W9).

DEVELOPMENT OF THE FONDATION PASTEUR SUISSE

As well as its foundation in the United States, based in New York, in 2010 the Institut Pasteur also set up a foundation under Swiss law, the Fondation Pasteur Suisse. It is composed of volunteer members and aims to develop scientific partnerships and to raise the funds needed to put them into action. Its headquarters are in Geneva. In 2011, as part of a new communications and development strategy, the foundation produced a presentation brochure and focused on building relations with the Swiss press. A fundraising dinner was also held, attracting a large number of private donors.

SCIENTIFIC RESEARCH SHOWCASED AT THE PASTEUR MUSEUM

The Institut Pasteur has continued its efforts to promote and explain its research to the public. Of the 30 press releases published this year, 20 focused on advances in research. Several

talks were also organized in Paris and throughout France. The "Mysteries of Science" and "Mr. Pasteur's Way" lectures, in particular, met with great success.

The Pasteur museum, which preserves the memory of Louis Pasteur's life and work in the apartment where he lived for the last seven years of his life, helps promote and raise awareness of Pasteurian history. The museum is involved in various activities and events to promote its work among the general public. It was approached by TV channel France 2 for the production of a docudrama entitled "Pasteur, the visionary" ("Pasteur, l'homme qui a vu"), broadcast in March 2011 and watched by over four and a half million viewers. The museum advised the script writers and allowed access to its document and image resources. The program clearly struck a chord with the public as the museum received over 10,000 visitors in 2011.



GENERAL ORGANIZATION

- GENERAL ORGANIZATION OF THE INSTITUT PASTEUR
- **BOARD OF DIRECTORS**
- **EXECUTIVE BOARD**
- **SCIENTIFIC COUNCIL**



BOARD OF DIRECTORS since July 2011

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ELECTED PASTEURIAN MEMBERS AND UNIT HEADS

Andrés Alcover

Head of Laboratory at the Institut Pasteur Head of the Lymphocyte Cell Biology Unit Immunology Department

Pedro Alzari

Professor at the Institut Pasteur Head of the Structural Microbiology Unit Structural Biology and Chemistry Department

APPOINTED PASTEURIAN MEMBERS AND UNIT HEADS

Ana Cumano

Head of Laboratory at the Institut Pasteur and Research Director at Inserm Head of the Lymphopoiesis Unit Immunology Department

Arnaud Fontanet

Head of Laboratory at the Institut Pasteur Head of the Epidemiology of Emerging Diseases Unit Infection and Epidemiology Department

APPOINTED EXTERNAL MEMBERS

Søren Brunak

Center for Biological Sequence Analysis Technical University of Denmark (Lyngby, Denmark)

Richard Moxon

Weatherall Institute of Molecular Medicine John Radcliffe Hospital, Headington (Oxford, UK)

Michel C. Nussenzweig

Laboratory of Molecular Immunology The Rockefeller University Howard Hughes Medical Institute (New York, USA)

David Sibley

Washington University School of Medicine Department of Molecular Microbiology (St. Louis, USA)



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Christophe d'Enfert

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Research Director at the CNRS (French National Center for Scientific Research) Head of the Viral Genomics and Vaccination Unit Virology Department

Antoine Gessain (Chairman)

Professor at the Institut Pasteur Head of the Oncogenic Virus Epidemiology and Pathophysiology Unit Virology Department

Lluis Quintana-Murci (Secretary)

Research Director at the CNRS (French National Center for Scientific Research) Head of the Human Evolutionary Genetics Unit Genomes and Genetics Department

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