2014 Institut Pasteur Annual Report

PASTEUR FOR THE WORLD

Institut Pasteur

Thanks to its 2014-2018 strategic plan, the Institut Pasteur is pursuing its ambitions with renewed energy – in particular, its four core missions of public interest: research, teaching, public health, and innovation, for the benefit of patients and society as a whole. The Institut Pasteur has played a pivotal role in the history of science, medicine and public health, and it continues to occupy a central place in today's global research landscape. It is committed to fulfilling the potential of its unique position, while looking ahead to the future with confidence. The strategic plan is based on a detailed, realistic analysis of the Institut Pasteur's strengths, the areas where improvement is needed, its rich heritage and its pioneering spirit. This dynamic vision for the future reflects the fundamental changes sweeping through the field, which are set to produce breakthrough innovations in the areas of research, medicine, and public health. Against this backdrop, the Institut Pasteur needs to embrace its role as a leader, in France and on the international stage.

"An ambitious, pragmatic strategic plan that strengthens the Institut Pasteur's leading role."

AN INTERDISCIPLINARY SCIENTIFIC VISION DRIVEN BY CURIOSITY

As the world faces a multitude of new scientific and health-related challenges – from rising life expectancy, global warming and globalized trade to emerging pathogens and resistance to anti-infective agents – the Institut Pasteur is rethinking its short- and medium-term scientific priorities. In the areas of excellence on which it has built its reputation, it has decided to prioritize a strategy of openness. By focusing on interdisciplinarity, transversal programs, translational research, stronger partnerships, and cutting-edge technology, the Institut Pasteur is in a position to offer a comprehensive, integrated response to the major biomedical issues facing the world today. Its goal is to improve our understanding of physiological and pathological mechanisms, with the aim of developing novel strategies for disease diagnosis, prevention, and treatment.

TALENTED PEOPLE AT THE HEART OF THE PASTEURIAN PROJECT

The Institut Pasteur's strategic ambitions are firmly rooted in its human resources. As it faces unparalleled demographic and scientific challenges, the Institut Pasteur needs to attract the very best talent in order to achieve excellence and extend its global reach. It has therefore decided to offer attractive recruitment packages, establish effective support structures, and create dynamic opportunities for professional development. These new measures are primarily geared towards young and mid-career scientists, with the aim of providing favorable conditions – including the creation of new research structures – to help them realize their potential. To support the development of these new research units, the Institut Pasteur is hosting more PhD students, postdoctoral fellows, visiting experts, and foreign researchers. It is actively promoting internal mobility within the International Network. Profit-sharing incentive schemes and new research chairs have also been set up to encourage innovation and scientific excellence.

TEACHING AND TRAINING: NEW AMBITIONS FOR THE FUTURE

Teaching and training have always been at the heart of the Institut Pasteur's missions, and they will have a key role to play in its future development. The Institut Pasteur's programs are taught by top scientists, leaders in their disciplines, who have the privilege of training the talented students and professionals that will form the scientific community of the future. This explains why teaching is one of the Institut Pasteur's top strategic priorities. The content of its courses reflects an interdisciplinary approach, and the topics covered are constantly being developed to keep step with emerging scientific issues. Emphasis is placed on international outreach and visibility, as illustrated by the development of the Pasteur-Paris University International Doctoral Program and the use of new digital methods that offer wider access to learning. The Institut Pasteur is committed to establishing and maintaining partnerships with the academic and industrial communities. It has also embarked on a plan to create an international campus by 2017, which will enable it to develop the resources it needs to achieve its ambitions in the area of teaching.

THE INTERNATIONAL NETWORK: STRENGTHENING AND OPTIMIZING A VALUABLE ASSET

The Institut Pasteur International Network, a vehicle for international cooperation in the fields of public health, teaching, and research, is composed of 32 institutes on every continent worldwide. As the research landscape experiences fundamental changes, with a new emphasis on global health and 'one health', the Institut Pasteur recognizes the major role the International Network can play in spearheading its plans for the future. It is therefore stepping up its efforts to develop interactions between the institutes in the network as an integral part of its policy. This will encourage and facilitate dialog among scientists and mobility between institutions, thereby boosting professional development, enhancing personal assessment processes, and helping secure funding for research programs. Efforts in some key areas are gradually being pooled. These include surveillance, monitoring, and issuing epidemiological and microbiological alerts, as well as developing research consortia on global public health issues relating to human, animal and environmental health.

32
institutes

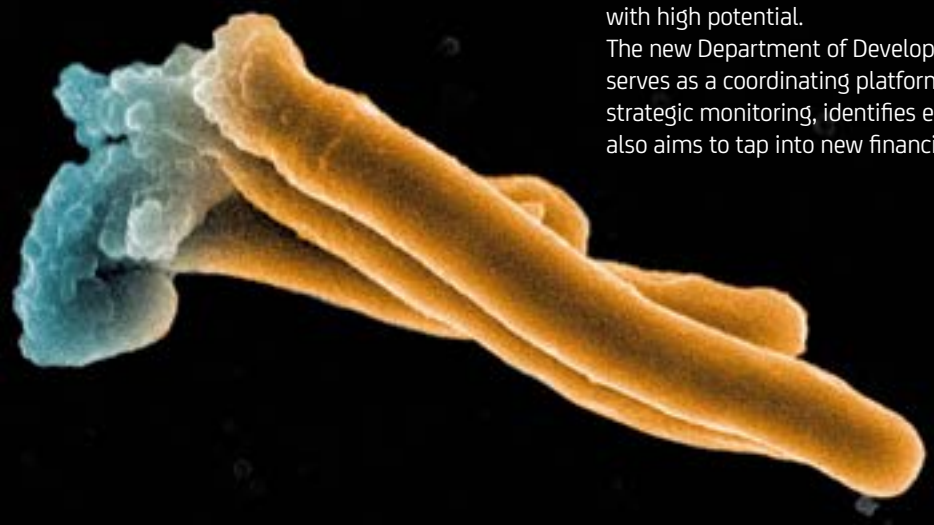
25
countries

ORGANIZATION OF RESEARCH: POOLING RESOURCES AND KNOWLEDGE

If the Institut Pasteur is to realize its ambitions for excellence, it needs an organizational structure that will enable it to develop its vision for open, collaborative, innovative research. It is therefore embarking on a large-scale structural transformation that will encourage transversality, interdisciplinarity, and the creation of synergies between its wide-ranging resources. The transversal research centers that were recently set up at the intersection of the scientific departments have a pivotal role to play in this new organizational structure. The aim of these new entities – the Center for Global Health Research and Education, which coordinates public health strategy; the Center for Biomedical and Translational Science, which serves as a "one-stop shop" for translational research; the Pasteur Center for Innovation and Technological Research; and the Center for Bioinformatics, Biostatistics and Integrative Biology, a leading bioinformatics hub – is to encourage internal cooperation and boost the Institut Pasteur's visibility with the outside world.
Finally, steps have been taken to pool collections of biological samples, and tools have been introduced to offer easier access to this outstanding heritage.

FLEXIBLE, TRANSVERSAL RESEARCH GOVERNED BY EFFECTIVE NEW STRUCTURES

The Institut Pasteur has introduced a series of interdisciplinary research programs to help maximize the potential of its research activities and enhance their international visibility and societal impact. These transversal programs, which can take various forms, are based on flexibility, transversality, and the pooling of resources and expertise, with the aim of encouraging cooperation among researchers, disciplines, and units. Transversal Research Programs are strongly based on interdisciplinarity. Inter-Pasteurian Concerted Actions must involve at least three institutes from the International Network, which collaborate on a pilot project or a specific international call for proposals. Targeted Incentivized Actions are smaller-scale projects financed by the institute's own funds. Major Federating Programs combine the work of several teams on topics with high potential.
The new Department of Development (Grant Office) serves as a coordinating platform: it carries out strategic monitoring, identifies eligible projects and also aims to tap into new financial resources.

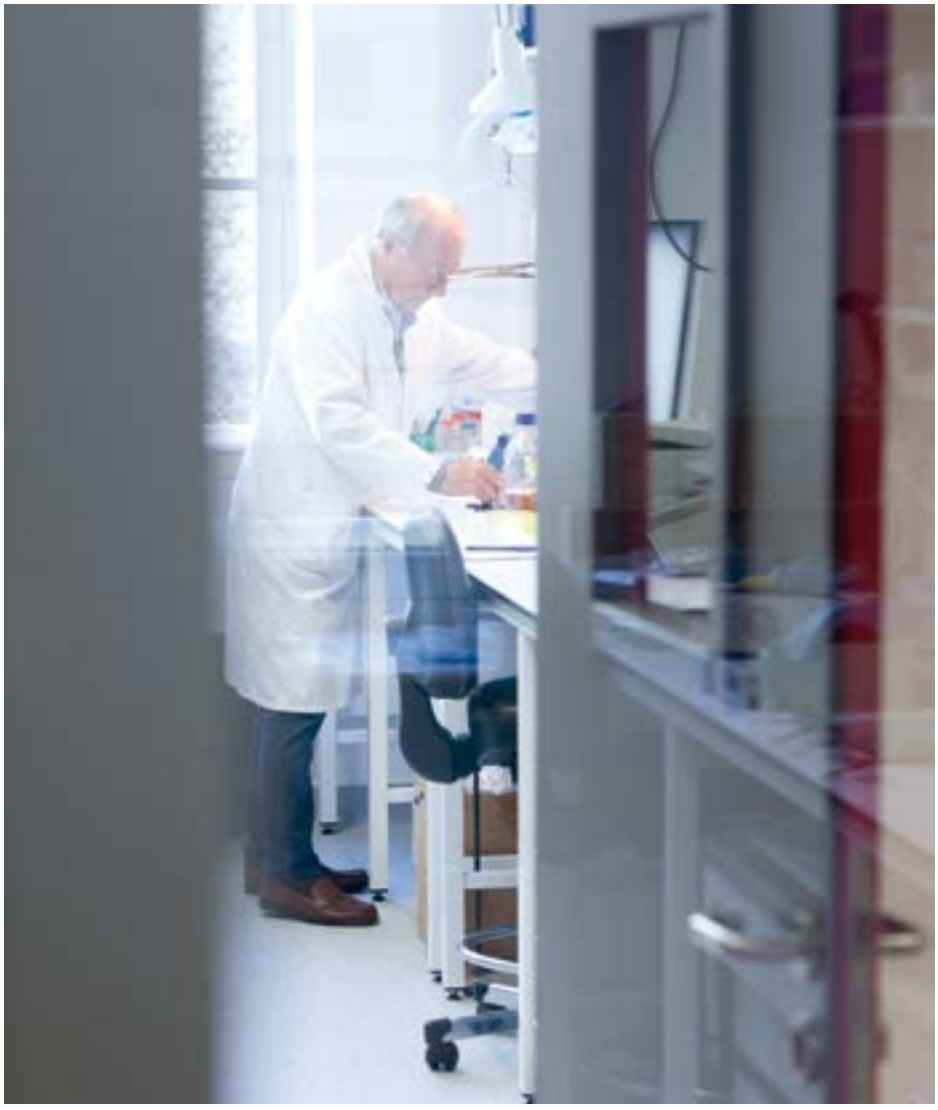


A KEY ROLE IN PUBLIC HEALTH, MEDICINE, AND TRANSLATIONAL RESEARCH

The Institut Pasteur's missions include epidemiological research and surveillance, and clinical research. Its National Reference Centers and WHO Collaborating Centers play a vital role in monitoring communicable diseases. New technological developments are helping sharpen their expertise in diagnostics and molecule characterization, and innovative "omics" approaches are used to shed new light on the complexity of the living organism. These new technologies are leading to the emergence of new, interdisciplinary professions. The Institut Pasteur is making an active contribution to these developments with an ambitious training program that is fully in line with its public health teaching missions. The Institut Pasteur is also stepping up its efforts to strengthen the translational nature of its activities, both basing its research on clinical observations and also ensuring that the latest advances in science benefit patients. This requires greater emphasis to be placed on medicine, and the Institut Pasteur is underpinning this new approach by involving an increasing number of doctors, veterinarians, and pharmacists in its activities.

AN INSTITUTE THAT PLAYS AN ACTIVE PART IN FRENCH AND EUROPEAN RESEARCH ECOSYSTEMS

The Institut Pasteur has developed an extensive network of partnerships. It hosts vast numbers of scientists, PhD students, and university lecturers/researchers as a result of its close links with public research organizations and universities in France. It is hoping to develop similar partnerships with the French Community of Universities and Institutions (COMUE). The Institut Pasteur is also stepping up its efforts to increase its visibility with French and European research funding bodies. An ambitious, focused strategy for calls for proposals, combined with proactive monitoring of funding opportunities by the Department of Development, should increase the Institut Pasteur's efficacy in this area. The Institut Pasteur also plays an active role in national research coordination bodies. A dedicated "Europe group" has been set up within the Department of Development to enhance its visibility within the European Research Area and its role in shaping European research.



TECHNOLOGY TRANSFER AND INDUSTRIAL PARTNERSHIPS: APPLYING AND SHARING RESEARCH FINDINGS

The protection and exploitation of research findings create a positive self-propagating cycle, generating real benefits for patients as well as resources and funding for new projects. In recent years, the Institut Pasteur has intensified its cooperation with academic and industrial partners. Compared to other institutions at the international level, the Institut Pasteur is particularly successful when it comes to generating revenue from business development, largely as a result of the work of the Research Applications and Industrial Relations Department (DARRI). This is an area in which the Institut Pasteur is constantly expanding its efforts, with the aim of consolidating its role as a leader in innovation, diversifying its patent portfolio, and encouraging new invention disclosures. It seeks to foster creativity by providing scientists with a supportive, competitive environment that includes incentive schemes for inventors. Support structures for business transfer and development activities have been strengthened at the international level, with new recruitments and the opening of dedicated offices in the US and China.

A BUILDING PROJECT FOR AN OPEN, COLLABORATIVE CAMPUS DRIVEN BY EXCELLENCE

The Institut Pasteur is housed on an outstanding site in central Paris. This campus is currently undergoing major changes with the aim of creating an environment where resources, knowledge, and talent can circulate freely, thereby facilitating collaborative projects.
The master plan that outlines the vision up to 2026 includes an initial stage, from the present until 2017, that involves building an international teaching and training center which will increase the space available for teaching activities by 80%. This puts the Institut Pasteur in a strong position to achieve its ambitions of developing partnerships with universities, increasing cooperation within the Institut Pasteur network, and setting up major courses on emerging topics. The Institut Pasteur is firmly on track for the future, with the creation of cutting-edge infrastructures including an Omics Center, a new research building, an electron microscopy platform, and an insectarium. The aim is to create a vast area for exchanging ideas and knowledge, a physical reflection of the spirit of openness and sharing that has always characterized the Institut Pasteur.

STEPPING UP FUNDRAISING, DONATIONS AND LEGACIES AND DIVERSIFYING RESOURCES

The relative share of government grants in the Institut Pasteur's revenue has continued to fall as a result of current tensions over public spending. The Institut Pasteur has been committed to increasing proceeds from donations since 2004, and this strategy to boost the share of private resources is becoming increasingly important. Fundraising is on an upward trend, largely as a result of a greater awareness among the general public of the Institut Pasteur's activities. Although the resources allocated to the Institut Pasteur are barely increasing, its overall return has risen considerably. The Institut Pasteur enjoys support from a huge number of small-scale donors, reflecting the long-standing Pasteurian commitment to serving the general public. It has embraced new digital methods for fundraising, including online donations and crowdfunding, and has continued to develop the possibilities for direct debit donations. The Institut Pasteur is committed to securing its financial stability by employing more targeted, tailored methods to appeal to major donors. It is particularly determined to extend the global reach of this strategy, especially in North America, China, Switzerland, and the Middle East.

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AWARDS AND APPOINTMENTS

FIVE-YEAR GROUPS
set up in 2014

5 young researchers recruited in 2014 to direct new five-year groups

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1st in-house call for proposals
Heart Morphogenesis five-year group

GIULIA MANINA
IBEID Laboratory of Excellence call for proposal
Microbial Individuality and Infection five-year group

JESSICA QUINTIN
Mycology Department
Immunology of Fungal Infections five-year group

PAULINE SPEDER
Revive Laboratory of Excellence call for proposals
Brain Plasticity in Response to the Environment five-year group

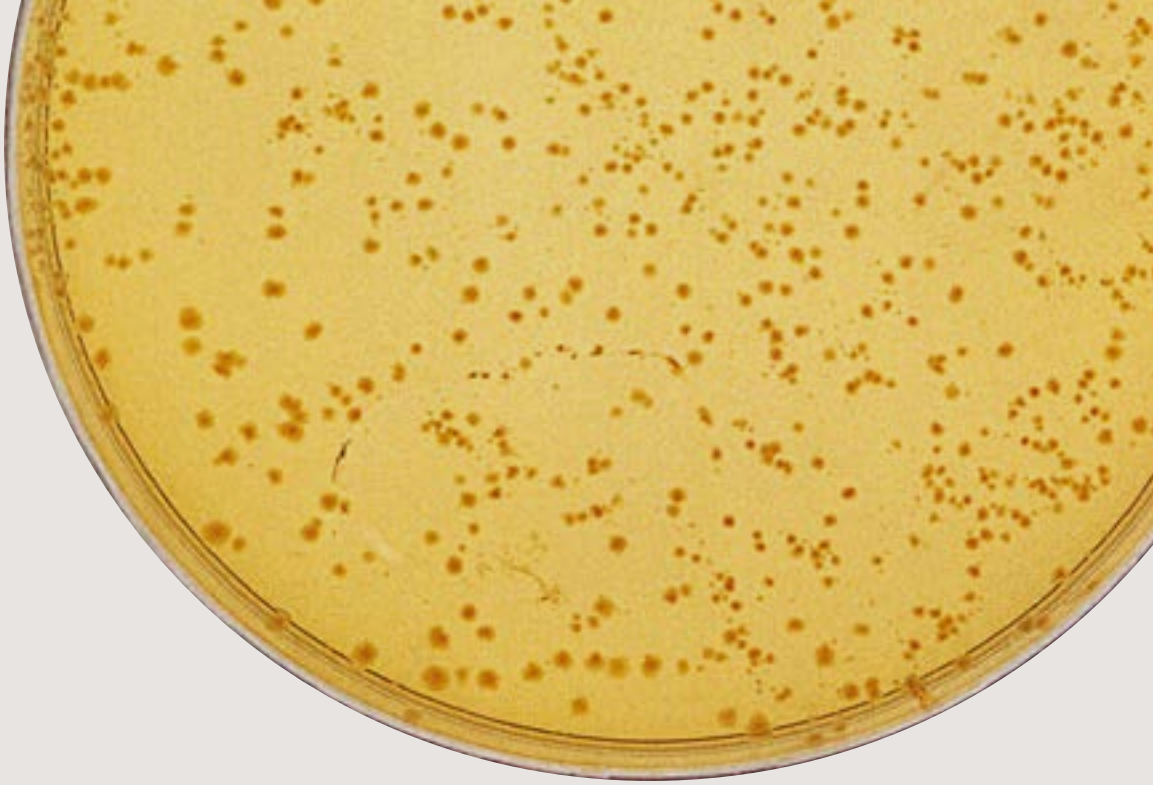
ELISA GOMEZ PERDIGUERO
Revive Laboratory of Excellence call for proposals
Macrophages and Endothelial Cells five-year group

3 five-year groups set up on campus in 2014

SVEN VAN TEEFFELEN
IBEID Laboratory of Excellence call for proposals
Microbial Morphogenesis and Growth five-year group

DAVID BIKARD
IBEID Laboratory of Excellence call for proposals
Synthetic Biology five-year group

HAN LI
Revive Laboratory of Excellence call for proposals
Cellular Plasticity and Disease Modeling five-year group



PEOPLE
appointed to the rank of professor in 2014

ROLAND BROSCH
Head of the Integrated Mycobacterial Pathogenomics Unit

ÉLISABETH CARNIEL
Head of the *Yersinia* Unit

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

MARIE-LISE GOUGEON
Head of the Antiviral Immunity, Biotherapy and Vaccines Unit

UNITS
set up in 2014

CHETAN CHITNIS
Malaria Parasite Biology and Vaccines Unit

OLIVIER GASCUEL
Center for Bioinformatics, Biostatistics and Integrative Biology

PIERRE BRUHNS
Antibodies in Therapy and Pathology Unit

MICHAELA MÜLLER-TRUTWIN
Host Determinants of Protection Against AIDS Unit

AGATHE SUBTIL
Cellular Biology of Microbial Infection Unit

ANNA-BELLA FAILLOUX
Arboviruses and Insect Vectors Research and Expertise Unit

MAJOR SCIENTIFIC AWARDS WON BY OUR SCIENTISTS IN 2014

PASCALE COSSART
Head of the Bacteria-Cell Interactions Unit

- FEBS/EMBO Women in Science Award
- The Institute of Medicine (IOM) of The National Academies

ANNE DEJEAN
Head of the Nuclear Organization and Oncogenesis Unit

- Inserm Grand Prix for medical research
- René et Andrée Duquesne Award

THOMAS BOURGERON
Head of the Human Genetics and Cognitive Functions Unit

- Fondation IPSEN Neuronal Plasticity Prize (under the aegis of the Fondation de France)
- Fondation FondaMental Chair of Excellence
- French Académie des sciences

PHILIPPE SANSONETTI
Head of the Molecular Microbial Pathogenesis Unit

- British Royal Society

CARMEN BUCHRIESER
Head of the Biology of Intracellular Bacteria Unit

- EMBO Member

LLUIS QUINTANA-MURCI
Head of the Human Evolutionary Genetics Unit

- Academia Europaea
- EMBO Member

PHILIPPE BOUSSO
Head of the Dynamics of Immune Responses Unit

- Fondation Victor et Erminia Mescle Award
- EMBO Member

MATTHEW ALBERT
Director of the Immunology Department – Head of the Dendritic Cell Immunobiology Unit

- Jacques Oudin Award (Société française d'immunologie)

MARIANA ALONSO
Perception and Memory Unit

- Axa-Académie des sciences Award – Major French research advances in biology presented by their authors

GÉRARD EBERL
Head of the Microenvironment & Immunity Unit

- Innovator Awards (Kenneth Rainin Foundation)

JÉRÔME GROS
Head of the Morphogenesis Regulation in Higher Vertebrates five-year group

- Schlumberger Foundation Award for education and research
- Vallee Foundation Award

MONICA ROLANDO
Biology of Intracellular Bacteria Unit

- Axa-Académie des sciences Award – Major French research advances in biology presented by their authors

MARIA CARLA SALEH
Head of the Viruses and RNA Interference Unit

- Langevin Award (French Académie des sciences)

NINA SESTO
Postdoc Institut Pasteur Memberships/Medals

- Jacques Monod Award (Fondation de France)

SHAHRAGIM TAJBAKHSH
Director of the Developmental and Stem Cell Biology Department – Head of the Stem Cells and Development Unit

- Générale de Santé Foundation International Prize for Research in Cell Therapy and Regenerative Medicine (French Académie des sciences)

PIERRE-OLIVIER VIDALAIN
CNRS/Institut Pasteur

- CNRS Bronze Medal

FERNANDO ARENZANA
Viral Pathogenesis Unit
• Georges, Jacques et Elias Canetti Award

ODILE PUIJALON
Visiting Scientist
• Fondation Georges Zermati Award

EDUARDO ROCHA
Head of the Evolutionary Microbial Genomics Unit
• Pasteur Vallery-Radot Prize

MICHAELA MÜLLER-TRUTWIN
Head of the Host Determinants of Protection Against AIDS Unit
• Pasteur Vallery-Radot Prize

BENOÎT ARCANGIOLI
Head of the Dynamics of the Genome Research Unit
• Fondation Thérèse Lebrasseur Award

International Network

PHILIPPE BUCHY
(Institut Pasteur in Cambodia, Virology)
• Christophe Mérieux Prize (Institut de France)

BENOIT WITKOWSKI
(Institut Pasteur in Cambodia)
• Traineeship Grants, Calmette & Yersin Program

GUILLERMO ARANGO DUQUE
(INRS–Institut Armand-Frappier Research Center, Montreal)
• Robert Deschiens Prize from the Society of Exotic Pathology

OANH THI HAI KHUAT
(Founder and Executive Director, Center for Supporting Community Development Initiatives, Vietnam)
• Dedonder Clayton Award

EXECUTIVE BOARD APPOINTMENTS

ISABELLE BUCKLE
Vice-President Research Applications and Industrial Relations

ODILE GELPI
Vice-President Medical Affairs and Public Health

JEAN-FRANÇOIS CHAMBON
Vice-President Communications and Fundraising

PIERRE LEGRAIN
Vice-President Development

ROSE-MARIE VAN LERBERGHE

"Our vision for the future of the Institut Pasteur is very clear."

What are the first conclusions that you have drawn from the strategic plan launched in spring 2014?

This plan created a project-based dynamic, clear motivation on campus, and a perceptible sense of fresh momentum for external observers. The plan provided for several major operational commitments, starting with the strengthening of the International Network, which will be given a central role in our organization. From our campus in Paris, we do not always realize the extraordinary reach these institutes have worldwide. In Africa and Asia, they are recognized as major players in public health, and we have a duty to support and maintain this mission, while developing research activities. We have therefore allocated additional resources to develop research in these centers. The second major focus area is bioinformatics. We have also freed up new resources to make sure we keep in step with the developments in life sciences, which are becoming increasingly dependent on data collection and analysis. The third priority, which is particularly important to me, is our human resources policy. This is absolutely vital for our success. With all these new measures set out in its strategic plan, I believe that the Institut Pasteur has a very clear vision for its future and is making sure it has the resources it needs for its development.

"From our campus in Paris, we do not always realize the extraordinary reach these institutes have worldwide."

What is the financial situation of the Institut Pasteur, and how are the various resources projected to grow?

The plan is based on the premise that our government contributions, as well as our donations and legacies, will remain stable. It also takes into account the prospect of growth in our business development and a significant increase in fundraising at international level. Our government grant has decreased in relative terms, but we hope that it won't fall any further as this grant reflects the contribution we make to the scientific visibility of our country. One of the most pressing concerns for the Board of Directors is to maintain a sound financial balance. The Board has held follow-up meetings to discuss the strategic plan on the basis of predefined indicators; this has enabled it to monitor the implementation of the plan and control any risks.

Is it necessary to attract major figures in scientific research to improve the Institut Pasteur's international visibility and appeal to donors?

I find this strategy reasonable as long as these scientists have the recognized skills and expertise needed to underpin our development. But my approach isn't merely based on attracting high-caliber scientists to the Institut Pasteur. I think that the Pasteurian spirit has always involved us serving as what we might now term an "incubator" for the development of young scientists. What's difficult is achieving a balance between external recruitments and internal promotions. We have responded to this challenge by putting together "packages" to attract foreign scientists and also creating "chairs of excellence" to encourage the development of internal talent.

What do you see as the main advantage of the Paris campus for young scientists?

Foreign scientists tell us that they appreciate the opportunity to meet experts from other disciplines on the Paris campus. I truly believe

that this interdisciplinarity is a real strength. They also feel able to take more risks at the Institut Pasteur than elsewhere. We are firmly committed to this approach which embraces risk-taking and interdisciplinarity. It's what helps us remain one step ahead of our competitors.

One of the Institut Pasteur's slogans alludes to the fact that its aim is to make discoveries, not profit. Does that still hold true today?

As a non-profit organization, we enjoy favorable tax treatment. This represents a contribution from the government, which, although we don't actually put a figure on it, is hugely important. But that doesn't mean that we are not interested in deriving value from our research – quite the contrary. We may not have shareholders and pay dividends, but our scientists make discoveries and file patents.

"We may not have shareholders and pay dividends, but our scientists make discoveries and file patents."

The centers in the International Network differ enormously from one to the next. How do you manage that diversity?

When I visited some centers in Africa and Asia, I was struck by the role they play in training and promoting local expertise. In countries with limited resources, whose universities are often poorly equipped, the Institut Pasteur has a role that goes well beyond its public health mission. That doesn't apply to the institutes set up recently in Asia and South America, whose cutting-edge research and technology attract scientists from all over the world. But we have a responsibility to all the institutes in the International Network. And the International Network is extremely valuable for our country's international development – that is something I am sure the French Foreign Ministry is well aware of.

CHRISTIAN BRÉCHOT

"We have given ourselves the resources we need to explore new frontiers in biomedical research and to develop a new, international, model for research at the Institut Pasteur."

The world of medical research is currently undergoing a major transformation, and the traditional boundaries between disciplines are becoming blurred. How can the Institut Pasteur best adapt to these new forms of knowledge, which are revolutionizing our understanding of disease and our approach to healthcare?

We are living through a unique period in which the lines that once separated scientific disciplines are disappearing, personalized medicine is gradually becoming a reality, and integrative biology and bioinformatics are rapidly gaining ground. This conceptual and technological revolution is affecting all fields of medical research. And the new landscape that is emerging is also changing the Institut Pasteur's scientific identity and our approach to public health. We have had to rethink the way we organize our research. In geopolitical terms, this new paradigm is leading to a new global order in which emerging and developing countries will have a significant role to play. We need to approach these changes with a clear scientific and organizational vision, and equip ourselves with new resources.

The strategic plan launched in spring 2014 was designed to meet these challenges. It was drawn up following a period of collective reflection and is based on four main pillars: the excellence of members of the Pasteurian community; interdisciplinarity and the development of bioinformatics and integrative biology; teaching; and the strengthening of the Institut Pasteur International Network. The Institut Pasteur is at the center of an extensive network of 33 institutes[1] around the world, which puts it in a unique position compared to other major players in research and public health when it comes to exploring these new frontiers in medical research and pursuing our public health, research and teaching missions. The Institut Pasteur International Network is at the heart of our strategy.

What have been the first outcomes of the strategic plan launched in 2014?

The initial priority was to strengthen the Institut Pasteur's attractiveness to the outside world, while developing an ambitious human resources policy on the Paris campus. To reach out to external experts, we put together highly attractive packages with the guidance of our International Scientific Council. Internally, we introduced new career development plans to better recognize the quality and diversity of our staff's career paths. We also set up a Chairs of Excellence program for our scientists for a transitional three-year period with the possibility of renewal. We have already firmly consolidated our bioinformatics and integrative biology activities, teaching, and the Institut Pasteur International Network. This strategy of excellence is largely based on our cooperation with other French research organizations and universities, particularly within Aviesan, an alliance for all those involved in life sciences research in France.

How can we remain at the forefront of research in such a wide range of disciplines? Aren't we at risk of spreading ourselves too thinly?

One of the hallmarks of the Institut Pasteur is that its research is underpinned by curiosity – it's the science itself that drives our work. But recent

developments in science mean that we currently work in a broad range of highly varied disciplines, including microbiology and infectious diseases, immunology, developmental biology, regenerative medicine, neuroscience, genetics, and cancer. We have deliberately chosen to maintain and nurture this multidisciplinarity, which provides us with a solid basis for success and discovery. One major element of our strategic plan is to promote transversal research organizations: we have set up four research centers to encourage synergy between the 11 research departments and the 33 institutes[1] in the International Network in the areas of bioinformatics and integrative biology, translational research, innovation and technological research, and global public health. We have also created transversal research programs. For example, we know that there are close links between microbes and chronic diseases via inflammation. Research is currently being carried out on the gut microbiota which plays an important role in the development of many chronic diseases such as cancer, obesity and diabetes, and possibly also neurodegenerative and psychiatric disorders. With our extensive knowledge of microbes, we can offer specific expertise in this field and can also encourage interaction with experts from different disciplines such as cancer research and neuroscience.

Medical research increasingly requires sophisticated, expensive infrastructures. How are you planning to fund all these projects, and how do you see your relationship with industry developing?

It is vital for us to strengthen our research infrastructures to ensure that we remain at the cutting edge in terms of our research equipment. We have recruited several high-caliber staff members in this area. Developing our industrial partnerships is a key component of our strategy – these partnerships have always been vital for the Institut Pasteur, and they continue to play an essential part in our development. They enable us to launch research projects that would be unthinkable without such alliances and funding. Our decision to strengthen our vaccinology research, a discipline firmly rooted in Pasteurian tradition with a crucial role to play today, illustrates the huge potential in combining fundamental research and the development of partnerships with industry. In 2014, we reorganized our Industrial Partnerships Department, placing a stronger emphasis on developing international partnerships with stakeholders in North America and Asia.

> "The core mission of the Institut Pasteur is to carry out fundamental research with the aim of improving public health throughout the world, for the benefit of the entire global population."

Has public health always been a key part of the Institut Pasteur's development?

The core mission of the Institut Pasteur is to carry out fundamental research with the aim of improving public health throughout the world, for the benefit of the entire global population. The major health crisis that we witnessed with the Ebola epidemic demonstrated the unique position our institute occupies in the area of public health. This crisis confirmed that we were capable of combining top-level fundamental research with highly effective action in the field. In today's world, severe epidemics can suddenly flare up without warning, as the latest Ebola episode reminded us. The Institut Pasteur International Network has a vital role to play in this area. We are currently setting up a new Institut Pasteur in Conakry to strengthen our presence in West Africa. We have also seen a significant rise in chronic diseases, and we must redouble our efforts to tackle this problem, too. The Institut Pasteur has the resources and the expertise – in terms of scientific know-how and public health – to step up to these two challenges.

Deciphering and analyzing genetic and biological data is increasingly important in medical research. How are you approaching this new trend?

We are living in the big data age, where the sheer quantities of data being shared are reaching ever new heights. We have achieved a conceptual breakthrough: disciplines that were previously separate are working together to develop technologies that enable us to explore all this data more easily. That makes a huge difference – we are seeing the arrival of major players from the world of computing with the potential to revolutionize global health. We have set up a Center for Bioinformatics, Biostatistics and Integrative Biology to reflect these new scientific and technological developments, placing ourselves in an ideal position to attract leading engineers. The creation of this center also illustrates the importance of developing transversal, multidisciplinary approaches, as set out in our strategic plan. Integrative biology is a new way of thinking and working that has an impact on all scientific disciplines.

So is "big data" another of the Institut Pasteur's areas for development?

Data sharing applied to medicine and public health has enormous potential. By making sure that each of our centers has the ability to perform high-throughput sequencing and bioinformatics analysis, we are developing a network of excellence at an international level. This is a major shift, and we know that our ability to analyze biological data will open up new possibilities for us. An institute such as ours has to rise to the challenge in this field by recruiting scientists who will prepare the ground for the exploration of these new frontiers. The center for bioinformatics and integrative biology will work with all our teams of scientists in the pursuit of this goal. Together they will be well placed to explore the new frontiers of research that will emerge over the next five to ten years.

1. Two cooperation agreements for the establishment of an Institut Pasteur in Conakry at the end of 2016 were signed by the Institut Pasteur: one with the Guinean Government and another with the French Development Agency (AFD).

EBOLA

The Ebola virus causes high fever and internal bleeding that often proves fatal. In 2014, the largest known outbreak to date swept through West Africa.

The Institut Pasteur Ebola Task Force

On September 1, 2014, the President of the Institut Pasteur decided to set up a task force composed of teams of scientists and epidemiologists in Paris and within the International Network. This task force was given clear objectives: to help address the urgent need to diagnose cases of Ebola in Guinea, to implement a research program to support emergency response actions during the ongoing crisis, and to prepare for the future by developing new diagnostic and therapeutic tools and/or vaccines.

Institut Pasteur response in Africa

The Institut Pasteur in Dakar, which houses the WHO Collaborating Center for Hemorrhagic Fever Viruses and Arboviruses, was contacted in March 2014 by WHO and the Guinean Government to help with the investigation of the outbreak. The Institut Pasteur in Dakar was the first African organization to set up a laboratory in Guinea (in Conakry) and to confirm suspected cases. Teams from the Institut Pasteur and the Institut Pasteur in Dakar also trained Guinean technicians in diagnosing the Ebola virus and in methods of taking samples from patients.

On November 19, 2014, a treatment center with 60 beds was opened at the center of the epidemic outbreak in Macenta, in Guinea's forest region. This center includes a diagnostic laboratory set up by the Institut Pasteur. Since then, teams of volunteer scientists, trained at the Institut Pasteur in Paris, have been screening those suspected of infection.

"Reducing the time and risks involved in the current diagnostic procedure is a vital step in improving treatment for patients."

The Institut Pasteur steps up its Ebola research in France

The National Reference Center for Viral Hemorrhagic Fevers analyzed samples from Guinea and made the first positive diagnosis. As well as analyzing samples and monitoring suspected cases in France, since the end of November 2014 this team has been involved in the work of the Macenta diagnostic center, in close cooperation with the Laboratory for Urgent Response to Biological Threats (CIBU). The CIBU lab helped diagnose the samples from Guinea and also trained volunteer scientists who were then sent to the center in Macenta to help with diagnosis.

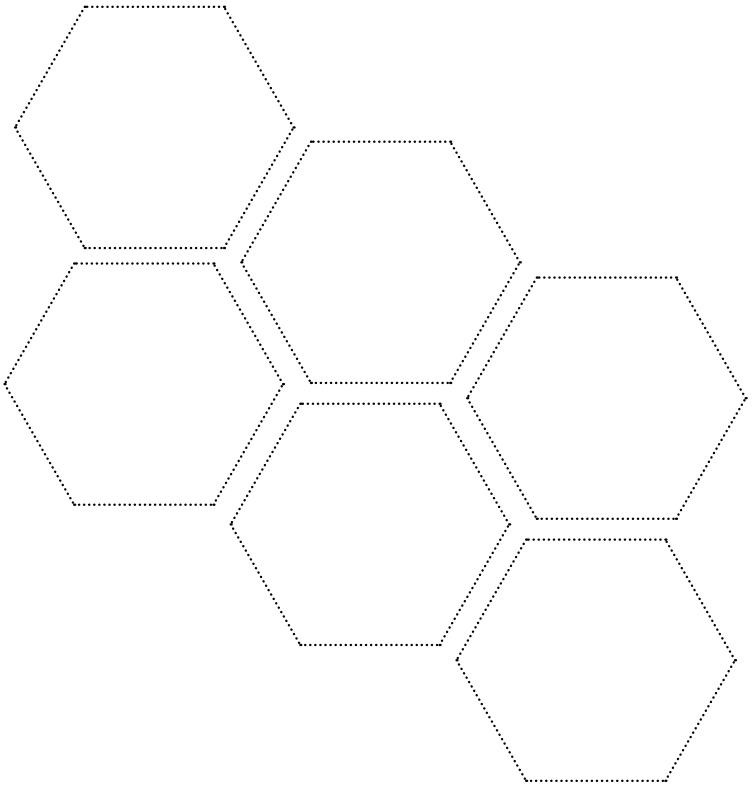
Improving diagnosis. The standard process used to diagnose Ebola currently takes two to three days and requires sophisticated equipment and highly qualified medical workers. Reducing the time and risks involved in the current diagnostic procedure is a vital step in improving treatment for patients. At the Institut Pasteur, several research programs have been set up for the development of rapid diagnostic tests that are cheap and easy to use in the field. The test currently being developed at the Institut Pasteur to detect the Ebola virus is at least as reliable as the standard tests and can provide a diagnosis in under an hour.

Vaccines for the Ebola virus. Two vaccines are currently being developed at the Institut Pasteur. The first is a preventive vaccine based on the technology used in the measles vaccine, one of the safest and most effective vaccines available on the market today. The scientists are currently testing different combinations of this vaccine model. The second vaccine is designed to act as a post-exposure treatment. This vaccine could therefore be given to those already infected by Ebola as well as to medical staff exposed to the virus. The technology used for this vaccine is based on lentiviral vectors.

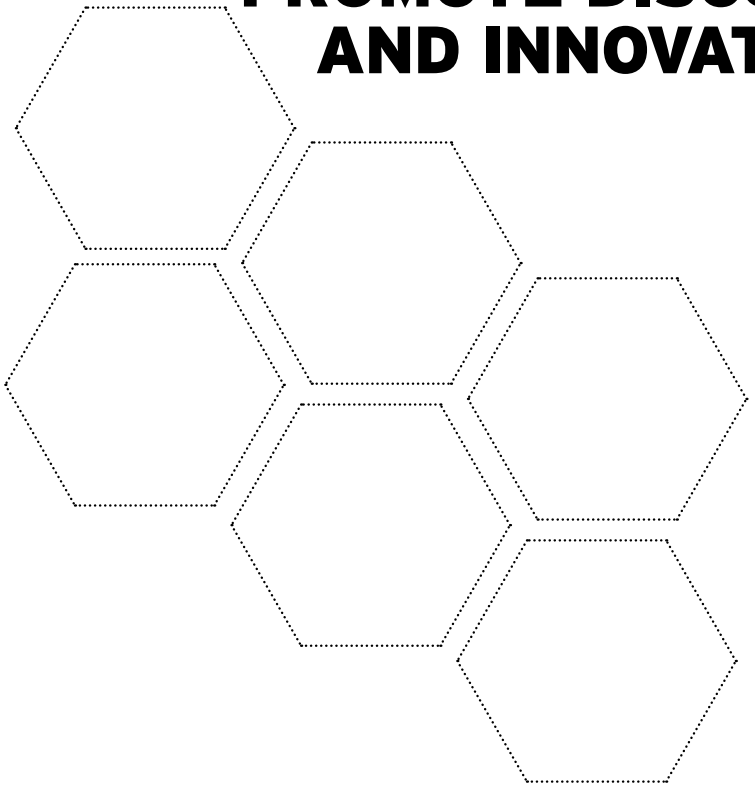
Improving our understanding of the Ebola virus. Developing effective treatment strategies involves keeping a close eye on the evolution of the Ebola virus. Scientists have analyzed samples from patients who were infected in different regions in Guinea during the epidemic. Monitoring variations in the virus also provides useful additional information to complement epidemiological studies on chains of transmission in Guinea. This data demonstrates the positive impact that control measures are having on the development of the epidemic, but it also highlights the challenges that need to be overcome in order to contain the virus in major urban centers.

"The ability to be surprised at the 'right moment' is the mind's first step towards discovery."

LOUIS PASTEUR



A MULTIDISCIPLINARY AND TRANSVERSAL APPROACH TO PROMOTE DISCOVERY AND INNOVATION



RESEARCH

130
research units

11
scientific departments

4
transversal research centers

1
Department of Development

The Institut Pasteur's scientific ambitions require a suitable research infrastructure that reflects and supports its priorities. The Institut Pasteur is currently organized into departments, but it has embarked on an ambitious program to transform its research infrastructure on the basis of transversality, interdisciplinarity and pooling of resources. The recent transversal research centers play a pivotal role in this new organizational structure.


Cell Biology and Infection
Developmental and Stem Cell Biology
Structural Biology and Chemistry
Genomes and Genetics
Immunology
Infection and Epidemiology
Microbiology
Mycology
Neuroscience
Parasites and Insect Vectors
Virology
Center for Translational Science
Center for Global Health Research & Education
Center for Innovation and Technological Research
Center of Bioinformatics, Biostatistics and Integrative Biology

4 transversal research centers

Center for Translational Science (CRT)

2014 was a pivotal year for the establishment of the Center for Translational Science (CRT). Following a period of reflection to determine the overall concept, in 2014 talks were held between all the teams involved and work began in earnest to get the Center off the ground.

The teams met at plenary meetings and working group sessions to lay the foundations for the processes that would enable the Center to become operational, based on the shared goal of **developing links between fundamental research and clinical application.** During 2014, the Center's team held meetings in each department with the various unit heads to explain its role and to offer assistance to scientists who wish to **add a translational dimension** to their projects.

The three complementary components of the Center (the clinical core, the technology cores, and scientific events and training) worked together to develop communications and activities based on this new concept, with the aim of raising awareness among scientists on campus as well as in the International Network, and also among health organizations and clinicians that might be interested in strengthening partnerships. The aim was also to increase visibility among industry stakeholders, whose involvement is vital for implementing projects. Several events were organized for this purpose; information can be found on the new dedicated website.

The preliminary phase in 2014 also provided an opportunity to determine the Center's governance structure. Matthew Albert directed the Center until the end of the year: his extensive scientific expertise and top-level international experience in translational research were invaluable for guiding the process of reflection and scientific development during this crucial initial stage, with the ultimate aim of creating a center with the potential to **be ranked among the leading international centers in the field.** An Executive Committee composed of Institut Pasteur scientists was set up and held regular meetings throughout the year; this proved to be highly constructive and resulted in the establishment of an effective structure.

Center for Innovation and Technological Research (Citech)

The Center for Innovation and Technological Research (Citech) has been established as a central technological hub to advance technological research and innovation and meet the immediate and future needs of biological projects developed on campus and within the Institut Pasteur International Network.

The Citech aims at **establishing itself as a leader** in new technologies for the biological community and breaking technological barriers to strengthen research and applications within the Institut Pasteur's global scientific and public health priorities.

The Citech brings together under a unique management the existing technological platforms, the animal and insect houses, and a newly created Technology Laboratory located on the 1st floor of the François Jacob building. The Citech will **stimulate interactions between research units and technology groups** in order to develop, give access to and share state-of-the-art technology equipment, expertise and training.

It will also nurture **interdisciplinary collaborations** and bring together physicists, mathematicians, chemists, computer scientists, biologists and medical doctors from the campus and outside, that are willing to combine their diverse expertise and solve emerging challenges at the frontiers of biological research. A number of innovative technologies will be hosted in the TechLab and be made available to scientists through calls for projects. This technological environment will contribute to the visibility and **attractiveness of the Institut Pasteur** worldwide.

It will also help **create new career opportunities** for scientists, engineers and technicians through internal mobility. Partnerships with institutional or industrial stakeholders and engineering schools and universities will also be actively pursued to encourage exchanges and external training.

Finally, the Citech technological innovations are also expected to **generate revenues** through licensing and/or the creation of technological start-ups.

Center for Global Health Research and Education (CGH)

The Center for Global Health (CGH), directed by Prof. Arnaud Fontanet and launched in September 2014, aims at strengthening the Institut Pasteur International Network's global health activities implemented around the world. The CGH has three lines of intervention.

Develop research to improve human health

The CGH promotes multisite, interdisciplinary research projects that target major global health challenges to develop innovative context-specific preventive, diagnostic, and therapeutic solutions.

Train tomorrow's scientists

The CGH develops new training initiatives to provide future scientists with hands-on experience, knowledge and skills that will enable them to lead ambitious, interdisciplinary cutting-edge research projects, taking into account animal and environmental dimensions, translational research, big data, etc.

Outbreak investigation

The CGH coordinates an international task force of scientists of different disciplines to respond to and investigate infectious disease outbreaks. The task force utilizes the Institut Pasteur's expertise and members are deployed at an early stage of an infectious disease outbreak upon request from national authorities and international organizations. The task force also develops epidemiological, basic and translational research on emerging pathogens.

Center of Bioinformatics, Biostatistics and Integrative Biology (C3BI)

Scientific research has entered the big data era. The ability to analyze, store, share, and protect considerable amounts of data is now a major strategic challenge for any world-ranking research institute. The Institut Pasteur set up this Center at the beginning of 2015 to respond to these challenges.

Substantial resources were allocated for the creation and development of the Center, with the recruitment of 40 bioinformaticians between 2014 and 2017 and plans to renovate the intern building to house the Center. The aim is to **facilitate collaborations** in bioinformatics and biostatistics, **to support and develop training** in these fields, to encourage exchanges between all the Institut Pasteur teams, and to **stimulate the development** of new computational and statistical approaches for biological data analysis and modeling.

In its pursuit of these objectives, the Center is supported by four key sources of expertise:

– a series of eight bioinformatics units or laboratories, two of which were recently created;

– the CIB, the Center of Informatics for Biology, which is responsible for developing and maintaining bioinformatics tools and for making large-scale databases available for Institut Pasteur teams;

– the IGDA, the International Group for Data Analysis, which works with the 32 institutes in the International Network, spread over 25 countries. IGDA is responsible for coordinating and pooling bioinformatics and statistics resources within the network, with a particular focus on training;

– the HUB, an innovative entity that was recently set up to provide support for the Institut Pasteur's research units and platforms in bioinformatics and biostatistics via an ongoing call for proposals; more than 40 projects have already been submitted, and 12 have been completed.

The aim of the Institut Pasteur's Bioinformatics platform, composed of the CIB, the HUB, the IGDA and the bioinformaticians in the Institut Pasteur's units, is to provide a **quality service** for the entire campus and the institutes in the International Network, and to generate greater international visibility for the methods, software, and servers developed at the Institut Pasteur.

Department of Development

The Department of Development was set up in September 2014 to help implement key components of the strategic plan, in particular to develop collaborative research between institutes in the International Network, to make sure the Institut Pasteur's research is structured effectively to tackle societal challenges and improve our knowledge of human biology, and to promote interdisciplinary research. In the pursuit of its missions, the department builds up detailed knowledge of all the research activities carried out on the campus in Paris and within the International Network.

A specific office was set up to offer support for scientists in applying for project funding from institutional sponsors at national, European and international level and from charitable foundations. Finally, a further office within the department is tasked with implementing strategic research programs, initially by using the Institut Pasteur's own funds to launch promising programs then by developing those programs with external funds through partnerships.

"Identifying, launching, supporting, contributing…"

Identifying, characterizing and mapping all the Institut Pasteur's research activities

This task is carried out using a tried and tested method, namely compiling information by conducting interviews with the scientists leading research projects and programs, and gathering available documentation such as publications, projects submitted for funding, partnership agreements, patents and invention disclosures, etc. All this information is grouped together in a database that can be accessed by all the Institut Pasteur departments.

Launching and supporting strategic research programs

The department launched a series of strategic research programs with a dedicated budget, clear scientific vision and leadership to encourage the development of synergies, guarantee long-term coherence, and promote field-based initiatives. The first Vaccinology program resulted in an international conference and a call for proposals on innovative ideas in vaccinology, which received submissions from a number of teams. Three projects were selected and are due to begin in 2015. The second program, Microbes and Brain, aims to develop interdisciplinarity between neuroscience, microbiology, and immunology. An internal conference was held to identify priority research areas, and a call for projects will be launched in 2015.

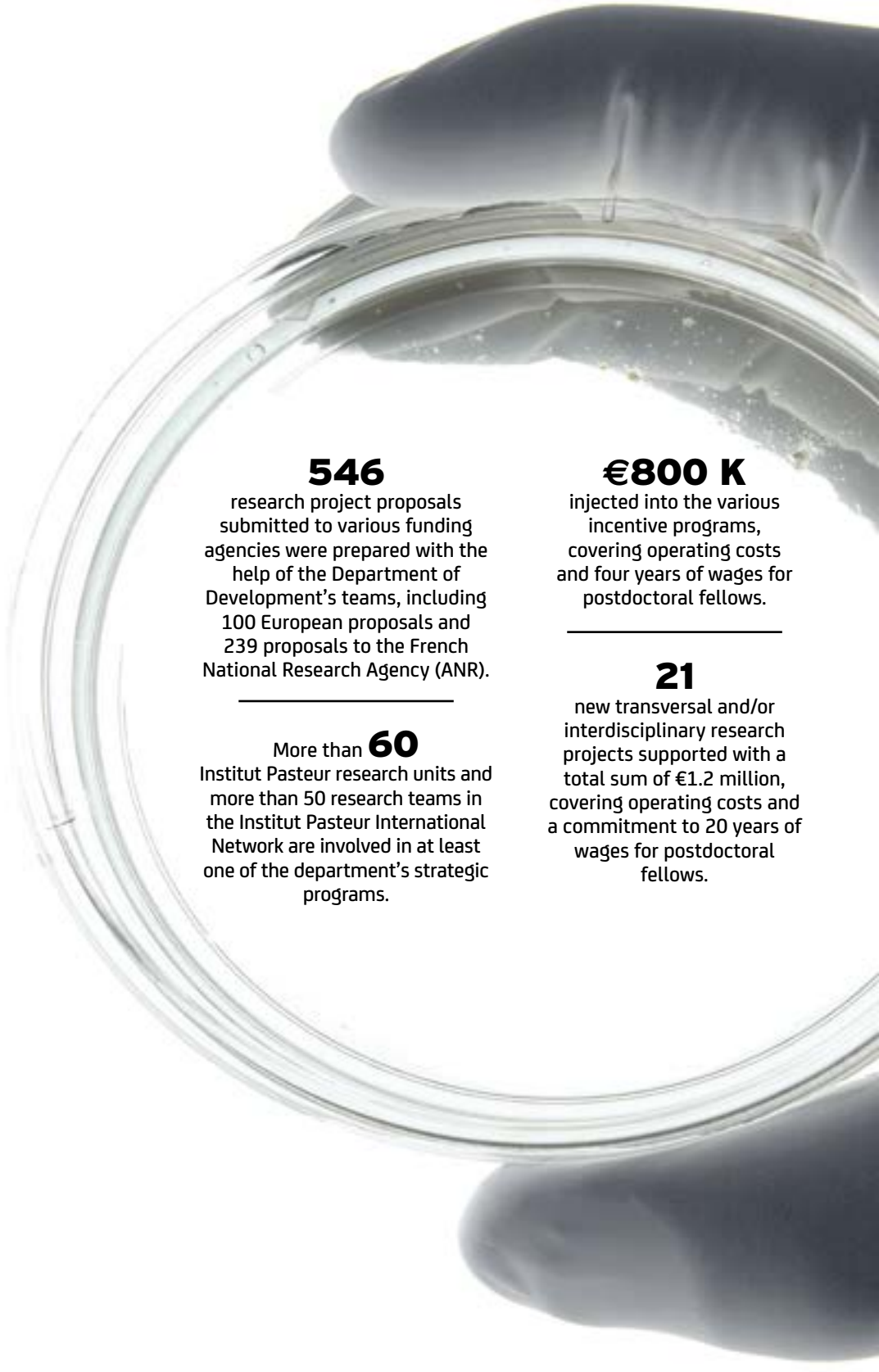
Targeted incentive measures were implemented to respond to scientific challenges or specific opportunities for impact. These include a project to tackle dengue involving complementary approaches to eradicate the mosquito vector and to develop new vaccines; a project in partnership with the Weizmann Institute in Israel on the highly competitive topic of non-coding regulatory RNAs in microbes; and an initiative on medical mycology that aims to revisit a number of scientific concepts in order to identify new therapeutic targets. An Ebola task force was also set up in response to the epidemic crisis, offering technical expertise in the field alongside a series of diagnostic, vaccine and therapeutic research projects and conceptual research into the Ebola virus itself. This latter initiative is a perfect illustration of the Institut Pasteur's missions of conducting research, improving our understanding of a wide variety of scientific fields, and transferring fundamental knowledge to human health applications for the benefit of patients, in the context of a globalized world and in the pursuit of universal access to healthcare.

Contributing to the Institut Pasteur's strategy to extend its international reach and partnerships in all its areas of activity

The Institut Pasteur adapted its annual call for interdisciplinary collaborative research projects to include all the institutes in the International Network. Ten projects were selected, all involving one or more teams from the network. This reflects a real determination to strengthen this scientific community, spread across 25 countries, so that it will be well placed to tackle major public health challenges.

Identifying new sponsors for the Institut Pasteur and developing strategic partnerships

To ensure the success of these strategic programs, it is vital to encourage new sponsors to support the Institut Pasteur. We implemented specific measures to target international foundations working in the area of human health, philanthropists living abroad, and major pharmaceutical and non-pharmaceutical companies that are stakeholders in the global economy. This is a long-term effort, but a partner has already been found to support the large-scale Microbes and Brain program.



546
research project proposals submitted to various funding agencies were prepared with the help of the Department of Development's teams, including 100 European proposals and 239 proposals to the French National Research Agency (ANR).

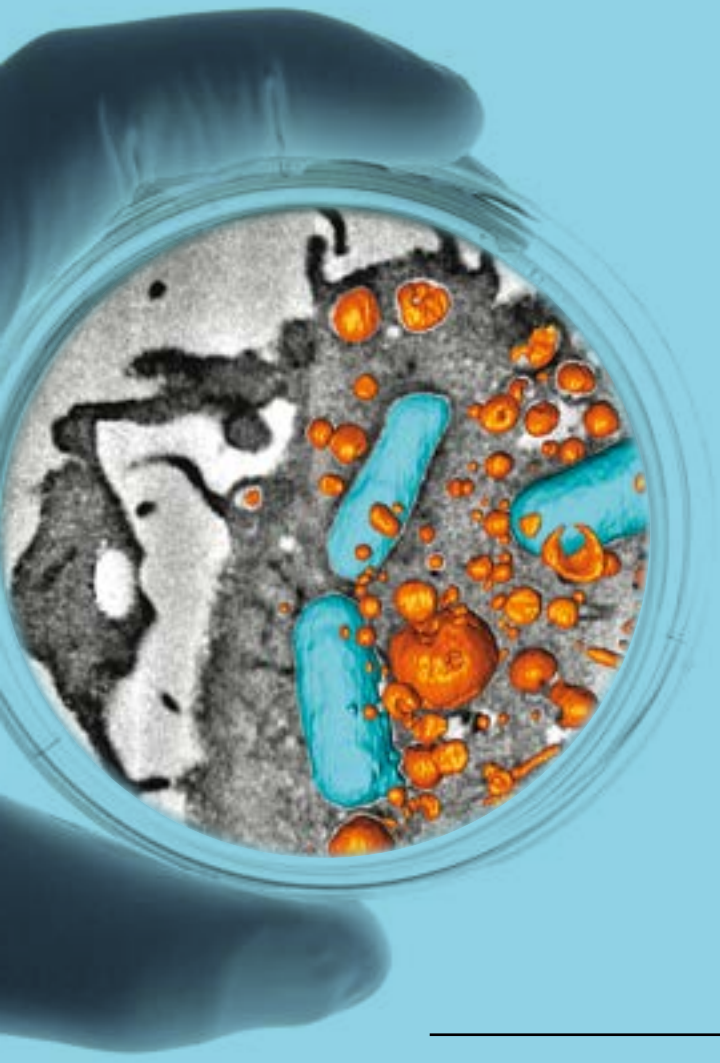
More than **60**
Institut Pasteur research units and more than 50 research teams in the Institut Pasteur International Network are involved in at least one of the department's strategic programs.

€800 K
injected into the various incentive programs, covering operating costs and four years of wages for postdoctoral fellows.

21
new transversal and/or interdisciplinary research projects supported with a total sum of €1.2 million, covering operating costs and a commitment to 20 years of wages for postdoctoral fellows.

CELL BIOLOGY AND INFECTION

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



Correlative microscopy (CLEM) of *Shigella* at the vacuolar stage. The bacteria are surrounded by micropinosomes.

The research carried out by the Cell Biology and Infection Department focuses on the interactions between infectious agents and their hosts.

Understanding infectious mechanisms requires a detailed study of cell function during infection. It is also crucial to understand the balance between commensal flora and host. Some teams concentrate on a particular infectious agent. Others focus on gaining a detailed knowledge of the cell, independently of any infectious context. A detailed understanding of cell functions is the only route towards providing an explanation of infection and disease mechanisms.

In addition, all departmental activities remain closely in tune with the development of new technologies, including imaging and image analysis, and genomics and postgenomics, and are committed to using a cross-disciplinary and quantitative approach.

DEREGULATION OF MEMBRANE TRAFFIC BY INTRACELLULAR BACTERIA

When they enter and are internalized by a host cell, intracellular bacteria are initially contained in a vacuole surrounded by a membrane. Rupture of the vacuolar membrane is an important process in reaching the host cytoplasm during infection, and concerns a large number of pathogenic bacteria such as *Listeria, Rickettsia, Francisella* or *Shigella.* For a long time, the molecular and cell mechanisms leading to the rupture of the vacuolar membrane remained poorly understood. The research team of Jost Enninga's unit uncovered new host cell subversion mechanisms used by *Shigella* to trigger vacuolar rupture. High-throughput screening identified a subset of host proteins that plays a key role in intracellular traffic and is involved in this process. In particular, the research team was able to find out how a bacterial effector succeeds in hijacking the host cell recycling compartment in order to disrupt the vacuolar compartment that contains the bacterium.

This research is also based on the use of state-of-the art techniques that combine fluorescence microscopy and focused ion beam scanning electron microscopy. It is an innovative approach, and has provided an unprecedented level of detail in furthering the understanding of the events giving rise to vacuolar rupture. These findings represent a significant conceptual advance in the general understanding of endomembrane integrity in hosts targeted by intracellular pathogens.

SEQUESTRATION OF AN ACTIVATOR BY A NEW TYPE OF RNA REGULATOR

Ethanolamine is a compound that is found in large quantities in the intestine. It is derived from phosphatidylethanolamine, which is present in all membranes and can be used by certain pathogenic bacteria for metabolism and energy production, giving them an advantage over commensal bacteria, which are unable to use phosphatidylethanolamine. The genes involved in this use of ethanolamine are called eut genes, and code for proteins that require vitamin B12 as a cofactor. Scientists from the Bacteria-Cell Interactions Unit, led by Pascale Cossart, discovered that, in the absence of vitamin B12, the *Listeria monocytogenes* bacterium produces non-coding RNA that sequesters the eut activator. This RNA is not produced in the presence of vitamin B12, and so the activator is free to activate the expression of eut genes. This is an example of a sophisticated type of regulation by a non-coding RNA that enables the expression of enzymes only when their cofactor is present. It is the first example of a type of regulation that was little known until now, and which is highly efficient and probably relatively common in bacteria.

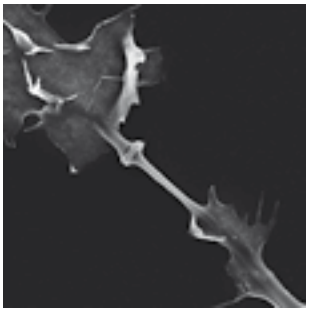
Prizes and awards

Grand prix Inserm 2014: Anne Dejean

FEBS EMBO Women in Science award 2014: Pascale Cossart

IEEE Signal Processing Society Distinguished Lecturer: Jean-Christophe Olivo-Marin

THE CELL'S DREAM



Intercellular bridge between two daughter cells before cleavage.

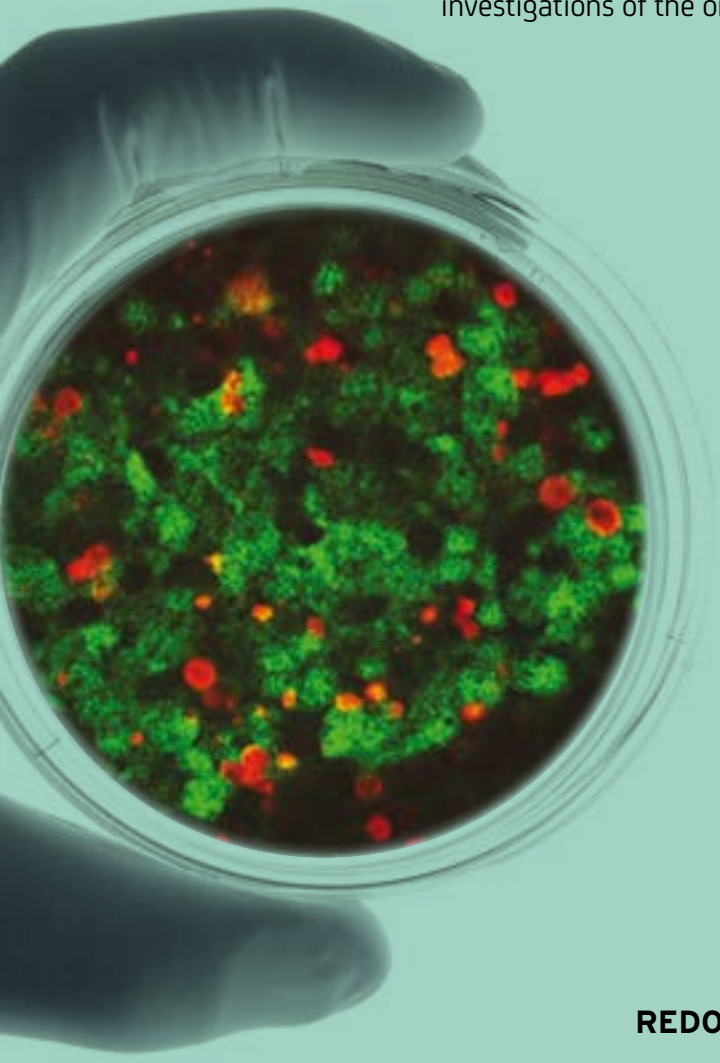
"The 'dream' of every cell is to become two cells" is a quote by Nobel Prize winner and Institut Pasteur scientist François Jacob. The team led by Arnaud Echard (G5 Membrane Traffic and Cell Division) is working to understand how a parent cell physically "cleaves" itself in two to create two distinct daughter cells. This process, called cytokinesis, requires the parent cell to contract and the intercellular bridge linking the two daughter cells to split.

In 2014, the team of scientists described the key role of the cell cytoskeleton and its place in the cytokinesis process and therefore in the orientation of the cell division axis, which is a crucial part of tissue growth and architecture. The laboratory also revealed that the intercellular bridge splits not once, but twice, on either side of the midbody, and in doing so releases a structure called "midbody remnant" (MBR) into the extracellular environment.

Surprisingly, the MBR binds to the surface of one of the daughter cells before being "engulfed" several hours later in a process akin to phagocytosis. In some instances, the MBR is recovered by a neighboring cell that wasn't even part of the division process. This discovery significantly changes our vision of MBR fate and could have a significant impact on cancer research, as the presence of MBR is thought to promote the uncontrolled production of tumor cells.

DEVELOPMENTAL AND STEM CELL BIOLOGY

The Department of Developmental and Stem Cell Biology covers a broad spectrum of multidisciplinary research activities ranging from studies on individual cells to investigations of the organism as a whole. This includes several projects on stem cells and their potential applications in biomedicine.



Cells undergoing apoptosis (red) in muscles (green) of Pitx2/3 deficient fetuses.

The Department has a unique cutting-edge research environment with a strong tradition in both classical genetics and gene manipulation. Multidisciplinary research focuses on diverse themes from DNA, to individual cells, to the organism as a whole. The main research focus included the study of 1) how cell identity is established and maintained, with a focus on transcription factors and chromatin structure; 2) the establishment of cell lineages in the embryo and adult; 3) cell movements and migrations and their roles in organogenesis; 4) roles of (epi-)genetic and non-genetic factors in determining phenotypes, the occurrence of congenital and metabolic pathologies, and the host's resistance to disease. The understanding of the formation of multicellular organisms from stem cells in the embryo and adult requires integration of research conducted from the molecular level to the physiology of the organism, and this is also done in an evolutionary context.

REDOX OR DIE, THE PARADIGM OF FETAL MYOGENESIS

During embryonic development major metabolic changes occur as cells become more specialized within a lineage. In the case of skeletal muscle, differentiation is accompanied by a switch from a glycolytic proliferative progenitor state to an oxidative postmitotic differentiated state. Such changes require extensive mitochondrial biogenesis leading to increased reactive oxygen species production (ROS) that need to be balanced by an antioxidant system. In 2014, Aurore L'honoré, in the laboratory of Molecular Genetics of Development headed by Didier Montarras, with Margaret Buckingham and in collaboration with J. Drouin (IRCM, Montreal) observed that two transcription factors, Pitx2 and Pitx3, play a critical role in this context. The analysis of double conditional Pitx2/3 mouse mutants during fetal myogenesis revealed excessive up regulation of ROS levels leading to DNA damage and apoptosis of differentiating muscle cells. This is a consequence of down regulation of NRF1 (nuclear respiratory factor 1) and genes for antioxidant enzymes, which are direct targets of Pitx2/3. Thus, the loss of Pitx2/3 results in decreased expression of antioxidant enzymes and impairment of mitochondrial function. This analysis identifies Pitx2 and Pitx3 as key regulators of the intracellular redox state preventing DNA damage as muscle cells undergo differentiation.

DECONSTRUCTING THE MUSCLE STEM CELL NICHE

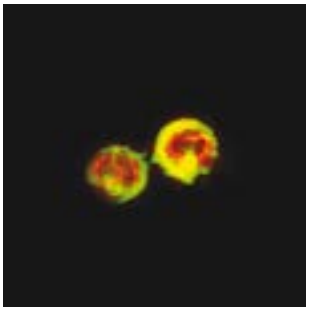
Stem cells in the body reside in a specialized microenvironment (niche) that can influence their capacity to self-renew and differentiate. The Unit of Shahragim Tajbakhsh showed previously that muscle stem cells can divide symmetrically (2 stem cells or 2 differentiated cells), or asymmetrically (1 stem cell and 1 differentiated cell). This balance ensures the proper maintenance of stem cells during growth, regeneration, disease and ageing. To mimic the stem cell niche, Siham Yennek in the Tajbakhsh lab in collaboration with Manuel Théry (CEA iRTS V) used custom designed micropatterns coated with extracellular matrix that can accommodate 1-2 cells. By rearranging the shape of the micropattern and therefore the adhesion surface, it was possible to alter the forces experienced by the stem cell and to study the resulting consequences on the fate of the daughter cells following cell division. Interestingly, an asymmetric pattern was found to promote about 4 times more asymmetric cell fates than a symmetric pattern. These observations show that stem cell fates are regulated by intrinsic as well as extrinsic parameters, particularly the topology of the microenvironment. This work has implications in the context of the therapeutic use of stem cells where a major aim is to retain their regenerative potential following extensive culture. The team is now examining in detail the composition of the stem cell niche with the hope of reproducing these conditions in culture to manipulate stem cell fates.

Creation of two new groups

Han Li leads the Cellular Plasticity and Disease Modeling Group and studies the cause and consequence of cellular plasticity in cancer and ageing. The group is seeking to understand how aberrant cellular plasticity is induced during tumorigenesis and how to modulate cellular plasticity for regeneration especially in ageing relating diseases.

Sigolène Meilhac leads the Heart Morphogenesis Group and studies how cells are coordinated at the level of the tissue and how their local behavior generates changes in overall organ shape. The group uses mouse heart models to explore links with congenital heart defects in humans in partnership with the *Imagine* Institute.

THE SEVERITY OF RIFT VALLEY FEVER

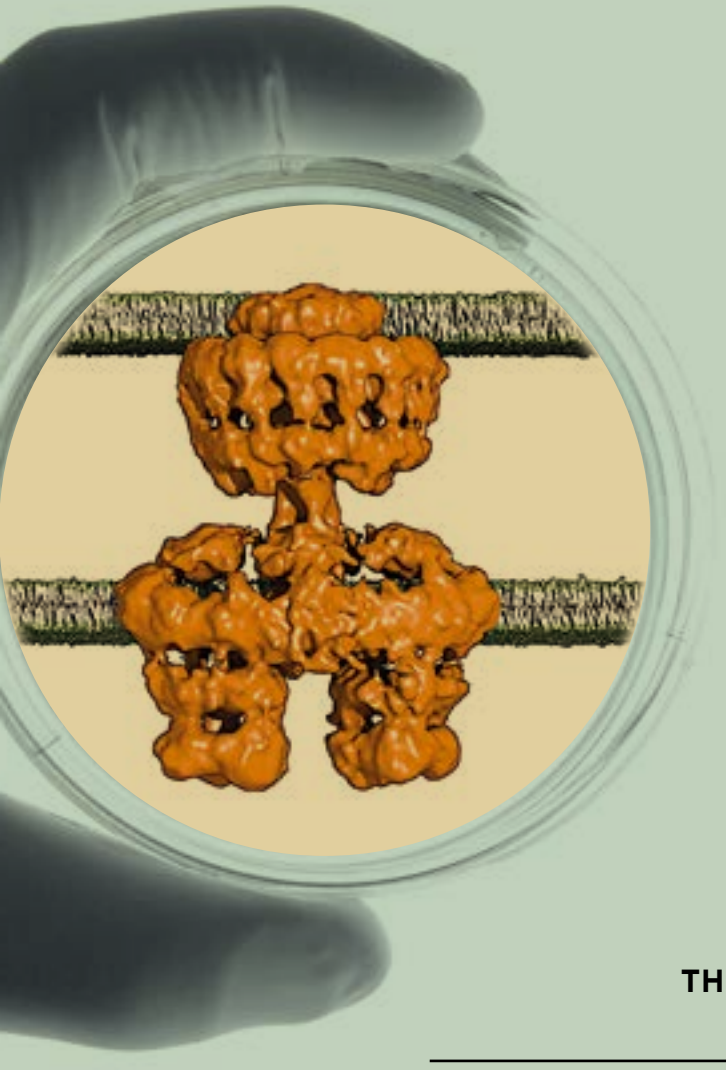


Macrophage infection by the Rift Valley fever virus.

Rift Valley fever is a serious emerging viral disease that affects ruminants and humans. Recurrent outbreaks have been documented in sub-Saharan Africa and have spread outside Africa to Madagascar, and the Arabian Peninsula, killing hundreds of thousands of animals and more than a thousand humans. Most infected people suffer a self-limiting, febrile illness. However 1 to 14% of the patients die from acute hepatitis or encephalitis. Doctors wonder about the causes of the distinct disease phenotypes following infection among patients. In 2014, the team of Jean-Jacques Panthier (Mouse Functional Genetics) gained interesting insight into this question following the investigation of novel strains of laboratory mice derived from wild founders. These scientists identified mice that were either susceptible or resistant to Rift Valley fever, and demonstrated that these differences are in part the result of three distinct chromosomal regions that influence susceptibility to Rift Valley fever virus infection. When individually transferred into a resistant genetic background, each of these chromosomal regions is able to confer and increase susceptibility to infection with the Rift Valley fever virus. The genotype of an individual is thus in part responsible for susceptibility or resistance to the disease.

STRUCTURAL BIOLOGY AND CHEMISTRY

The structure of a molecule is intricately linked to its function. The units in the Structural Biology and Chemistry Department focus their research on the three-dimensional organization, properties and synthesis of molecules of biological interest, especially those that play a role in human pathology. This research reveals vital information for the development of new therapeutic and vaccine strategies.



3D representation of the type IV secretion system which is naturally embedded in the bacterial envelope.

The department studies the three-dimensional structure of molecules to improve understanding of their biological functions and their role in the development of infectious diseases, genetic diseases, and cancers. The scientists aim to shed light on the molecular mechanisms involved in the assembly of protein complexes associated with pathological or infectious processes in order to design chemical tools to block these mechanisms. The department adopts a molecular approach to study these interactions using cutting-edge technologies:

- **crystallography, which shows the 3D structure of a molecule and is the tool of choice for designing drugs;**
- **nuclear magnetic resonance (NMR), which explores the structures of smaller molecules and provides information about their movements and molecular interactions;**
- **electron microscopy, which provides highly detailed images of the structures of large biological complexes;**
- **molecular modeling, which is vital for determining structures;**
- **mass spectrometry, which enables scientists to examine the stoichiometry, conformation, and dynamics of large protein complexes with unparalleled precision;**
- **chemical synthesis, which is essential for therapeutic and vaccine development.**

THE UNEXPECTED ARCHITECTURE OF A BACTERIAL VIRULENCE MECHANISM

Bacteria attack host cells or other bacteria by injecting specific virulence factors that cross the bacterial envelope via “secretion systems”. Deciphering the molecular architecture of these nanomechanisms is vital for us to understand how they work and ultimately be in a position to block them. Working in cooperation with the team of Prof. Waksman from Birkbeck College, London, the five-year group Structural Biology of Bacterial Secretion, directed by Rémi Fronzes, successfully extracted an intact type IV secretion system from the bacterial envelope.
This complex is responsible for the virulence of several bacteria that are pathogenic for humans, including those that cause ulcers and gastric cancer, legionellosis and whooping cough. It also enables genetic material to be passed between bacteria, a major contributing factor in the spread of antibiotic-resistant genes and the emergence of multiresistant bacteria.

The scientists identified all the components of this mechanism: a total of eight different proteins, each in multiple copies. They used high-resolution electron microscopy to create a 3D reconstruction of its architecture, which proved to be unexpected and entirely different from the structure of other secretion systems. This surprising discovery offers new prospects for improving our understanding of the secretion mechanism.

MOLECULAR SIEVING

An exploratory molecular chemistry research project carried out in the Chemistry and Biocatalysis Unit made it possible to design novel chemical libraries with no specific preconceptions as to their potential biological activities. These new entities were assessed by the Biological Screening and Chemical Library facility on various infectious disease models, with the collaboration of several Institut Pasteur teams. A significant broad-spectrum antiviral effect for two pyrazole derivatives was demonstrated in late 2011 in cooperation with Frédéric Tangy's Viral Genomics and Vaccination Unit. A process involving successive iterations of synthesis and biological evaluation of analogs in the pyrazole series led the scientists to a highly effective family of antiviral compounds. At the same time, research to decipher the action mechanism of this series enabled them to pinpoint the target of the compounds, dihydroorotate dehydrogenase (DHODH), one of the key enzymes for *de novo* nucleotide synthesis, and to establish a new functional link between the biosynthesis pathway of pyrimidines and the innate antiviral response. DHODH inhibitors are used in medicine to treat autoimmune diseases such as rheumatoid arthritis or multiple sclerosis. Our series of compounds could be used in the long term for the development of a potential alternative to these treatments.

Very-high-frequency NMR spectrometry for developing new therapies

Understanding the structural and dynamic aspects of the biological processes involved in host-pathogen relationships and the signaling pathways that are disrupted in human diseases is vital for fundamental research and also for the development of new therapies.
NMR, a cutting-edge technique that can be used in conjunction with crystallography, electron microscopy, imaging, and modeling, has a crucial role to play in the development of structural biology approaches. A specialist solution NMR center (NMRCHR – the NMR Center for Health Research), for atomic-scale research into macromolecular systems involved in host-pathogen interactions and human pathologies, will soon be opened. The center will be equipped with a very-high-frequency spectrometer (800 MHz) with a cryoprobe, purchased with funds from the Île-de-France (Greater Paris) region, which will be a valuable addition to the Institut Pasteur's existing 600 MHz and 500 MHz spectrometers.

UNDERSTANDING HOW BACTERIA ADAPT TO THEIR ENVIRONMENT

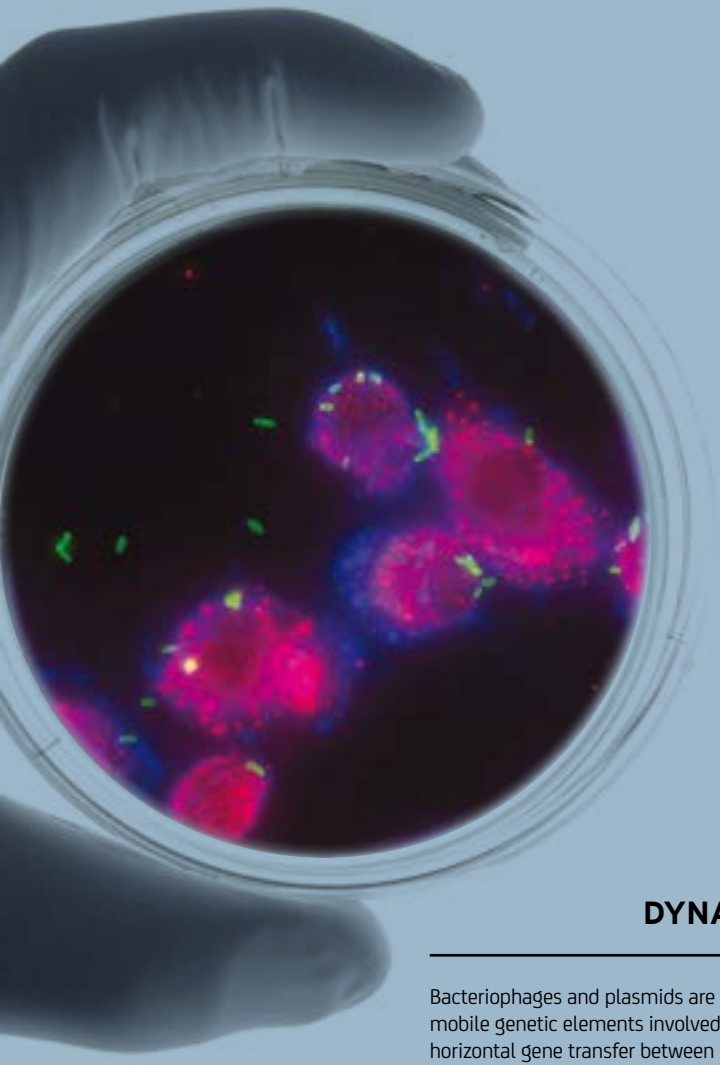
The Structural Microbiology Unit, directed by Pedro Alzari, specializes in analyzing the three-dimensional structure of proteins using X-ray crystallography. For several years it has worked in cooperation with other European research teams to investigate various biomolecules, particularly protein kinases and two-component systems that enable bacteria to adapt to their environment. These systems are used by bacteria to communicate among themselves for the formation of "biofilms", to adapt their physiology in response to environmental signals, and to regulate their virulence and/or develop resistance to antibiotics in the case of pathogenic bacteria. In 2014, the scientists provided the first description at atomic level of the phosphorylation chemical reaction that is a key part of the action mechanism of all two-component bacterial systems. Understanding the 3D structure and action mechanism of these systems could pave the way for the synthesis of a new class of antibacterial agents with high potential in the battle against antibiotic resistance.

GENOMES AND GENETICS

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

The department explores the genetic information of the human body and microorganisms such as yeast and bacteria. The genomes of the tuberculosis bacilli, *Vibrio, Legionella,* and other pathogenic bacteria and models are studied in depth with the aim of understanding how they live and what determines their pathogenic nature. Yeasts are also studied, both for their own properties and as models to help us understand human genetics.

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



Legionella **bacteria (in green) infecting cells.**

TOWARDS AN UNDERSTANDING OF THE ADAPTIVE DYNAMICS OF BACTERIAL MOBILE GENETIC ELEMENTS

Bacteriophages and plasmids are mobile genetic elements involved in horizontal gene transfer between bacterial populations. These elements often carry genes that confer selective advantages such as virulence or antibiotic resistance factors, promoting the emergence of new infectious diseases. After infection, these elements can co-exist with their hosts for long periods, forging shared evolutionary interests. The Evolutionary Microbial Genomics Unit investigated how these elements are integrated in bacterial genomes and how they subsequently adapt. Temperate phages co-evolve with their hosts to minimize the detrimental effects of their integration. Once they have been integrated, they are soon partially inactivated. Surprisingly, they then remain in the genome for a long period of time. This suggests a two-phase evolutionary dynamic, involving the swift disarmament of the phage's replication tools, followed by a long process in which their adaptive functions are domesticated by the bacteria. But the way in which these new functions adapt to the physiology of the bacteria after transfer is still unknown. Working in collaboration with INRA, the unit demonstrated that the emergence of the plant–bacteria mutualism that leads to nitrogen fixation often involves a transfer of plasmids coding for mutator polymerases that enable rapid co-evolution of the plasmid and the bacterial chromosome. These results demonstrate that the co-evolution of mobile elements and hosts requires stages of adaptation and domestication. The scientists are currently analyzing how to better characterize these stages and assess their role in the adaptation of pathogenic and ecologically significant bacteria.

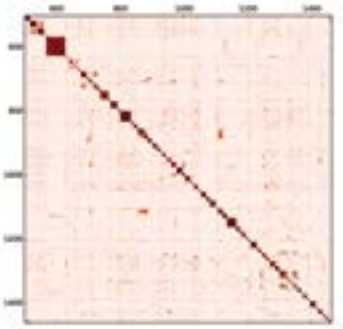
HUMAN GENOMICS OFFERS A NEW PERSPECTIVE ON AFRICAN AGRICULTURE AND HISTORY

The emergence of agriculture heralded an unprecedented technological, cultural, and environmental revolution for human beings, involving changing pathogenic pressures. It has often been suggested that on every continent the biggest demographic explosions ever seen in humans were triggered by the abundance of resources generated by agriculture, coupled with domestication and the adoption of a sedentary lifestyle. Recent work carried out by Lluis Quintana-Murci's Human Evolutionary Genetics Unit challenges this theory on the basis of an in-depth analysis of the entire genome of more than 300 individuals in Central Africa, from both pygmy hunter-gatherer populations and sedentary farming populations. Although the development of agriculture in sub-Saharan Africa dates back some 5,000 years, this genomic study demonstrates that the main demographic explosion that occurred in the ancestors of farming communities actually took place more than 7,000 years ago. This suggests that the ancestors of today's farming communities, who would have been hunter-gatherers, experienced such demographic success that they had to adopt a new lifestyle and turn to agriculture. The scientists are now trying to understand the genetic mechanisms behind the demographic growth or decline seen in these populations. They believe that these genetic mechanisms could be linked to the various environmental constraints to which these ethnic populations were exposed in the past, including those caused by pathogenic agents.

Elected as a member of the German Academy of Sciences

Carmen Buchrieser was elected as a foreign member of the German Academy of Sciences, known as the Leopoldina Academy. She leads the Biology of Intracellular Bacteria Unit, which focuses on the genetic characteristics associated with the intracellular pathogenic power of *Legionella* bacteria and their role in interactions with their known hosts, humans and amebae.

MICROBIAL METAGENOMICS: A VITAL TECHNOLOGICAL DEVELOPMENT

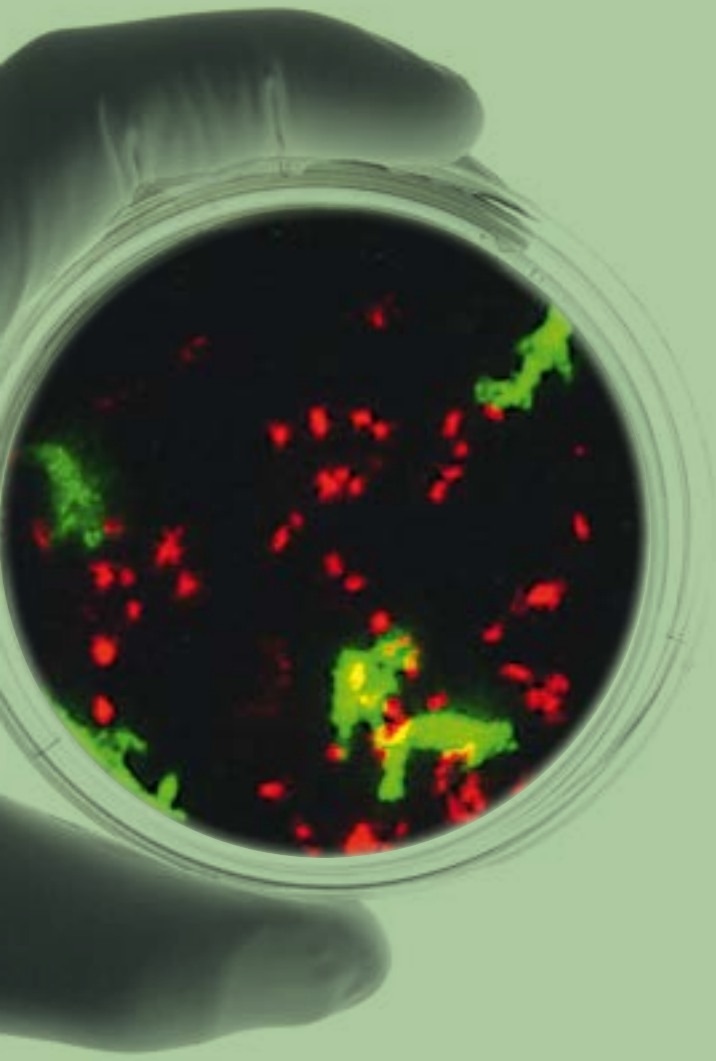


Matrix of interactions built from 77 species found in mouse stools. Each square along the diagonal represents a species of the microbiome under study (R. Koszul laboratory).

Microbial communities and the biochemical activities they engage in are key components of environmental ecosystems as well as those that make up the human commensal flora and play a crucial role in human health. These communities are composed of a complex combination of several species of microorganisms (bacteria, yeast, etc.) that are often difficult to isolate. The discipline of metagenomics examines these ecosystems through the direct characterization of their gene content, allowing scientists to infer how the various species interact with each other. The ever lower cost of sequencing means that a near complete catalog of the DNA content of these communities can be produced. But assembling the small DNA sequences obtained from sequencing into full genomes remains a tricky task, restricting our ability to analyze the full complexity of the system. The Spatial Regulation of Genomes five-year group (G5) recently developed meta3C, a metagenomic analysis and assembly method based on the fact that the genome of every species has a specific three-dimensional architectural signature. This signature is created by contacts between DNA molecules, which are important if the molecules belong to the same genome and are hosted in the same cell, and meaningless if they belong to genomes from different organisms. The group used the chromosome conformation capture technique to quantify these contacts, demonstrating the potential of this approach by showing that it can be used to reconstruct the genomes of mixed microorganisms with no prior knowledge. The team is working to apply meta3C to mammalian microbiomes, which would enable the complete characterization of these complex ecosystems.

IMMUNOLOGY

The Immunology Department's research focuses on the development and regulation of the immune system, and protective and pathological immune responses in the context of human disease.



Cutaneous immune cells (in green) and parasite (in red) in a host infected with *Leishmania major.*

The department's work is based on three main research areas:

• development of the immune system: several teams are working on the differentiation of immune cells, the formation of lymphoid organs, and cellular dynamics during the immune response;

• innate and acquired immunity: innate, non-specific and immediate immunity, together with adaptive, specific or acquired immunity, contribute to immune responses. Other teams are studying these responses, the cells behind them and their interactions;

• immune response and pathology: some teams are studying protective, anti-infectious and anti-cancer immunity; others are focusing on immunologic disorders such as allergies or autoimmune diseases. The aim is to strengthen the former and ameliorate the latter.

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

PROTECTIVE TEAMWORK

The production of nitric oxide by cells of the immune system is critical for controlling an intracellular pathogen such as *Leishmania major.* How nitric oxide production leads to parasite clearance was not clear. Researchers of the Dynamics of Immune Response Unit demonstrated that, when alone, an infected cell producing nitric oxide is inefficient at getting rid of its parasite content. In fact, only the collective production of nitric oxide by numerous cells allowed the host to control this infection. In this case, nitric oxide- producing and non-producing cells were equally protected thanks to the efficient diffusion of nitric oxide.
This cooperative mechanism allows the immune system to control the infection at the tissue level.

TYPE I INTERFERON RESPONSE: THE IMPORTANCE OF BEING WELL CONTROLLED

Type I interferons are old cytokines well known to virologists, immunologists and clinicians. Yet 60 years after their discovery, these mediators still surprise us for their complex biological function. Indeed, type I IFNs are potent anticancer and antiviral agents that however, without proper control, can become quite harmful. An international team of geneticists and neuro-pediatricians led by Jean-Laurent Casanova, together with the unit of Cytokine Signaling led by Sandra Pellegrini, recently uncovered an unexpected layer of type I IFN regulation whose dysfunction is damaging in humans. Rare patients with complete deficiency in ISG15, a ubiquitin-like modifier of protein function, were reported to have enhanced susceptibility to the BCG vaccinal strain against tuberculosis. These patients survived bacterial infection and do not suffer overt disease. More recently, an additional family with ISG15-deficiency was identified with one child suffering from seizures due to brain calcifications. Brain imaging revealed that all ISG15-deficient patients, whether BCG vaccinated or not, developed calcifications reminiscent of the auto-inflammatory pathology found in other genetic disorders known as interferonopathies. The latter are characterized by high expression of IFN-induced genes (IFN signature) in blood cells indicative of an alteration in the control of the IFN system. Fine biochemical dissection of IFN signaling in patients' fibroblasts unexpectedly revealed that ISG15, itself induced by IFN, takes part in the regulatory loop which attenuates the IFN response. ISG15 does so by binding to and stabilizing the *bona fide* negative regulator of the IFN response, USP18. These findings exemplify how critical a "regulator of the regulator" can be to ensure a balanced IFN response and prevent auto-inflammation.

New research unit

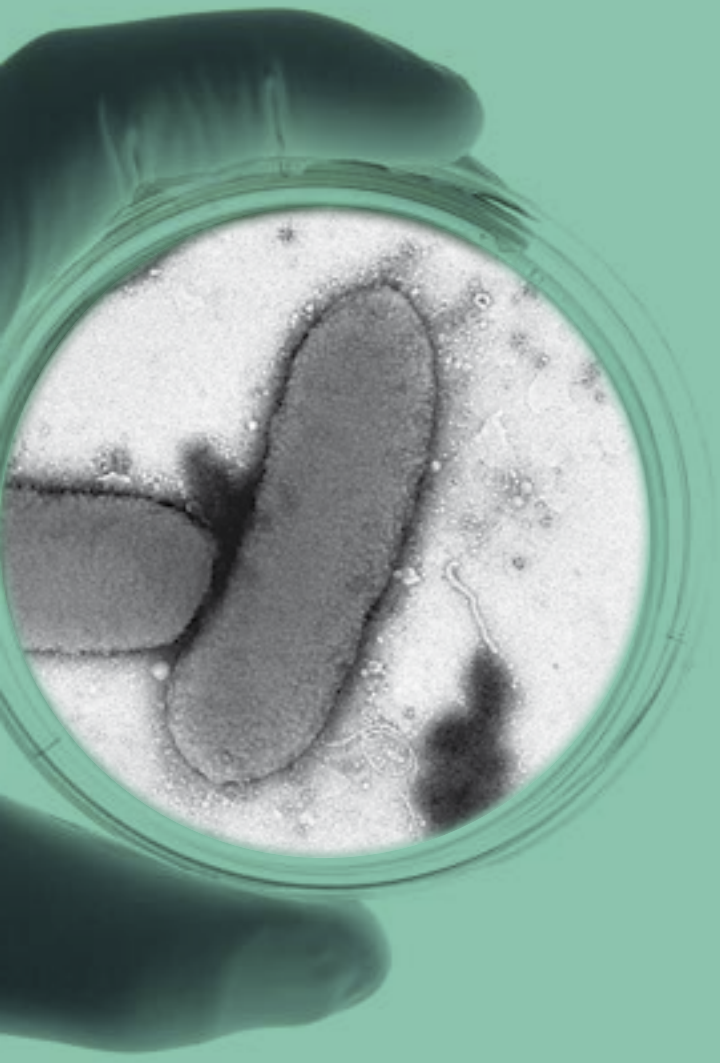
Antibodies are a key component of the immune system's protective arsenal. They may also be involved in pathologies such as rheumatoid arthritis or serious allergic reactions such as anaphylaxis. These protective and pathological processes are the focus of the research project currently being undertaken by the Antibodies in Therapy and Pathology Unit, which was created in 2014 and is led by Dr. Pierre Bruhns. This new unit is seeking to understand the mechanisms responsible for anaphylactic drug reactions, specifically focusing on determining the class of antibodies, cells and molecules involved in this life-threatening immune reaction. The unit also uses a new microfluidic technology in order to identify pathological antibodies in allergic patients. This new technology will be applied to the identification of therapeutic antibodies.

LABEX *MILIEU INTÉRIEUR* PROJECT

The Laboratories of Excellence *Milieu Intérieur* project has the ambition to provide insight into the genetic, epigenetic and environmental factors that impact the immune response and define its variability among the general population.
The question of how our bodies remain healthy is a highly important one, as predisposition to infection and the effectiveness of treatments or vaccines vary considerably from one person to another. This constitutes the very essence of the project currently under way in the laboratories of the Institut Pasteur's Immunology Department and five other partner institutes. The first data, published in *Immunity,* gives the results obtained for 25 of the 1,000 healthy subjects who make up the *Milieu Intérieur* cohort. This study used technology developed with Myriad RBM. Twenty-seven immune system stimulants were incorporated into TruCulture tubes to determine how healthy subjects' immune systems would respond to bacteria, fungi, viruses, therapeutics and vaccines.
Data analysis revealed a unique pattern of immune system responses for each stimulant tested. The scientists reported that two of the first 25 subjects studied were unable to produce interleukin 1 alpha, (IL1α) – a protein produced by immune system cells – under bacterial stimulation. This type of information could help to explain the susceptibility of a given individual to a specific disease, or to predict response to immune-modulating treatments.

INFECTION AND EPIDEMIOLOGY

The Infection and Epidemiology Department develops fundamental and translational research in the field of infectious diseases, and remains deeply committed to public health issues.



Transmission electron microscopy image of *Rouxiella chamberiensis,* a new bacterium identified in parenteral nutrition bags.

The department investigates all elements of infectious diseases: pathogen reservoirs and transmission mechanisms, virulence factors, host immune response, tissue lesion development and pathophysiological processes, therapeutic strategies and the impact of vaccination. These challenges are met using approaches and tools from a range of disciplines, including epidemiology, microbiology, dynamic imaging, immunology, histopathology, genetics, comparative genomics, cell biology, biochemistry and bioinformatics. In addition, the department plays a key role in public health issues, via nine National Reference Centers, four WHO Collaborating Centers, and the Laboratory for Urgent Response to Biological Threats (CIBU). These activities call for close collaboration with the Institut Pasteur International Network.

A NEW BACTERIUM: *ROUXIELLA CHAMBERIENSIS*

In December 2013, following the death of three premature babies and infection of a fourth at Chambéry hospital, the team led by Jean-Claude Manuguerra (CIBU) was tasked with identifying the pathogenic agent responsible for the infection. It was discovered that parenteral nutrition bags used for feeding the newborns were contaminated by a bacterium of a hitherto unknown genus. Whole genome sequencing and characterization of this bacterium revealed a new enterobacterium, which the scientists named *Rouxiella chamberiensis.* This bacterium displays unusual properties. Unlike most enterobacteria, which are unable to multiply at temperatures below 8°C, *R. chamberiensis* multiplies at 4°C. It stops multiplying at 37°C. These properties make it highly likely that the bacterium developed during storage of the nutrition bags at 8°C in refrigerators. Research is continuing, and aims to develop a specific test to detect this bacterium, in collaboration with other teams at the Institut Pasteur, including the Cytokines and Inflammation Unit, led by Jean-Marc Cavaillon, and the hydrology laboratory at the French Agency for Food, Environmental and Occupational Health & Safety (ANSES).

For more information: Le Flèche-Matéos A. *et al. International Journal of Systematic and Evolutionary Microbiology,* 2015 Mar 6.

HUMAN PAPILLOMAVIRUS LINKED TO AUTOIMMUNE DISEASE

Erosive oral lichen planus (OLP) is a dermatological autoimmune disease resulting in an abnormal immune response against oral and genital mucocutaneous cells. It is characterized by lesions and the destruction of skin cells called keratinocytes. The disease is chronic and recurrent, and may give rise to severe complications, including pain, eating difficulties and cancer. Little was known about the underlying biological mechanisms of OLP until teams led by Marie-Lise Gougeon from the Institut Pasteur (Antiviral Immunity, Biotherapy and Vaccines Unit) and Nicolas Fazilleau (UMR 1043, Toulouse) showed that the immune response leading to the destruction of keratinocytes involves the same lymphocytes as those responsible for the immune response to human papillomavirus (HPV). These lymphocytes were found in the blood of OLP patients and in biopsies of lesional tissue.

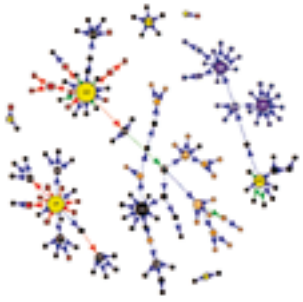
One of the theories put forward by the scientists was that keratinocytes in OLP patients might express a surface autoantigen similar to the HPV-16 antigen. This could be a source of confusion for T-lymphocytes which, having already been exposed to HPV, might trigger a cytotoxic immune response against keratinocytes. This research suggests that the autoimmune disease OLP could involve T CD8 lymphocytes specific to HPV-16. This is the first time that a link has been established between infection by HPV-16 and an autoimmune disease.

For more information: Viguier M. *et al. J Invest Dermatol,* 2015; 135(2):418-24.

Center for Global Health Research & Education

Arnaud Fontanet was appointed as Director of the Center for Global Health Research & Education. The center has 4 key objectives:
1) promote multi-site, interdisciplinary research projects targeting major global health issues;
2) train tomorrow's global health scientists in the new challenges of interdisciplinarity, animal and environmental perspectives, and the contribution of translational research to develop specific diagnostic, preventive and therapeutic solutions;
3) increase the visibility of global health initiatives led by the Institut Pasteur campus in Paris and the Institut Pasteur International Network;
4) coordinate a task force for investigating epidemics mobilizing Institut Pasteur staff in the event of an infectious disease outbreak.

A BETTER UNDERSTANDING OF EBOLA TRANSMISSION FOR A MORE EFFECTIVE FIGHT AGAINST THE EPIDEMIC



Ebola virus transmission trees. For cases that infected more than three people, the date of onset of symptoms is given in the circles. Circle size is proportional to the number of people each case went on to infect.

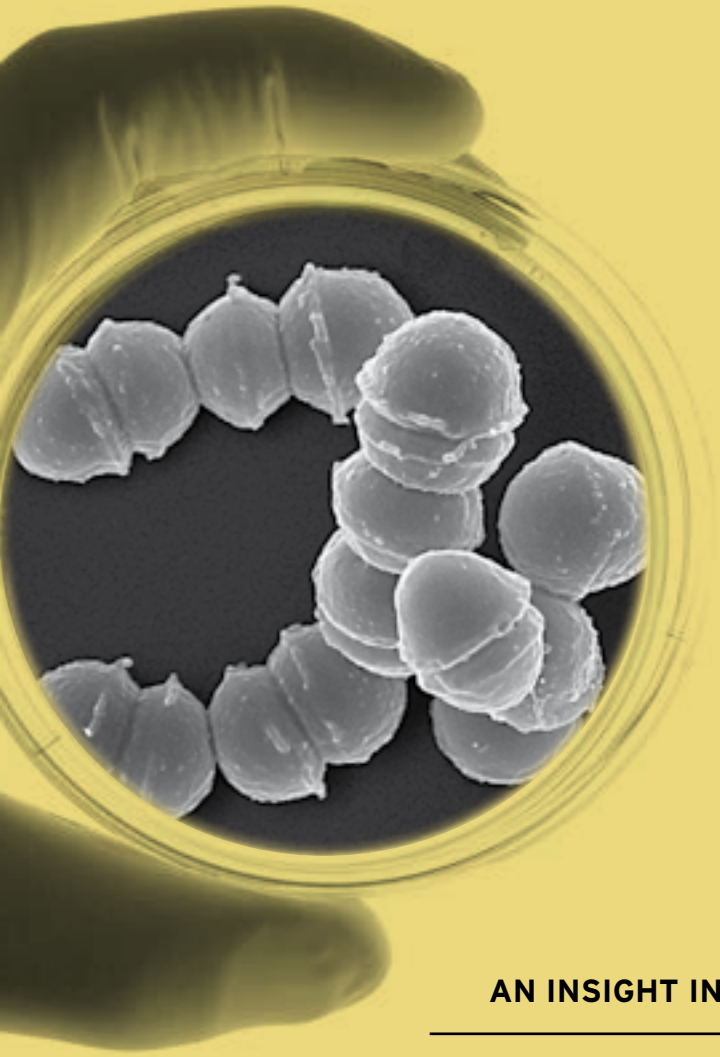
The team led by Simon Cauchemez (Mathematical Modeling of Infectious Diseases Unit), in collaboration with the team led by Amadou Sall (Arboviruses and Viral Hemorrhagic Fevers Unit at the Institut Pasteur in Dakar), reconstructed the chains of transmission of the virus in the Guinean capital between February and August 2014, with the aim of providing a better understanding of Ebola transmission factors and improving control strategies.

In March 2014, viral transmission during funerals of victims accounted for 15% of all cases, and hospital transmission 35%. After implementation of safe burial practices and the opening of a treatment center these two transmission rates dropped to 4% and 9% respectively. The scientists also established that, on average, hospitalized patients infected half as many people in the community as patients who were not hospitalized. This data shows that the majority of viral transmission takes place within families and that, while unable to halt the epidemic altogether, strengthening control and isolation measures for patients substantially slowed its spread. By detailing transmission conditions, these analyses highlight the challenges that must be met in order to contain this epidemic in large urban centers, and should lead to an improvement in response in the field.

For more information: Faye O. *et al. Lancet Infect Dis,* 2015; 15(3):320-6.

MICROBIOLOGY

As well as causing infectious diseases, bacteria can also serve as models to help us understand fundamental biological mechanisms. The research carried out in the Microbiology Department focuses on the molecular characterization of functions that enable bacteria to interact with their environment and, in some cases, go on to cause disease.



Group B streptococcus chain in scanning microscopy.

The Microbiology Department's scientists study various microorganisms (bacteria and archaea and their viruses) both at the cellular and molecular levels as model systems for fundamental research in areas such as genomics, genetics, and metabolism. They also focus on the mechanisms that render some of these microorganisms pathogenic and enable them to evade the host immune system, or to develop resistance to antibiotics. These studies not only improve our understanding of the life cycle of these microorganisms, but are a prerequisite to the development of new therapies or new diagnostic tools for treating bacterial infections.

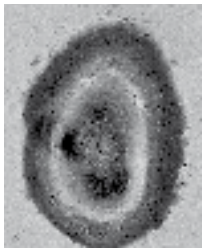
AN INSIGHT INTO THE EMERGENCE OF AN INFECTIOUS DISEASE

Neonatal group B streptococcal (GBS) infections emerged in Europe and the USA in the 1960s, and have become a primary cause of infection in newborns. Group B streptococci are commensal bacteria found in the digestive and urinary tracts in approximately 20% of the population. As a preventive measure, systematic screening is carried out at the end of pregnancy, and mothers are given an antibiotic treatment during labor to protect their newborn infants. The reasons behind the emergence of GBS infections remained unknown. Philippe Glaser's group, in the Biology of Gram-Positive Pathogens Unit, led by Patrick Trieu-Cuot, used an evolutionary genomics approach to provide some answers to this mystery. As part of an international collaboration initiative, the scientists analyzed the genomes of 230 isolates. The vast majority of strains belong to a small number of clones with little diversity, which indicates a recent origin – which scientists have dated at mid-20th century. These clones share the same resistance to tetracycline. Widespread use of tetracycline from the 1950s onwards led to the GBS population being replaced by these clones, which became responsible for the emergence of infections. The scientists suggest that resistant GBS clones with the highest potential for colonization – and therefore for causing infection – were disseminated in this way. This research highlights yet another reason to advocate the responsible use of antibiotics.

HOW TO HIT THE RIGHT TARGET

Vancomycin is a last-resort antibiotic used for treating penicillin-resistant staphylococcal and enterococcal infections. This molecule targets the bacterial cell wall, which is a rigid structure that gives the cell its shape and preserves its integrity. It binds to the ends of major components, thereby inhibiting assembly and crosslinking, which are essential to cell survival. Some bacteria resist to vancomycin by a sophisticated mechanism involving the elimination of components that are targeted by the antibiotic and the production of substrate analogs that are not recognized by the antibiotic due to the conversion of the amino acid alanine into serine. An enzyme known as VanXY degrades the precursors of target components, namely a dipeptide and a pentapeptide, allowing the resistant components to predominate.

Structural and functional studies of VanXY, conducted by Djalal Meziane-Cherif, from the Antibacterial Agents Unit, led by Patrice Courvalin, in collaboration with the University of Toronto, showed how this enzyme eliminates sensitive precursors while preserving those that are resistant to vancomycin. The origin of this selectivity is a subtle adaptation of the substrate recognition site that excludes serine. The research also retraces the evolution of VanXY, and demonstrated the capacity of bacteria to adapt their own enzymes in response to antibiotics. Understanding the relationship between the structure and the activity of resistance enzymes will contribute to the development of inhibitors able to resensitize bacteria to vancomycin.

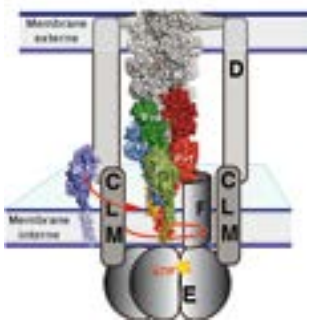


Above: *Clostridium difficile* spores.

The Clospore project

Spores are the most resistant life forms on earth, permitting bacteria to survive extreme conditions – for example oxygen, which represents a major form of stress for anaerobic clostridia. Spores play a key role in the dissemination of *Clostridium difficile* in hospital environments, and in contamination of the food chain by *Clostridium perfringens* and *Clostridium botulinum*. The cell differentiation process (sporulation) and return to active bacterial growth (germination) are key stages which must be considered when developing therapeutic strategies to limit infections. The aim of the Clospore project is to provide an understanding of these processes. The project is funded by the Marie Curie Innovative Training Network (ITN), which includes the Pathogenesis of Bacterial Anaerobes Laboratory, led by Bruno Dupuy, along with other European institutes and universities.

A MOLECULAR ARCHIMEDES SCREW



Detailed structure of the pseudopilus acting in much the same way as an Archimedes screw in the protein secretion system.

The bacterial membrane plays a crucial role as a protective barrier, a source of energy and an exchange surface with the outside environment. A double membrane gives better protection for Gram-negative bacteria, with the resulting limitation in exchanges with the environment being offset by surface appendages and systems for transporting proteins across the bacterial envelope. The Macromolecular Systems and Signaling Laboratory, led by Olivera Francetic, is examining the type II secretion system of protein, which belongs to a family of nanomachines specialized in the assembly of small membrane proteins known as pilins into extracellular filaments. In this system, short filaments known as pseudopili play a crucial role in transporting enzymes or toxins to the external environment. In order to understand its molecular function, the scientists determined the detailed structure of the pseudopilus using a combination of approaches including microscopy, structural modeling and biochemistry. Precise dissection of the various pilin interfaces showed their role in the successive stages of fiber assembly or stabilization. Only the addition of pilins at the base of the fiber is essential for secretion. This is coupled with a rotational movement, induced by ATPase at the base of the system which provides the driving force. These results suggest that the pseudopilus acts in very much the same way as the endless screw invented by Archimedes over two thousand years ago.

MYCOLOGY

The Mycology Department was created in November 2014 and aims to promote fundamental and translational research in the field of medical mycology. With fungal infections becoming increasingly common, this is a timely initiative and the Institut Pasteur's decision to step up resources in this field is fully justified.

Over the last thirty years, fungal infections have become a major public health concern. It is estimated that, globally, annual deaths from fungal infections stand at 1.5 million – a figure on a par with deaths from malaria and tuberculosis. The high mortality of invasive fungal infections reflects both the delays in their diagnosis and the limitations of the antifungal drugs currently available to treat them.

The Mycology Department is focusing its work on the three main fungi responsible for invasive fungal infections: *Aspergillus fumigatus, Candida albicans* and *Cryptococcus neoformans*. Multidisciplinary approaches are applied in order to understand the biology of these pathogenic fungi and their virulence mechanisms, with the aim of developing new diagnostic, prevention and treatment strategies for fungal infections. Via the National Reference Center for Invasive Mycoses and Antifungals, the department also provides expertise to partner institutions and hospitals.

THE CELL WALL OF THE FILAMENTOUS FUNGUS *ASPERGILLUS FUMIGATUS* PROVES A SOURCE OF NEW IMMUNOMODULATION STRATEGIES

Interactions between the filamentous fungus *Aspergillus fumigatus* and the bacterium *Pseudomonas aeruginosa*.

Aspergillus fumigatus is an ascomycete filamentous fungus, and is responsible for causing respiratory diseases in both immunocompetent and immunocompromised patients, for whom invasive pulmonary aspergillosis is often fatal. The team led by Jean-Paul Latgé (*Aspergillus* Unit) is studying cell wall biosynthesis and the extracellular matrix, as well as the role of these components in the pathogenicity of the fungus. The cell wall of *A. fumigatus* plays a crucial role in the interactions with its host and the microorganisms of its close environment. *A. fumigatus* spores – or conidia – have an outer wall comprising melanin and amyloid hydrophobins structured in the form of rodlets. Melanin and hydrophobins are responsible for the immunological inertia of *A. fumigatus* conidia. The outer layer of the mycelium is structured in a different way from conidia, and contains two polysaccharides, α-1,3 glucans and galactosaminogalactan, which are highly instrumental in counteracting host defense mechanisms. Galactosaminogalactan is the first polysaccharide virulence factor identified in this species. The immunosuppressive properties of galactosaminogalactan, resulting from its effect as an interleukin IL-1 inhibitor, make it a promising candidate for the development of new immunomodulation strategies.

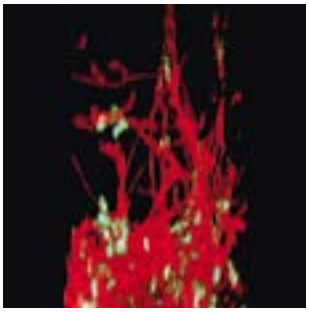
NEW SEQUENCING TECHNOLOGIES IN FUNGAL INFECTION EPIDEMIOLOGY

Invasive fungal infection epidemiology is one of the topics of focus for the team led by Françoise Dromer (Molecular Mycology Unit). Within the framework of the missions of the National Reference Center for Invasive Mycoses and Antifungals, in 2002 a regional observatory was set up to monitor yeast fungemia, – an infection associated with healthcare treatment in nearly all cases. A study covering only the most common *Candida* species and the period between 2002 and 2010 (involving 2,507 patients) showed that the incidence of these infections, as well as mortality at 30 days, significantly increased over time in intensive care units (although not in other hospital departments), while diagnostic and therapeutic strategies improved in parallel. This worrying phenomenon remains unexplained. The observatory also shed light on the unusual nature of several clusters of infections in hematology units caused by a little-known fungal pathogen, *Saprochaete clavata.* A national alert has led to the identification of 30 cases since 2011, which have been studied in collaboration with the genotyping of pathogens platform and the French National Institute for Health Monitoring. Genome analysis of the strains involved in these cases, using new sequencing technologies, uncovered a clone responsible for the epidemic, but the source was not definitively identified. This study shows the powerful potential of new sequencing technologies to investigate epidemics caused by pathogenic fungi for which the genome has not yet been sequenced nor annotated.

Creation of the five-year group Immunology of Fungal Infections

Jessica Quintin joined the Institut Pasteur to head up the five-year group Immunology of Fungal Infections. Following a doctoral thesis on host-fungus interactions in Drosophila and postdoctoral research during which she brought to light new mechanisms involved in mammalian immunity towards fungal infection, Jessica Quintin aims to discover new approaches to immune system modulation that could potentially improve current antifungal strategies, which still offer limited efficacy. For this she will base her research on an in-depth study of the innate immune response to pathogenic fungi in humans and animals.

NEW SURFACE PROTEINS INVOLVED IN THE FORMATION OF BIOFILMS BY *CANDIDA ALBICANS*

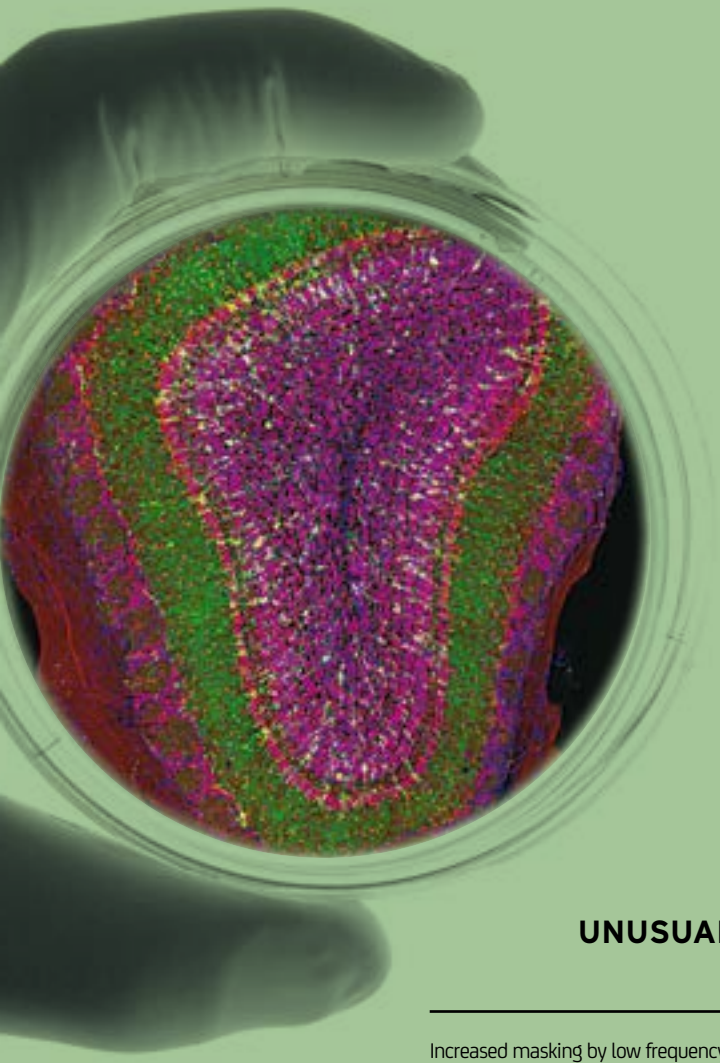


Biofilm formed by *Candida albicans* and *Candida parapsilosis.*

Hemiascomycete yeasts of the genus *Candida,* in particular *Candida albicans,* are responsible for the majority of disseminated fungal infections seen in intensive care patients and those undergoing chemotherapy or awaiting transplants. The ability of *C. albicans* to form biofilms on implantable medical devices is a key factor in this yeast's virulence. These biofilms are extremely tolerant of antifungals – which makes them impossible to eradicate and allows candidiasis to thrive. The team led by Christophe d'Enfert (Fungal Biology and Pathogenicity Unit) is exploring the mechanisms involved in the formation of biofilms and has developed an approach whereby the impact of the overexpression of each of 6,000 *C. albicans* genes on the formation of biofilms may be studied. This approach recently succeeded in demonstrating the involvement of several proteins located on the surface of *C. albicans* in the interaction between biofilm cells themselves or between biofilm cells and the substrate on which the biofilm develops. These proteins, whose function had hitherto not been understood, may serve as targets for new antibiofilm strategies in the treatment of candidiasis.

NEUROSCIENCE

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



Cross-section of an olfactory bulb showing adult-born neurons (in green), pre-existing neurons (in red) and all cell nuclei (DNA shown in blue).

The Neuroscience Department offers a research facility focusing on the organization and function of the central nervous system, including all hierarchical levels, from molecules to behavior. Knowledge of the organization and physiology of the nervous system go hand in hand with the study of its pathological states – in other words neurological diseases, behavioral disorders and sensory deficiencies. Neuroscience at the Institut Pasteur therefore focuses not only on medical issues (deafness, autism, addiction, neurodegeneration, mood disorders, etc.) but also on major social issues (educational sciences, social psychology, etc.).

Our mission is to support and strengthen neuroscience research via the improvement of knowledge of both the function of the nervous system and the deficiencies, disorders and diseases that affect it. By establishing priorities, the department should not only be able to take advantage of the strengths of our campus in the diverse fields of life sciences, but also to support innovative future neuroscience projects. In order to define and develop these priorities, the department has put in place a valid strategy in which the fundamental and clinical disciplines of neuroscience are mutually enriching and encourage the emergence of a real "translational" approach.

UNUSUALLY STRONG INTERFERENCE BETWEEN HIGH AND LOW FREQUENCY SOUNDS IN THE COCHLEA

Increased masking by low frequency sounds is one of the perceptive consequences of localized damage to auditory sensory cells. The sub-membrane protein Nherf1 is a component of the ciliary tuft of external hair cells during differentiation. Mutant mice lacking this protein have defects in the ciliary tufts of external hair cells predominating at the base of the cochlea, where high-frequency sounds are normally analyzed. However, despite major cell dysfunction, there is only a slight raising of their perception threshold (22-35 dB). In addition, in contrast to non-mutant mice, the electrical responses of these mice to short, high-frequency sound tests (20-40 kHz) are not inhibited by a prolonged simultaneous sound of a neighboring frequency, although they are inhibited by lower sounds. This masking of high-frequency sounds by low-frequency sounds is incompatible with the current explanatory model, and therefore suggests a different mechanism: in mice, high-frequency sounds may propagate along the tectorial membrane to the apical region of the cochlea, normally dedicated to the analysis of low-frequency sounds, where they could, in this morphologically intact region, interact very efficiently with a simultaneous low-frequency sound. This observation reveals a possible source of misinterpretation of audiometric thresholds, which may be falsely encouraging in certain patients in whom perception deficiencies are actually much more serious than suggested, due to their extreme vulnerability to the masking effect of low-frequency sounds.

See Kamiya *et al, Pnas,* 111:9307-9312 (2014).

MENTAL STATES CONTROL THE INTEGRATION OF NEW NEURONS IN THE ADULT BRAIN

Although it has been known for several years that the adult brain is capable of producing new neurons, how these neurons are integrated into existing, functional nerve circuits has hitherto remained a mystery. We showed that new neurons set up a denser network of connections with the rest of the brain in contexts of active (as opposed to passive) motivation and learning. It is therefore our mental states (attentive or otherwise), rather than the type or diversity of the sensory environment, that drive the functional activity of adult-born neurons.

To reach these conclusions, we focused on the production of new neurons in adult mice, in particular those neurons that integrate into the olfactory bulb, which is the first brain region involved in processing olfactory information. These adult-born neurons are seen as key elements in promoting neuronal plasticity – a crucial part in olfactory learning and memory. We proved that the development and maturation of young neurons is profoundly changed in the context of olfactory learning in mice. Connections between adult-born neurons and regions of the cerebral cortex are strongly reinforced when odorants are associated with rewards, and these connections are less dense when the animals are simply exposed to these same odorants.

The psychophysiological context – here the fact that learning is reinforced by the animal's motivation to receive a reward – is thus a decisive element in the construction of links between adult-born neurons and the rest of the brain. Functional maturation of young nerve cells in the adult brain is therefore based on the meaning attributed to various sensations, and is not the result of mere sensory exposure.

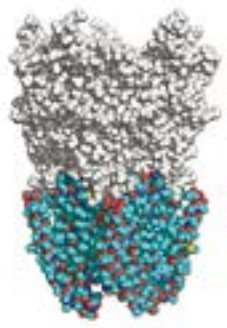
If we transpose these findings to humans, we can better understand the role played by various mental states, such as attention, motivation, anticipation, expectation and pleasure, in the survival and functional integration of adult-born neurons and, conversely, the role played by adult neurogenesis in learning and memory capacities in adults.

See Lepousez *et al, Pnas,* 111:13984-13989 (2014).

3D architecture of dendritic spines from human neurons

The study of dendritic spine morphologies is crucial for the understanding of brain synaptic activities. The Human Genetics and Cognitive Functions Unit, directed by Thomas Bourgeron, is investigating factors underlying susceptibility to autism. The scientists demonstrate that genetic mutations cause a deficit in specific proteins such as SHANK and therefore may alter the development of synaptic transmission. A major challenge is to characterize the defects in the contacts between neurons (dendritic spines and synapses). The research of Isabelle Cloët-Tayarani and Laura Gouder (PhD student) focuses on the analysis of the cellular and molecular properties of human neurons obtained from skin biopsies of control individuals and patients with autism. The neurons are made fluorescent using gene transfer technology and visualized by confocal microscopy. Using 3D reconstruction and quantification of the morphological parameters of each synapse, the scientists aim at identifying defects that may cause autism in order to design knowledge-based treatments.

USING THE STRUCTURE OF GLYCINE RECEPTORS TO ANALYZE HEREDITARY MUTATIONS AND DESIGN NEW THERAPEUTIC MOLECULES



3D structure of the GLIC bacterial receptor "chimera" (in white) containing the membrane domain of the human glycine receptor (in blue).

Nicotinic, GABA and glycine receptors play a major role in neuron transition in the brain. They are important therapeutic targets for general anesthetics, anxiolytics, analgesics, and cognitive enhancers. Mutations in these receptors can cause hereditary diseases such as myasthenia, epilepsy, and hyperekplexia. The receptors are protein complexes that are embedded in a cell membrane, where they form an ion channel. Their structure is notoriously difficult to study. We developed a genetic engineering approach to collect three-dimensional, atomic-resolution structural information. Working in collaboration with the unit directed by Marc Delarue, we integrated the transmembrane domain of the human glycine receptor into an ancient bacterial receptor and used X-ray diffraction to generate three-dimensional protein crystals and resolve the protein's structure. This research reveals the molecular mechanisms used by some therapeutic compounds to govern regulation. It also sheds light on why some mutations that increase or reduce channel activity cause hyperekplexia, a rare, severe syndrome characterized by non-epileptic seizures in patients when they are touched or startled by a noise. These findings provide a structural basis for the development of new targeted pharmacological treatments.

Moraga-Cid *et al., Pnas,* 112:2865-2870 (2015).

PARASITES AND INSECT VECTORS

The Parasites and Insect Vectors Department investigates the life cycle of parasites and their vectors. This research addresses global public health concerns and tackles the ongoing need for better prevention, control, and treatment.

A tsetse fly after a blood meal. The color and dilatation of the abdomen indicate a large volume of blood.

The department focuses its research on three key eukaryotic parasites responsible for severe diseases of major health and economic burden in most of the world's regions: *Plasmodium* species, which cause malaria; *Leishmania* species, the causative agents of leishmaniasis; and *Trypanosoma* species, responsible for sleeping sickness. The *Anopheles* mosquito (the vector of *Plasmodium* and viruses) is also studied, as is the tsetse fly (the sleeping sickness vector). The department combines fundamental research on *in vitro* and *in vivo* models – including field work, particularly in Africa and Asia – with applied research, for example on the resistance of the malaria parasite to antimalarial drugs, and the identification of new antiparasitic drugs. Novel experimental models and tools are developed to help understand the dynamic interactions between these microorganisms and their hosts, identify the fundamental bases of parasitism and transmission by vectors, reveal host invasion mechanisms, and determine the virulence factors, pathology, and survival strategies of these organisms.

MALARIA: THE MECHANISM USED BY THE PARASITE TO HIDE FROM THE IMMUNE SYSTEM REVEALED

Plasmodium, the parasite responsible for malaria, infects red blood cells, where it produces proteins that bind to the surface of the host cell. These are known as adhesion proteins. They prevent the red blood cells from circulating correctly in the blood capillaries, and can trigger the symptoms of severe malaria. The parasite has 60 genes coding for 60 different adhesion proteins, only one of which appears on the surface of the red blood cell at any one time. The various adhesion proteins are therefore presented in turn, and the parasite keeps one step ahead of the host's immune system, which must learn to recognize and then destroy infected cells. Scientists in the team led by Artur Scherf (Institut Pasteur, CNRS) discovered this previously unknown mechanism used by the *Plasmodium* parasite to outmaneuver the immune system time and time again. An enzyme-type protein, known as RNase, was found to be at the root of the process used by the parasite. It destroys the precursor of the messenger RNA that produces adhesion proteins. The destructive activity by the enzyme allows only one of the 60 types of adhesion protein to appear on the surface of the infected red blood cell at any one time. The parasite expresses different adhesion proteins in turn. The proteins expressed change so quickly that the antibodies in the immune system don't have time to recognize each one. This newly discovered gene regulation system had never previously been observed; it is highly likely that it is also found in other organisms.

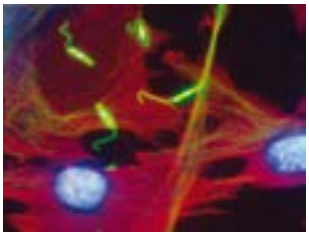
VECTORS: PROTECTION AGAINST ONE PATHOGEN CAN OPEN THE DOOR TO OTHERS

Mosquitoes are responsible for the transmission of arboviruses and malaria, and the risks associated with arboviruses are on the rise all over the world. One vector control measure used to tackle this problem involves releasing mosquitoes with higher immunity to a specific pathogen into the wild, with the aim of replacing field mosquitoes by resistant mosquitoes. The Genetics and Genomics of Insect Vectors Unit, directed by Kenneth Vernick, investigated the antiviral immune response to the O'nyong-nyong arbovirus in the mosquitoes that are the primary vector of malaria in Africa. This study showed for the first time that there is a balance between the complex mechanisms that govern resistance or susceptibility to various human pathogens. The compartmentalization of the mosquito's immune response determines which antiviral pathways are operative against the virus. In mosquitoes, like in humans, the microbial flora is an important component of the digestive tract. Reducing the intestinal flora in mosquitoes increases their infection by the malaria parasite, but the opposite is true for viral infections, which decrease in parallel with a reduction in intestinal flora. This research demonstrates that the effect of the intestinal flora on mosquitoes' susceptibility to a given infection depends on the pathogen in question. It would be disastrous if mosquitoes supposed to be more resistant to *Plasmodium* became susceptible to other pathogens.

Profile

Chetan Chitnis joined the department in 2014 to set up the Malaria Parasite Biology & Vaccines Unit. His unit will investigate how malaria parasites invade human erythrocytes and use these findings to develop new malaria vaccines. Dr. Chitnis completed his PhD at the University of California, Berkeley, in 1990 and conducted postdoctoral research on malaria at the US National Institutes of Health. He returned to India in 1995 and set up a highly efficient laboratory that combines fundamental and translational malaria research. Dr. Chitnis is a Fellow of the Indian Academy of Sciences and was previously a Wellcome Trust Senior Research Fellow and a Howard Hughes International Research Scholar. He is a recipient of the Infosys Prize in Life Sciences and the Bhatnagar Award in Medical Science, two of India's most prestigious life sciences awards.

CUTANEOUS LEISHMANIASIS: HOW TO INCITE PARASITES TO COMMIT COLLECTIVE SUICIDE

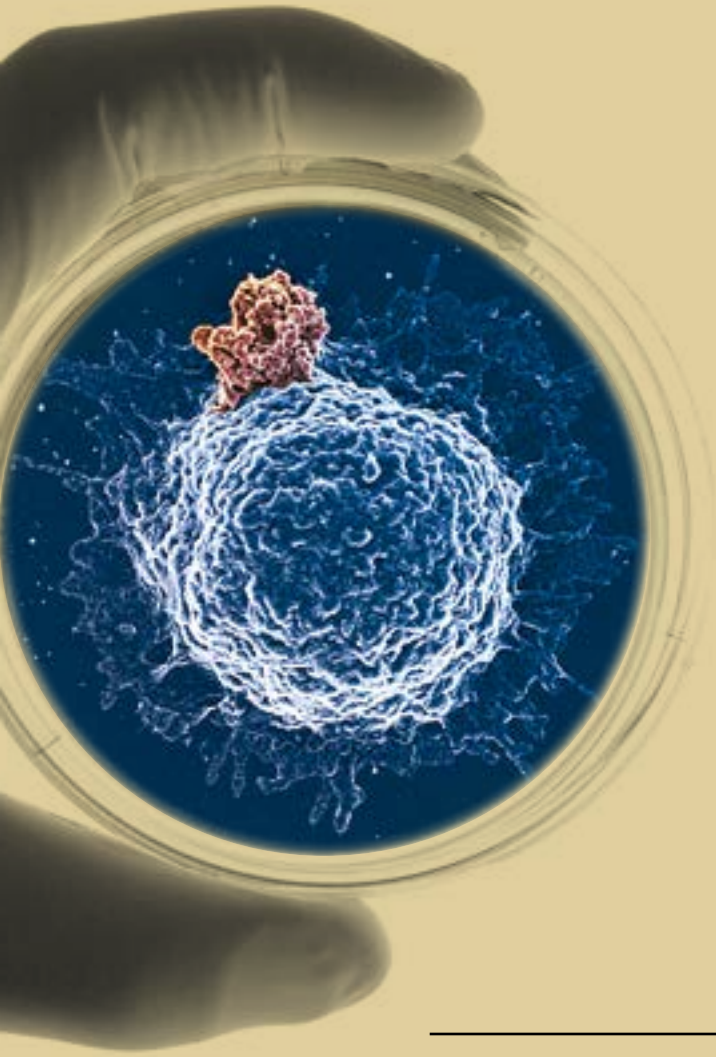


Immunofluorescence analysis of mammalian cells (actin in red) and the protozoan parasite *Leishmania* (tubulin in green). The nuclei are stained with Hoechst 33346 (blue).

Leishmaniasis is a severe parasitic disease in humans caused by parasites from the genus *Leishmania.* One crucial aspect in the virulence of these parasites is their ability to detect and adapt to highly different environments. This enables them to survive and develop within an insect vector and a vertebrate host via different stages of development. This differentiation process is triggered by environmental changes, which are usually detected and transduced by signaling cascades involving protein kinases. The Molecular Parasitology and Signaling Unit, directed by Gerald Spaeth, recently demonstrated that the *Leishmania* protein kinase, MPK10, plays a vital role in detecting environmental changes. Deletion of part of the protein resulted in a significant increase in MPK10 activity, indicating that its activity may be regulated by an autoinhibitory mechanism. Overexpression of this truncated hyperactive protein in transgenic parasites led to a dominant negative effect, causing massive cell death in the parasite and demonstrating the essential nature of MPK10 autoinhibition for parasite viability. These findings reveal novel aspects of developmental regulation in *Leishmania* through the detection of signals from the mammalian host environment, pinpointing MPK10 as a potential new antiparasitic target.

VIROLOGY

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



Viral biofilm (in orange) produced by a T lymphocyte in a patient infected by HIV-1, shown by scanning electron microscopy. These viral particle aggregates embedded in an extracellular matrix cocoon are produced at the surface of infected cells and create a highly effective transmission mechanism for these viruses when they come into contact with target cells.

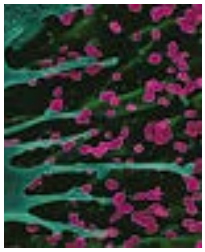
The department's 19 units focus their research on viruses, investigating their molecular organization, pathogenicity determinants, proliferation, and interactions with host defense mechanisms. The viruses under study include respiratory viruses such as influenza; viruses that cause cancer (papillomaviruses, HTLV, and the hepatitis B and C viruses); retroviruses such as HIV; insect-borne viruses that are responsible for severe diseases including dengue, chikungunya, yellow fever, and Rift Valley fever; and viruses causing hemorrhagic fever (such as the Lassa fever virus). The department's scientists work in close collaboration with others on the Paris campus and also with the Institut Pasteur International Network. The Virology Department also implements translational research projects for the development of vaccines, drug candidates, and diagnostic tools. It houses several National Reference Centers and WHO Collaborating Centers, thereby playing a major role in the epidemiological monitoring of viral infections.

SURPRISING SIMILARITY BETWEEN VIRAL AND CELLULAR PROTEINS

The Structural Virology Unit described the first three-dimensional structure of EFF-1, a cellular protein responsible for cell-cell fusion. This study was carried out on a model organism, the nematode *Caenorhabditis elegans,* in which the EFF-1 protein mediates cell fusion during embryonic development. Cell fusion plays a major role in muscle and bone morphogenesis, tissue regeneration following injury, and metastasis development and formation. Despite the fundamental nature of these processes, until now there had been very little information available at the molecular level relating to the mechanisms that give these proteins their fusogenic role. The most surprising result of this study is that the EFF-1 structure is very similar to that of the chikungunya and dengue virus envelope proteins. These viruses are surrounded by a lipid membrane containing viral envelope proteins that are responsible for the fusion of the viral and target cell membranes, thereby enabling the virus to invade the cell. Comparing EFF-1 structure with these viral proteins shows that they are homologs that are derived from the same ancestral gene, which has been taken over by both viruses and cells for exactly the same purpose: to induce membrane fusion. This illustrates the importance of the genetic material exchanges that take place between viruses and cells and their role as a driver for the evolution of species.

PREDICTING THE MUTATIONS THAT CAUSE VIRAL EPIDEMICS

Molecular mechanisms for the replication and multiplication of RNA viruses generate errors, or mutations, in their genetic code, leading to the production of viruses that are slightly different from each other. Some of these mutations confer advantages in terms of multiplication and transmission to the viruses carrying them, which may result in new epidemics. The Viral Populations and Pathogenesis Unit developed a method to predict mutations with strong epidemic potential in a mosquito-borne chikungunya virus population. During the cycle of a pre-epidemic strain of the virus in the mosquito and the mammalian host, the scientists were able to reproduce the emergence of a majority viral population carrying the mutation that appeared in the 2005-2006 chikungunya outbreak in the Indian Ocean. The method was then applied to the epidemic strain to simulate what could happen in a future chikungunya epidemic: the scientists recreated a full transmission cycle (mosquito to mouse to mosquito) in a laboratory setting. Following this cycle, two new mutations emerged in a majority of the population. This research can be used as a tool to identify mutations with epidemic potential. These findings will also help scientists target and improve the monitoring of viral populations between and during epidemics.

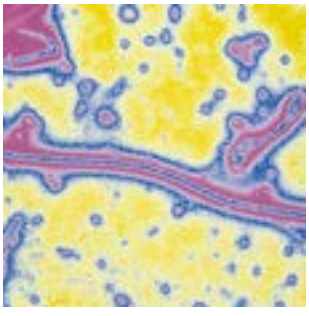


Above: chikungunya viruses (pink) at the cell surface.

A vaccine for chikungunya

The Viral Genomics and Vaccination Unit developed a vaccine for chikungunya which was successfully tested in humans in a phase I clinical trial performed in Austria by Themis Bioscience. This vaccine is based on a measles vaccine virus that was modified to express structural antigens of the chikungunya virus. The clinical trial in 42 adult volunteers demonstrated that the vaccine is safe, well tolerated and immunogenic, generating neutralizing antibodies against the chikungunya virus in 90% of participants from the first administration. Pre-existing immunity to measles did not affect the response to the experimental vaccine. A phase II clinical trial is due to be launched shortly. This result shows the feasibility of this vaccine platform.

ZAIRE EBOLAVIRUS IN WEST AFRICA: AN EPIDEMIC ON AN UNPRECEDENTED SCALE

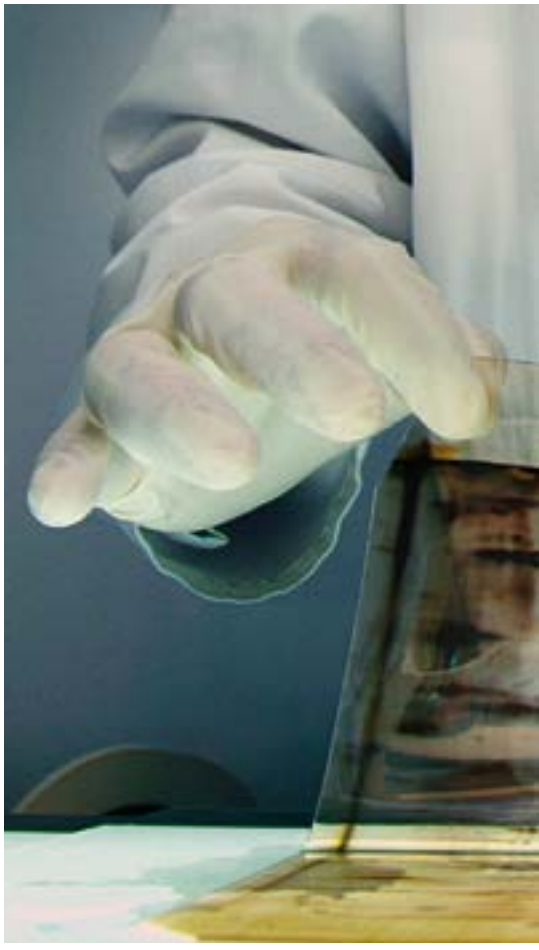


Ebola virus.

In March 2014, the National Reference Center for Viral Hemorrhagic Fevers, hosted within the Lyon-based Biology of Emerging Viral Infections Unit, was approached by Médecins Sans Frontières, which was dealing with a hemorrhagic fever outbreak in Guinea's forest region. The scientists were able to confirm that the outbreak was caused by the Ebola virus. Sequencing performed in cooperation with the Genotyping of Pathogens facility at the Institut Pasteur in Paris and the Bernhard Nocht Institute in Hamburg enabled them to identify the virus as Zaire ebolavirus, the most pathogenic of the five known species, with a mortality rate of 90%. Outbreaks of this virus had previously only been recorded in a few countries in Central Africa, and its presence in West Africa was completely unexpected. This leap of 2,500km could be explained by the migration of infected bats from the center of the continent. The epidemic spread widely across the whole of Guinea and also to Liberia and Sierra Leone, becoming the most severe Ebola outbreak to date since the virus was first described in 1976. The severity of the epidemic has undoubtedly been aggravated by socio-economic, demographic, and cultural factors. This shows that, depending on the context, an identical virus can cause geographically restricted and rapidly contained outbreaks, as in Central Africa, or a major uncontrollable epidemic, as in West Africa.

Technological platforms

With sophisticated technological platforms, a Central Animal Facility, a Mouse Genetics Engineering Center, and a Center for the Production and Infection of *Anopheles,* the Institut Pasteur ensures that its teams have all the resources they need to perform cutting-edge research. All these platforms are now part of the new Center for Innovation and Technological Research (Citech) that was set up in July 2014.



Genopole

When it comes to microorganisms, humans, or anything in between, high-throughput sequencing has revolutionized the analysis of genetic information. This technique can be used to decode the genomes of hundreds of microbes so that scientists can improve their understanding of microbial evolution and carry out epidemiological survey. In 2014, the Genopole helped demonstrate that the widespread use of tetracycline from the 1950s onwards contributed to the emergence of neonatal infections caused by group B streptococcus. Sequencing all the coding regions (the exome) in humans is currently the most effective way of identifying the mutations that predispose individuals to some diseases. Large-scale transcriptional analysis has improved our understanding of how organisms function in a normal or pathological state. It enables scientists to address fundamental questions in microbiology and in the field of genetic and epigenetic programming during embryo development and throughout the cancer process. The development of single-cell analysis can help shed new light on stem cell differentiation. Computational and statistical analysis is a major part of this research. The Genopole is working with the Center of Informatics for Biology to develop and implement methods to analyze and process genomic and functional genomic data.

At the Genopole, 17 scientists, engineers and technicians with a wide variety of skills are involved in fundamental research and public health projects. All four Genopole platforms have received official accreditation from the GIS IBiSA[1] and are partners of France Génomique, the national biology and healthcare infrastructure. They are now part of the new Center for Innovation and Technological Research.

Proteopole

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

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

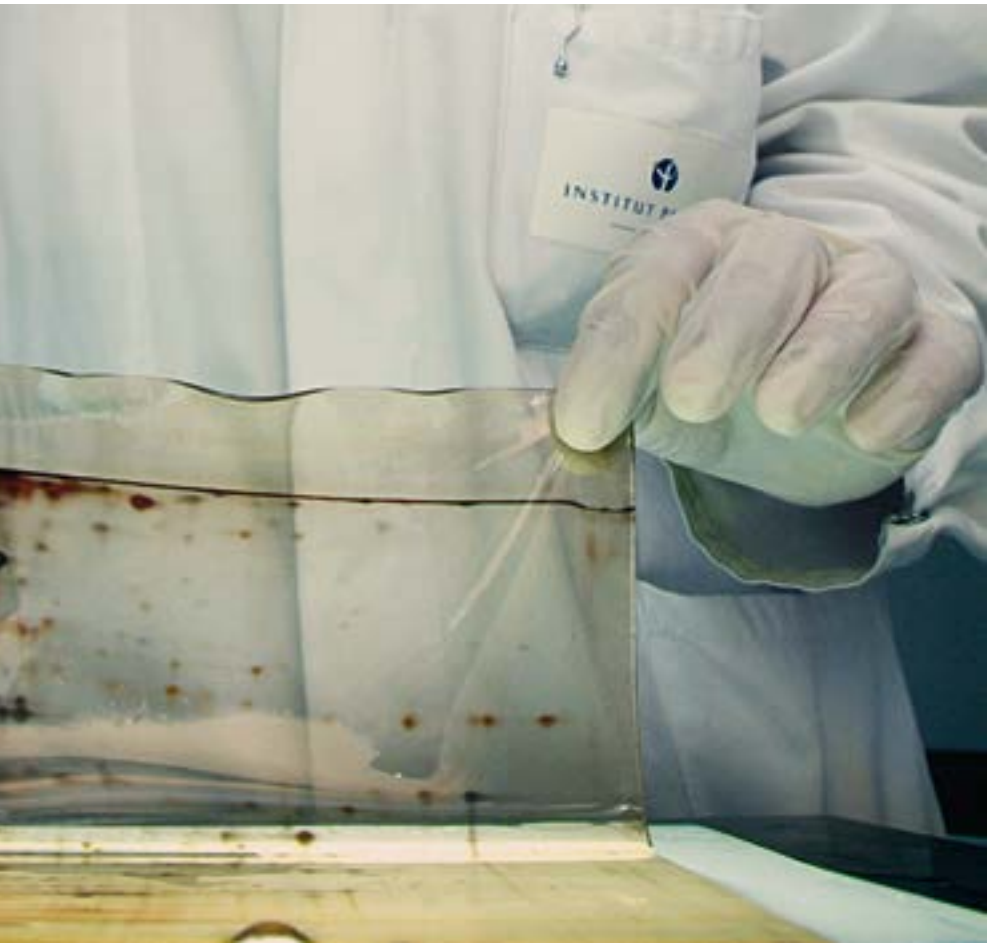
By leveraging synergies between different methods of analysis, Pasteur-Proteopole provides research teams with the tools they need to answer existing questions and also pinpoint new areas for analysis. The Proteopole is divided into five platforms (Recombinant Proteins, Antibody Engineering, Proteomics, Molecular Biophysics, and Crystallography), all of which are now part of the Center for Innovation and Technological Research (Citech). Its current staff of 32 scientists and technicians provides a wide range of services to the research community, and is closely involved in a number of biological and methodological research projects in collaboration with laboratories from the Institut Pasteur and other French or foreign institutions, particularly in the field of structural biology of infectious diseases.

Imagopole

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

Research

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



factors that influence the variability of the human immune system.

Development

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

Mouse Genetics Engineering Center

The discovery of new genes and genetic sequences of interest opens up the possibility of generating new transgenic animals to analyze their biological functions and provide *in vivo* confirmation of expression profiles and gene regulation mechanisms. Each year, the Mouse Genetics Engineering Center (CIGM) produces several mouse strains that have been genetically modified using transgenesis – both "classical" (random integration of an exogenous gene) and "targeted" (a deficiency or specific alteration at an endogenous locus) techniques – by microinjecting preimplantation stage mouse embryos. The center is involved in research projects conducted mainly by Institut Pasteur units but also by other national and international research institutions. The CIGM team comprises a head engineer and three technicians, all of whom have highly specific skills in embryonic stem cell culture, microsurgery, and embryo microinjection, and can boast expertise in handling mice at all stages of development (from embryo to fetus and adult). Targeted transgenesis, which was initially based on microinjecting Embryonic Stem cells modified by homologous recombination, is developing very fast with new techniques for gene editing using specific nucleases. After our first modifications using zinc-finger nucleases (ZFNs) (in rats, 2012) and TALE nucleases (in mice, 2013), in 2014 we extended our research by microinjecting new CRISPR/Cas9 systems into mouse zygotes, a technique which proved to be highly effective and versatile for performing targeted gene modifications *in vivo.*

Central Animal Facility

The use of animal models remains a necessity for the Institut Pasteur's research programs, but research using animals is governed by strict regulations, and all such projects are examined by the Institut Pasteur Committee for Ethics in Animal Experimentation and require authorization from the French Research Ministry.

The Central Animal Facility has a total capacity of 16,000 cages, which includes almost all the resources deployed for working on rodents and lagomorphs. It also breeds more than 400 genetically modified mouse strains and is responsible for the production and use of defined-flora mice and for technical operations such as the cryopreservation and decontamination of strains. The 48-member team is led by three veterinarians, one engineer, and an operations manager.

The new animal facility in the François Jacob building, which opened in November 2012, has replaced various older facilities, which have either been renovated or closed down. It features state-of-the-art, sophisticated equipment including a large high health status breeding and experimental area for rodents, with a total capacity of around 8,300 cages, and a restricted BSL3 area for rodents infected with biological agents from risk groups 2 and 3, with a capacity of 2,500 cages. Another animal facility has been renovated to house a center for investigating rodent behavior and the Institut Pasteur's gnotobiology center.

The Institut Pasteur has made significant investments to provide its scientists with a highly competitive, attractive research infrastructure.

CEPIA

The activities and organization of the Center for the Production and Infection of *Anopheles* (CEPIA) are focused on research into the interactions between the *Plasmodium* parasite, responsible for malaria, and its mammalian hosts (mice or cell lines) and insect hosts (*Anopheles* mosquitoes).

The center's infrastructure is composed of the following entities:

- three insectariums for mosquito production;
- laboratories for the infection and dissection of mosquitoes infected by rodent *Plasmodium* (*P. berghei* and *P. yoelii*);
- secure laboratories to investigate infection by *P. falciparum.*

The platform mass-produces two *Anopheles* species (*A. gambiae,* the African vector, and *A. stephensi,* the Asian vector). Moreover, the CEPIA produces gametocyte-stage cultures of the human parasite *P. falciparum,* and experimentally infects *A. gambiae* mosquitoes with these gametocytes.

A. stephensi mosquitoes are mainly used to study the early stages of *P. berghei* and *P. yoelii* in rodent models.

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

"The microbe is nothing and the terrain is everything."

LOUIS PASTEUR

The Institut Pasteur International Network

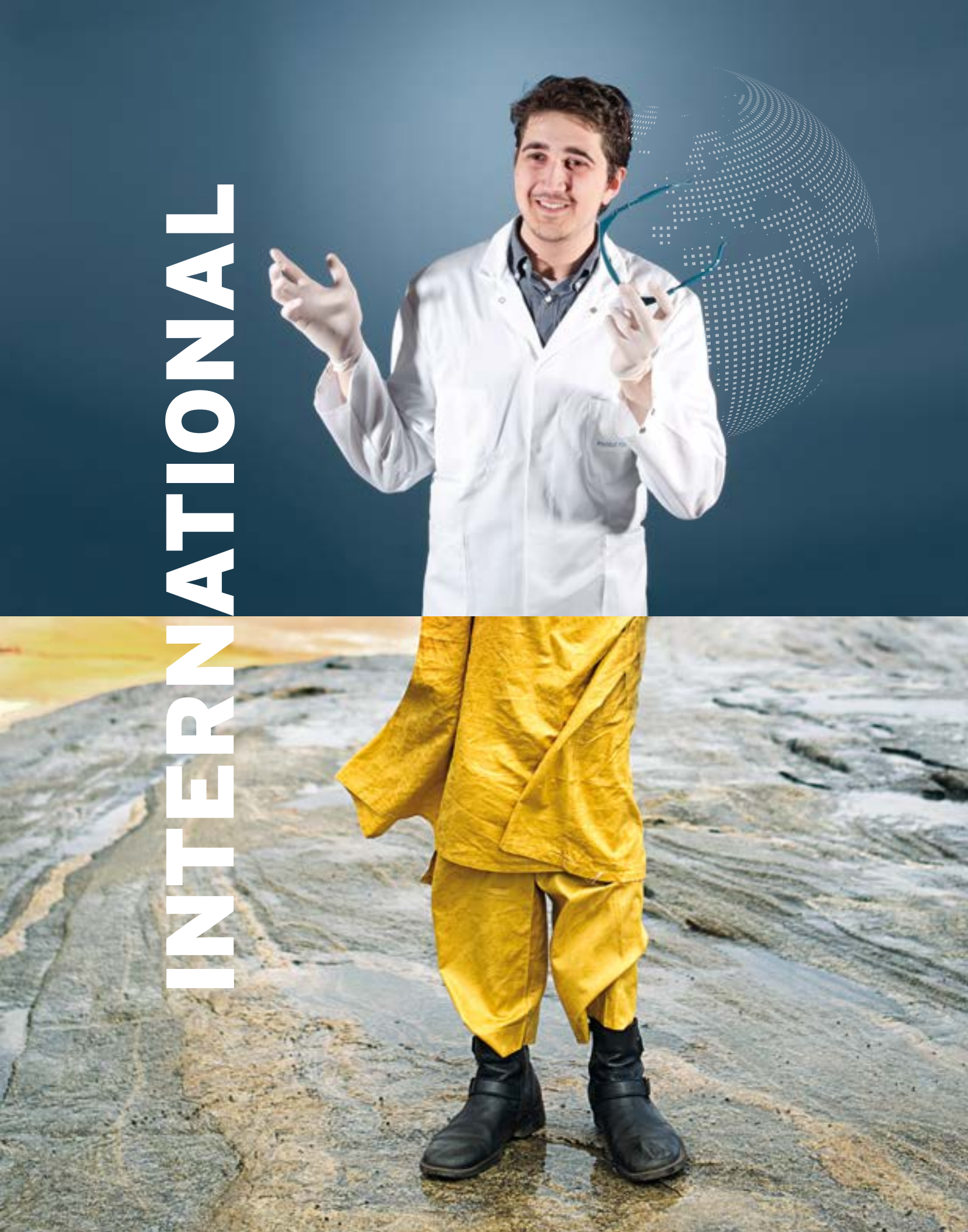
The Institut Pasteur is an international institute with 32 members in 25 countries spanning every continent. It is composed of a vast human and scientific community that performs vital work in the areas of public health, research and training; as such, it is a key player in global health, in constant dialog with local authorities, research institutions, and major international organizations.

The Institut Pasteur International Network is strongly committed to the implementation of the 2005 International Health Regulations, by strengthening capacities in the areas of prevention, detection, reporting and response in the event of international public health emergencies.

On the front line in epidemiological surveillance and diagnosis

One example was the launch, in 2014, of the ASIDE project (http://asideproject.org/), funded by the US Department of Health and Human Services, which is geared towards surveillance of respiratory viruses and other emerging or re-emerging viruses in five countries in Africa and one in South-East Asia, according to the public health priorities of each country. The Institut Pasteur is also coordinating the EU-funded MediLabSecure project (http://www.medilabsecure.com/), which aims to establish a network of laboratories in 19 countries in the Mediterranean and Black Sea regions to strengthen response capacities in the event of virus outbreaks in humans or animals.

INTERNATIONAL



A decisive commitment to the Ebola response

In 2014, the International Network engagement has proved crucial in responding to the health crisis caused by the sudden emergence of Ebola in West Africa. Dr. Amadou Sall's team from the Institut Pasteur in Dakar was on the ground in Guinea just hours after the first cases were confirmed by the Lyon-based Biology of Viral Emerging Infections Unit. It was the first African organization to set up a mobile diagnostic laboratory at Donka Hospital in Conakry and confirm suspected cases in Guinea. This active involvement in the fight against Ebola that has lasted for over a year demonstrates the preparedness and rapid reaction capability of the Institut Pasteur International Network and the quality of its expertise. In every country of the affected region where a member of the International Network is present, it has become a central hub for Ebola public health screening and diagnostic efforts. The Institut Pasteur also reacted quickly by installing a high-tech diagnostic laboratory at the Macenta treatment center in Guinea's forest region and announced the upcoming establishment of an Institut Pasteur in Conakry. This new institute will focus on diseases with high epidemic potential, especially arboviruses and viral hemorrhagic fevers.

Above: the sudden outbreak of Ebola in West Africa triggered a fast and effective response from the International Network.

Far right: Ebola crisis in 2014, Prof. Christian Bréchot's visit to the Macenta Ebola treatment center in Guinea's forest region on November 29, 2014.

> "One of the main priorities of the Institut Pasteur International Network is research into major global infectious diseases."

Responding to major global health challenges

One of the main priorities of the Institut Pasteur International Network is research into major global infectious diseases. As an example, the International Network member institutes are particularly involved in research on biological, molecular, and epidemiological determinants of resistance to malaria and how it spreads; in examining new diagnostic tools for pediatric tuberculosis; and looking at how to improve early HIV diagnosis in children.

They are involved in a number of research consortia that have been set up to respond to the major challenges raised by infectious diseases at global level. The French Development Agency is funding the ECOMORE project, which is assessing the consequences of economic development and environmental changes on human health in South-East Asia. In the same region, the multi-institute South-East Asia Encephalitis (SEAe) program, funded by the French National Alliance for Life and Health Sciences (Aviesan), the Total corporate Foundation and the European Commission, has been developed to study the pathogenic agents responsible for infectious encephalitis and to strengthen diagnostics and care for patients.

Mobility within the Institut Pasteur International Network

One of the key missions of the Institut Pasteur International Network is to offer training for young scientists.

The Calmette and Yersin fund, awarded by the Institut Pasteur Department of International

EBOLA

Three questions to Christian Bréchot

How did the Institut Pasteur respond to the Ebola outbreak in West Africa?

C. B.: We set up a task force that drew on the expertise of several institutes in the International Network. This dramatic outbreak demonstrated our high level of responsiveness in emergency situations. Our teams were rapidly deployed to the affected areas, and I would particularly like to pay tribute to their efforts. One reason the Institut Pasteur was able to respond so quickly was because of its ongoing research into hemorrhagic fevers. The teams from Paris, Lyon, and Dakar published the first description of the Zaire strain that caused this epidemic in the *New England Journal of Medicine* in April 2014.

What is the next step?

C. B.: We will continue this work, because even once this severe outbreak has died down, we know that there will be further outbreaks caused by other strains of the virus. This epidemic led us to set up a specialist investigation group within the new Center for Global Health, which was created in 2014. The aim of this group is to provide the Institut Pasteur with the resources it needs in the long term to react rapidly to these sorts of challenges.

What lessons have you learned from this episode in regard to the Institut Pasteur International Network?

C. B.: This epidemic clearly highlighted the difficulties facing us as we seek to apply the results of scientific progress in countries with fledgling healthcare systems. But the International Network is composed of institutes which are firmly established in their local communities – some have been there for more than 100 years – and work in close partnership with local health authorities. Their ongoing efforts in the fight against diseases, for the benefit of the most vulnerable populations, have earned them the trust of local governments and the general public. This places them in a strong position to implement emergency response initiatives during crises, which are supported by local authorities and accepted by the general public.

“From Paris to Montevideo: a wonderful experience and a springboard for the development of new collaborative projects.”

These three months working at the Institut Pasteur in Montevideo have been a wonderful experience abroad in terms of my scientific, intellectual and personal development. The basis for the trip was a scientific project in the Neurodegeneration Unit directed by Luis Barbeito, but the experience as a whole really gave me a new insight into the realities and missions of the institutes in the Institut Pasteur International Network. It was also a great opportunity for us to share our respective skills, to train members of the team and to come up with ideas for new collaborative projects.

GABRIEL LEPOUSEZ
RESEARCH ASSOCIATE IN THE PERCEPTION AND MEMORY UNIT AT THE INSTITUT PASTEUR IN PARIS

Right:
Institut Pasteur in Korea, a researcher with a student intern.

Below:
Institut Pasteur in Madagascar (Antananarivo).

Affairs, supports an ambitious training program for international scientists and researchers. This program is a unique opportunity for scientists to complete training through research. Each year, the Institut Pasteur awards international grants to scientists from developing countries so that they can attend courses or complete internships in Paris, at another institute of the International Network or at another research institute outside of the network.

More than 100 scientists from the International Network complete their training with courses or internships at the Institut Pasteur in Paris every year.

The international training program for PhD students and postdoctoral fellows gives scientists from France and abroad the opportunity to complete their thesis or postdoctoral training at International Network institutes in countries in endemic areas and/or with limited resources.

For more than 15 years, the Pierre Ledoux Jeunesse Internationale Foundation, under the aegis of the Fondation de France, has been helping train up young scientists by improving their awareness of the international context. A partnership between the Fondation de France and the Institut Pasteur provides funding for grants that allow French students to carry out internships in biomedical research in a developing country within the International Network.

A policy to attract a wide variety of young scientists

The Institut Pasteur has introduced a "five-year group" scheme to support talented young scientists and encourage them to develop international research groups within the International Network, with the aim of

strengthening fundamental research and improving the response to new emerging infectious agents. This program enables talented young scientists from developing countries to lead innovative research programs on infectious diseases in their own countries. It also attracts ambitious international scientists looking to develop new research partnerships. Since 2013, the Institut Pasteur has selected four scientists who have set up research groups in Cameroon, Bangui then Madagascar, Dakar, and Cambodia.

To encourage mobility within the International Network, from 2014 onwards all scientists recruited by the Institut Pasteur will spend at least three months at an institute in the International Network during the first two years of their contract. Gabriel Lepousez, for example, a new Research Associate in the Perception and Memory Unit directed by Pierre-Marie Lledo, began a stint at the Institut Pasteur in Montevideo in December 2014.

Strengthening bioinformatics activities

Dr. Magnus Fontes arrived at the Institut Pasteur in April 2014 with the task of boosting data analysis and bioinformatics activities throughout the Institut Pasteur International Network by means of research, training, infrastructures, and support. In June 2014, the International Group for Data Analysis (IGDA) and the International Network for Data Analysis (INDA) were set up as a first step in the coordination and international management of this ambitious priority. The aim of INDA is to boost international cooperation between experimentalists and bioinformaticians and to promote openness, collaboration, and teaching within the International Network. This has already led to close cooperation with the Institut Pasteur in Montevideo. The URUGENOMES project, launched in September 2014, will sequence the genomes of 80 people. The team led by Magnus Fontes is closely involved in this project and will particularly be focusing on analyzing the genomes to identify possible genetic bases for some diseases in Uruguay. Several other partnerships involving members of the Institut Pasteur International Network are in the planning stages, including projects on dengue, malaria, and pediatric enteropathies.

In 2014, 12 courses and workshops funded by the International Network were run in six countries, including two in Africa, one in Asia, one in Latin America, one in Europe, and one in North Africa.

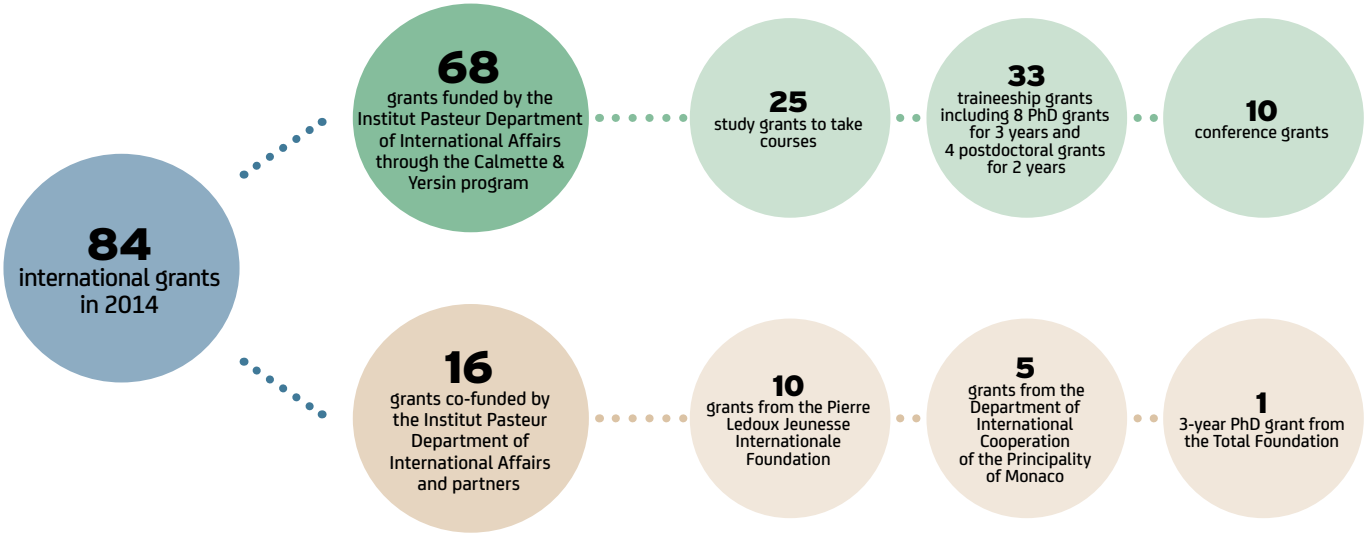
Some examples of recurrent courses run in the International Network:

- **The Malaria workshop - Institut Pasteur in Madagascar.**
- **A course on Cell Biology, Virology and Immunology at the Hong Kong University-Pasteur Research Pole.**
- **A course run by the International Network on foodborne infectious diseases and salmonellosis surveillance, held in Cameroon, Saint Petersburg, Madagascar, and Tunis in partnership with the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) in the United States.**
- **A course on bioinformatics in North Africa, Asia, Latin America, and Europe.**
- **Theoretical and practical courses run by the Institut Pasteur in Montevideo on new technologies for the Latin American scientific community.**

A first two-week course was held in December at the Institut Pasteur in Montevideo to provide students with the theoretical and practical tools they need to analyze data generated by high-throughput sequencing. From 2015 onwards, this course will be run twice a year at International Network member institutes. The next course will be held at the Institut Pasteur in Dakar in September 2015.

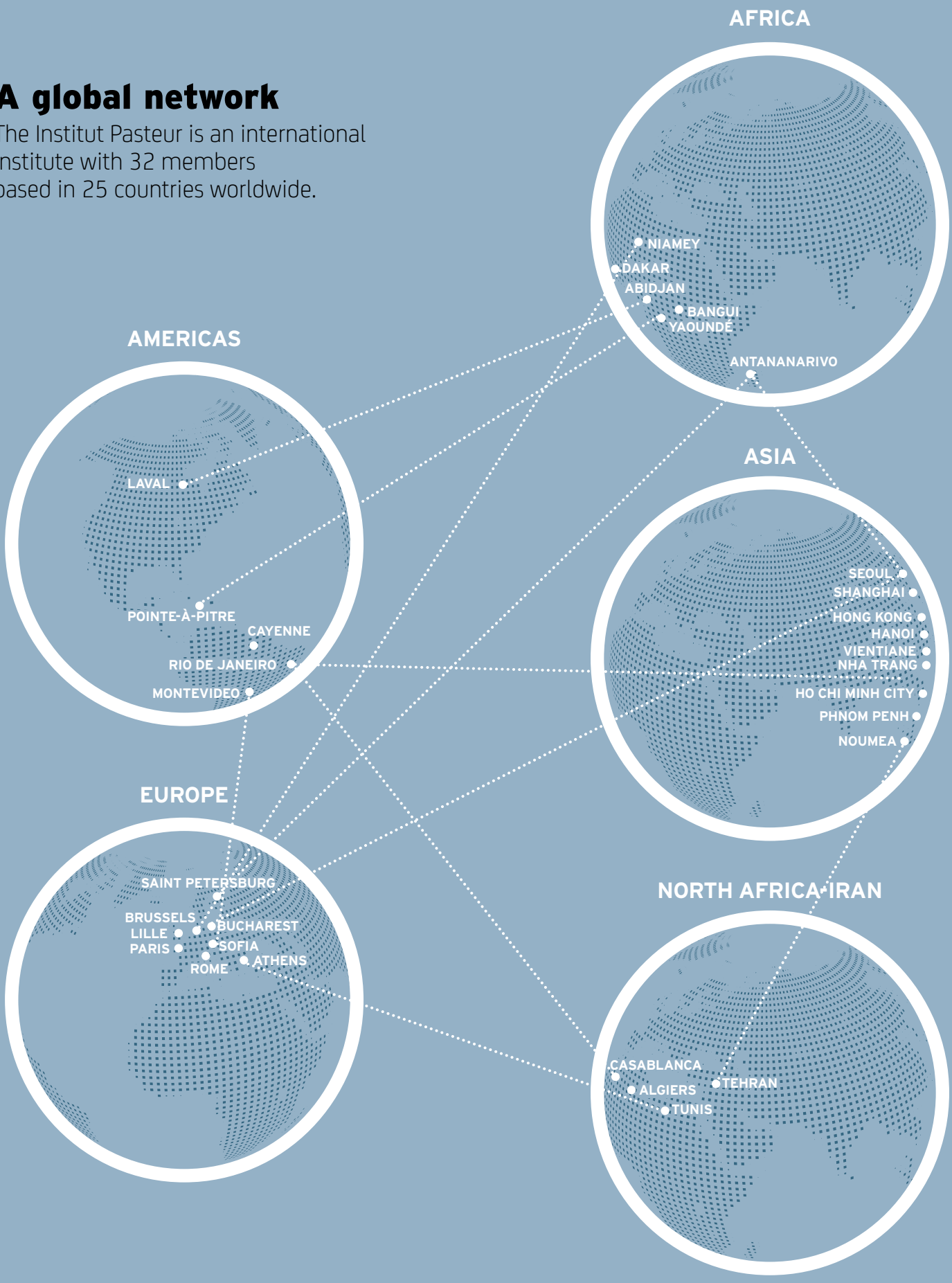
Teaching – a priority for the International Network

The International Network develops international courses in partnership with universities, health authorities, and local stakeholders. Training activities are intended for staff from member institutes but also for local scientists, technicians, and students, whose newly acquired skills are widely recognized by regional, national and international structures.



A global network

The Institut Pasteur is an international institute with 32 members based in 25 countries worldwide.



"The greatness of human actions is measured by the inspiration that it brings."

LOUIS PASTEUR

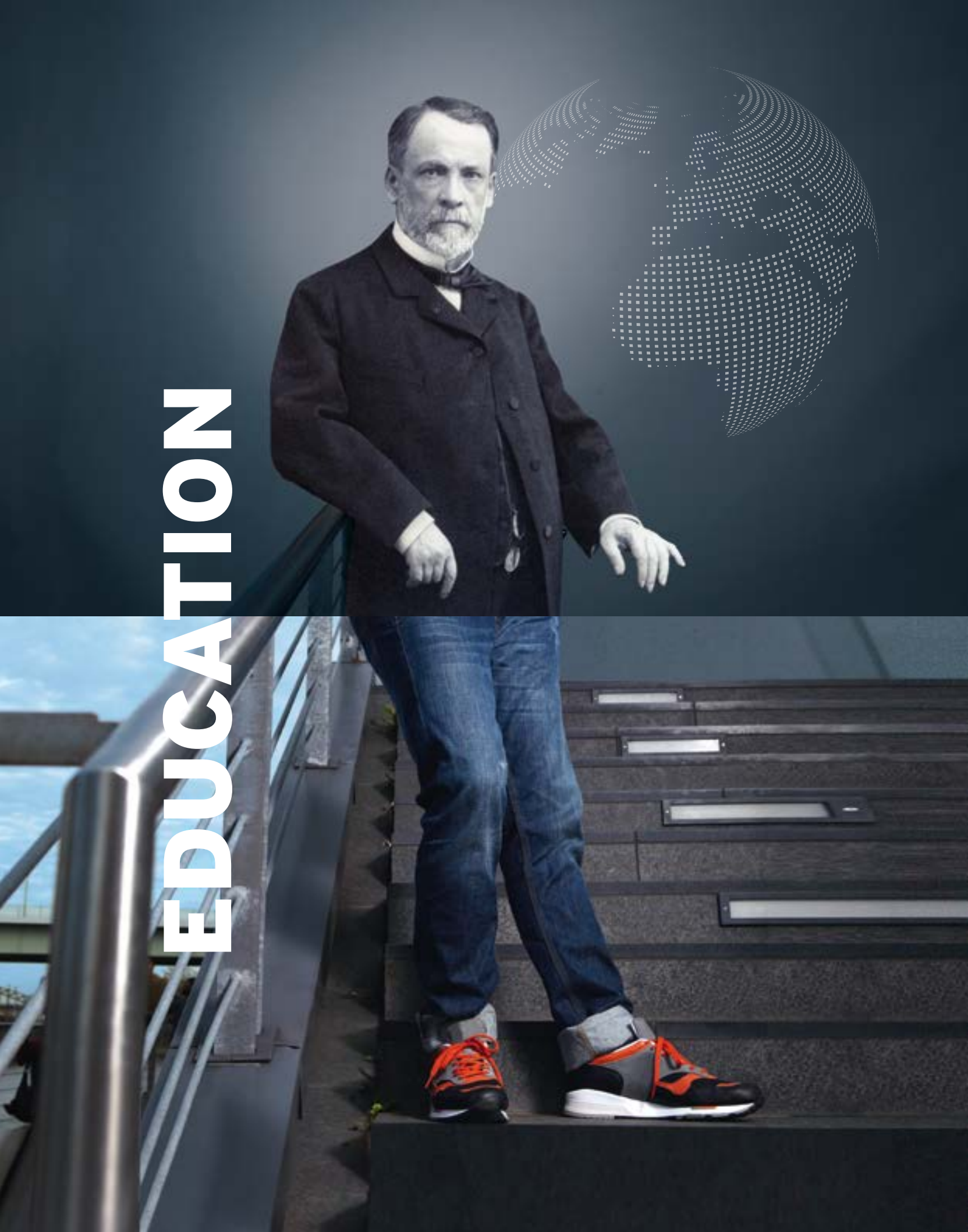
Teaching and training

Since the Institut Pasteur was inaugurated on November 14, 1888, teaching and training have been a key part of its mission.

Each year, more than 500 students take the courses run at the Institut Pasteur Teaching Center, and more than 300 young scientists are welcomed at Institut Pasteur laboratories to learn about what it means to be a researcher and conduct their Master's and PhD research projects. The initial and continuing education offered at the Institut Pasteur is widely recognized at international level, enjoying a visibility that attracts outstanding young scientists from across the globe and promoting the development of an international network of Institut Pasteur-trained scientists. This visibility has also helped position the Institut Pasteur as one of the leading research institutes on the international stage.

Restructuring teaching activities

At the beginning of 2015, Institut Pasteur President Christian Bréchot launched a major overhaul of the Institut Pasteur's teaching and training activities, based on the principles set out in the 2014-2018 strategic plan. Several new appointments have been made in connection with this reform. These include: Monica Sala, Executive Director for Education; Dominique Franco, responsible for developing MOOCs (massive open online courses), the Institut Pasteur's MD-PhD training program and entrepreneurship; Roberto Bruzzone, responsible for the international teaching and training program of the Institut Pasteur; and Paul Lazarow, Dean of the Pasteur-Paris University International Doctoral Program.


EDUCATION

The Institut Pasteur: a unique training environment

The excellence of the research carried out at the Institut Pasteur creates a unique training environment to familiarize young scientists from France and abroad with the world of research. The various research structures at the Institut Pasteur host students for internships at undergraduate, postgraduate, and PhD level.

In addition to this initial training in research through research, the Institut Pasteur also offers high-level continuing education for science professionals.

32
courses

60
nationalities represented

These courses are run by the Institut Pasteur Teaching Center and are organized and taught by Institut Pasteur scientists, with a significant contribution from lecturers from partner organizations (such as Paris Descartes, Pierre & Marie Curie, Paris Diderot and Paris-Sud universities, the CNRS, and Inserm) and from universities and research institutes across the world. The Institut Pasteur is unique in that it includes a major practical component in all its courses, in addition to the excellent theoretical teaching. This twofold approach is highly sought after by both French and international students.

A dedicated environment and varied course selection

The Teaching Center has a dedicated, strongly committed team (including engineers, technicians, laboratory technicians, technical assistants, and secretaries) and an outstanding infrastructure for theoretical and lab sessions in a wide range of disciplines related to infectiology, virology, microbiology, immunology, vaccinology, mycology, neuroscience, genomics, cell biology, bioinformatics and biostatistics, and various areas of epidemiology. It offers some thirty courses each year, running from one to twelve weeks.

The courses (taught in French or English) are aimed at current Master's and PhD students from French and foreign universities and university hospitals, as well as working professionals – scientists, doctors, pharmacists, veterinarians, and engineers – wishing to top up their training.

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

New courses are regularly set up to keep step with the latest developments in the field. In 2013, two courses were launched: "Progrès de la biologie des cellules souches" (Progress in stem cell biology) in partnership with the LabEx (Laboratories of Excellence) project "REVIVE", and "Human population genomics and genetic epidemiology" in partnership with the LabEx project "Milieu intérieur" ("The environment within").

550
students

250
PhD students

In 2014, the courses "Introduction aux relations entre sciences et société" (An introduction to the relationship between science and society) and "Frontiers in biological psychiatry" were set up, demonstrating an openness to new training subjects that reflect a growing move towards interdisciplinarity as a vital source of knowledge.

The Institut Pasteur's technological platforms (particularly the Imagopole) and the Center for Human Immunology offer valuable support for its teaching activities.

Since September 2007, the Teaching Center has been based in the refurbished premises of one of the two wings of the former Institut Pasteur hospital (the Louis Martin wing). The management team of the Institut Pasteur has recently launched a major enlargement plan to boost the activities carried out at the Teaching Center. By the end of 2017, the Émile Roux wing will have been incorporated into the Teaching Center, doubling the surface area; the existing infrastructures will also be improved, and all the staff involved in the center's activities will be housed on the same site. In anticipation of this upcoming enlargement, the Teaching Center has already extended its course selection, with four new courses planned for the 2015-2016 academic year. The new facilities will also help consolidate the Institut Pasteur's role at the forefront of teaching and training.

Teaching students from around the world

The Teaching Center welcomes students, scientists, doctors, pharmacists, engineers, and veterinarians from all over the world. Each year, more than 200 students from around 60 different countries come to take courses at the Institut Pasteur. With the growing number of foreign students and lecturers, an increasing number of courses are taught in English. Reflecting the commitment of the management team of the Institut Pasteur to move towards innovative teaching strategies that suit the needs of today's students and researchers, the Teaching Center has recently begun developing MOOCs (massive open online courses; a first vaccinology MOOC is currently being finalized), e-learning tools, lecture streaming, and video conferences, so that as many people as possible – particularly those at the institutes in the International Network – can benefit from the Institut Pasteur's training. The Teaching Center is often the venue for courses run by Institut Pasteur scientists in partnership with the European Molecular Biology Organization (EMBO).

The Institut Pasteur is truly a higher-education hotspot for many young scientists. Each Institut Pasteur research laboratory is affiliated to a doctoral school accredited by a Parisian university and is actively involved in supervision and training for doctoral students. Some 250 doctoral students per year conduct research projects in Institut Pasteur laboratories. The four new transversal research centers (http://www.pasteur.fr/en/research/transversal-research-centers) recently set up by the management team of the Institut Pasteur also offer training in connection with their scientific activities. These centers are a vital additional source of training for Master's and PhD students at the Institut Pasteur, offering an interdisciplinary approach, promoting additional training activities such as workshops and seminars, and serving as reference centers for specific scientific fields.

"Each year, more than 200 students from around 60 different countries come to take courses at the Institut Pasteur."

The specialized Master's in Public Health, recognized by the French *Conférence des Grandes Écoles,* is run in partnership with the French National Conservatory of Arts and Trades (CNAM) and the French School of Public Health (EHESP) at the Pasteur-CNAM School of Public Health. It is geared towards health professionals, final-year students, doctors, veterinarians, pharmacists, biologists, staff members of health agencies, and personnel from international organizations. Following one semester of theory, the students complete a six-month internship on infectious diseases, either in France or in one of the institutes of the Institut Pasteur International Network, after which they write a dissertation.

This year, in a bid to familiarize doctors with scientific research at the beginning of their career, the Institut Pasteur is launching a medicine-science program (MD-PhD), in partnership with the ENS, the Institut Curie, PSL, ESPCI ParisTech, and the Collège de France. This joint program will offer a range of high-level medical and scientific training. Since 2008, the Institut Pasteur has also developed the Pasteur-Paris University International Doctoral Program, which involves agreements with Paris Descartes, Pierre & Marie Curie, and Paris Diderot universities and is open to students who have completed a Master's at a foreign university. In September 2013, Paul Lazarow took over from Michaela Müller-Trutwin as Dean of this three-year program, which leads to a PhD from one of the three partner French universities. The "Alexandre Yersin" class of 2014 included 10 students from Europe (Portugal, Russia, and Italy), the Americas (Canada and Mexico), and Asia (India and Taiwan). Each year, a new set of students specializing in a wide variety of different fields are given the chance to meet and exchange ideas during joint activities, organized by the Pasteur-Paris University organizing committee, such as bibliography seminars and an annual retreat. This year, the retreat took place in April and once again offered all current PhD students the chance to attend a conference where they discussed the progress of their research in a focused but informal setting, with the aim of providing constructive suggestions to improve their projects.

In conclusion, education at the Institut Pasteur is the result of highly coordinated local, national, and international efforts, driven by the dedication of subject specialists who are fully committed to teaching and training. The Institut Pasteur is keen to consolidate its education activities, reflecting the vision of the new management team of the Institut Pasteur, to ensure that it remains at the forefront in terms of the subjects taught and the methods used, and to consolidate its position as a leading player on the international stage.

PhD graduation ceremony

On December 12, 2014, the second PhD graduation ceremony was held at the Institut Pasteur for students who submitted and defended their theses during the 2013-2014 academic year. Despite the formality of the occasion, there was a relaxed, friendly atmosphere. The guest of honor was the mathematician and 2010 Fields medalist Cédric Villani, who gave a fascinating lecture about being a scientist and making new research discoveries, and spoke about his own career. The ceremony was attended by Institut Pasteur staff, family and friends of the PhD students, representatives of partner organizations, and figures from political, diplomatic and business circles with links to the Institut Pasteur.
Since the first edition in 2013, this ceremony has become a major event in the Institut Pasteur's calendar, a showcase for the professional excellence produced by its research and training. The next ceremony will take place on December 11, 2015, with Françoise Barré-Sinoussi, winner of the 2008 Nobel Prize in Medicine, as guest of honor.

“Presenting my PhD project to a general public in just three minutes!”

I was delighted to take part in the competition “My thesis in 180 seconds – MT180” and to be rewarded by the Sorbonne-Universities 2015 “People’s Choice Award”. Summarizing and presenting years of scientific results accumulated in the lab for my thesis topic to a lay audience was an incredibly challenging exercise in summary and communication skills, but it was one that I really enjoyed. What could be more worthwhile than having the opportunity to share my PhD project with as many people as possible?

I would particularly like to thank the Institut Pasteur, and especially my PhD supervisor, Fabrice Agou, who encouraged me to take part in this competition.

KEÏS NABHANE SAID HALIDI

PHD STUDENT AT THE INSTITUT PASTEUR
WINNER OF THE “PEOPLE’S CHOICE AWARD” AT THE SORBONNE-UNIVERSITIES 2015 MT180 COMPETITION

http://www.sorbonne-universites.fr/actions/recherche/college-doctoral/concours-ma-these-en-180-secondes/

"Cure sometimes,
relieve often,
comfort always."

LOUIS PASTEUR

Medicine, clinical research and public health

The year 2014 was one of challenges but also fresh impetus for all the teams involved, with renewed focus on developing translational and clinical value within research projects and addressing public health issues arising from the work of the National Reference Centers.

The key strands of the Institut Pasteur's strategic plan, as discussed and finalized during 2014, have had a major impact on the various teams that report to the Medical Affairs and Public Health Department. The year was one of challenges but also fresh impetus for all the teams involved, with renewed focus on developing translational and clinical value within research projects and addressing public health issues arising from the work of the National Research Centers.

The emphasis on cross-disciplinarity, as reflected in the establishment of transversal research centers, has introduced a new approach that has required extensive work on careers, synergies, processes, and the information system dedicated to all these fields.

This transitional stage was an opportunity to lay solid foundations for a new, more efficient organizational structure, which will become fully operational in 2015 but which started to impact our activities in 2014.

HEALTH

National Reference Centers and WHO Collaborating Centers

The National Reference Centers (CNRs) under the responsibility of the Institut Pasteur draw on the scientific environment of their host units and the various support structures such as the Laboratory for Urgent Response to Biological Threats (CIBU). Seven of these CNRs are also WHO Collaborating Centers (WHOCCs), and one CNR/WHOCC has been designated as a reference laboratory for the World Organization for Animal Health.

Ebola

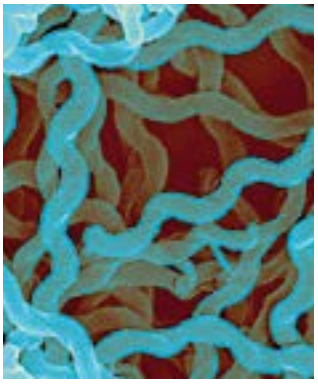
In March 2014, the National Reference Center for Viral Hemorrhagic Fevers (VHFs) diagnosed what would become an unprecedented outbreak of the Ebola VHF, which has resulted in close to 24,000 reported cases and 10,000 deaths in Guinea, Sierra Leone and Liberia. The CNR was then closely involved in the response to Ebola in France, in cooperation with the National Institute for Public Health Surveillance (InVS) and the Ministry of Health (DGS); this involved diagnosing possible cases in those returning from affected countries, providing virological monitoring for repatriated patients, and acting in an advisory capacity. In Guinea, the CNR offered advice and expertise to the health authorities and the French Embassy in Conakry at the start of the outbreak. It also set up a diagnostic laboratory at the Ebola Treatment Center in Macenta, Guinea, that can be used for etiological diagnosis and also to provide biochemical and biological parameters. It is hoped that this laboratory will help bring about significant improvements in treatment and survival rates. The VHF CNR therefore played a vital role in the fight against the Ebola virus in West Africa.

Meningitis

Meningococcal infections are generally spread via respiratory droplets. The National Reference Center for Meningococcus described an international outbreak of invasive serogroup C meningococcal disease among men who have sex with men (MSM). A coordinated international effort resulted in the identification of the mechanisms underlying the emergence of this outbreak. A "multi-omic" approach (genomic and proteomic methods) was used to analyze the outbreak isolates. This showed the unique ability of meningococci to adapt to sexual transmissibility and the subsequent reacquisition of virulence through the modulation of innate immunity. These data were used to lead a targeted vaccination campaign within the MSM community in France and Germany. The results reveal how subtle genomic changes during microevolution can lead to adaptation. They also show that "omics" approaches can be used in real-time epidemiological surveillance to facilitate decision-making on vaccination strategies.

Top: *Leptospira* bacteria. The pathogenic species are responsible for leptospirosis, in which humans are occasional hosts in a cycle involving wild and domestic animals.

Bottom: Ebola crisis in 2014, training voluntary scientists at the Institut Pasteur in Paris.



Leptospirosis

The National Reference Center for Leptospirosis reported a two-fold increase of leptospirosis cases in Mainland France compared with the previous year, which had already seen the highest incidence in the past decade. 2014 is a year with a record incidence of more than 0.9 cases per 100,000 inhabitants. The CNR, which is also a WHO Collaborating Center, was informed that the number of cases had also increased in several other European countries, including the Netherlands, which had three times more cases than in previous years. This suggests that leptospirosis is an emerging zoonosis in Europe. The reasons for this increase are not known but could be related to climate change and global warming.

Botulism

The National Reference Center for Anaerobic Bacteria and Botulism carried out diagnosis and surveillance activities for human botulism from 129 serum samples, 53 stools, and 180 food samples. The most significant event in 2014 was a botulism cluster involving two patients, one of whom developed a particularly severe form and required respiratory assistance for 46 days. The outbreak was identified as botulism due to *Clostridium baratii* type F. These were the first two cases identified in France of this rare type of botulism, which has mainly been reported in the USA. The *C. baratii* strain, isolated from the patients' stools, was characterized by whole-genome sequencing.

Cholera

In September 2014, the Institut Pasteur was invited by WHO to become a member of the Global Task Force on Cholera Control, in recognition of the scientific and public health activities of the National Reference Center for Vibrios and Cholera in the field of cholera. A first international meeting of the "Laboratory Surveillance" working group was held at the Institut Pasteur on December 19, 2014, with the financial support of the Department of International Affairs. This meeting particularly involved members of the Institut Pasteur International Network.

“Curiosity, challenge, and reflection – resulting in the identification of a new bacterial species, *Rouxiella chamberiensis.*”

We receive bacterial strains of human, animal or environmental origin on a daily basis, from all over the world. These strains can belong to known or unknown species and are sometimes difficult to culture. We use cutting-edge techniques to identify these strains. Our laboratory described one of the latest bacterial species to be recognized, *Rouxiella chamberiensis.* This new species was isolated from parenteral nutrition bags in Chambéry. Curiosity, challenge, reflection, and exchange of material or ideas within the scientific community – all part of daily satisfying work at the Institut Pasteur.

ANNE LE FLÈCHE-MATÉOS
HEAD OF THE BACTERIAL IDENTIFICATION CENTER
LABORATORY FOR URGENT RESPONSE TO BIOLOGICAL THREATS (CIBU)
WHO COLLABORATING CENTER FOR ARBOVIRUSES AND HEMORRHAGIC FEVER VIRUSES
ENVIRONMENT AND INFECTIOUS RISKS UNIT

Medical Center

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

In addition to vaccinations and travel advice for children and adults, with a special focus on vulnerable patients (i.e. patients living with HIV, organ transplants or other immune deficiencies) and those traveling for humanitarian reasons (including those traveling to regions affected by the Ebola epidemic in 2014), a significant part of the Medical Center's work also involves treating diseases contracted abroad, HIV infection, cosmopolitan infectious diseases such as Lyme disease, and post-exposure rabies treatment. Another area of activity is dermatology, with a particular focus on hidradenitis suppurativa (HS). An innovative therapeutic strategy for HS adjusted to the severity of the condition has resulted in most patients obtaining clinical remission. Some of these diseases are monitored in collaboration with Necker-Enfants Malades University Hospital, via the Necker-Pasteur Center for Infectious Diseases.

The Medical Center also offers allergy consultations, with a multidisciplinary team that is able to diagnose and treat all types of allergies.

In addition, the Medical Center is involved in clinical research directly related to its medical focus areas: cohorts in the area of HIV infection; the pathophysiology of hidradenitis suppurativa (microbiology and genetics, in collaboration with Necker Hospital and the ICAReB Platform); vaccinology (for example, the interaction of yellow fever and measles vaccines in children); and the pathophysiology of post-infectious anosmia.

69,887
vaccines administered

48,805
visits to the international vaccine center

13,857
consultations for infectious and tropical diseases and travel medicine

2,766
consultations for rabies

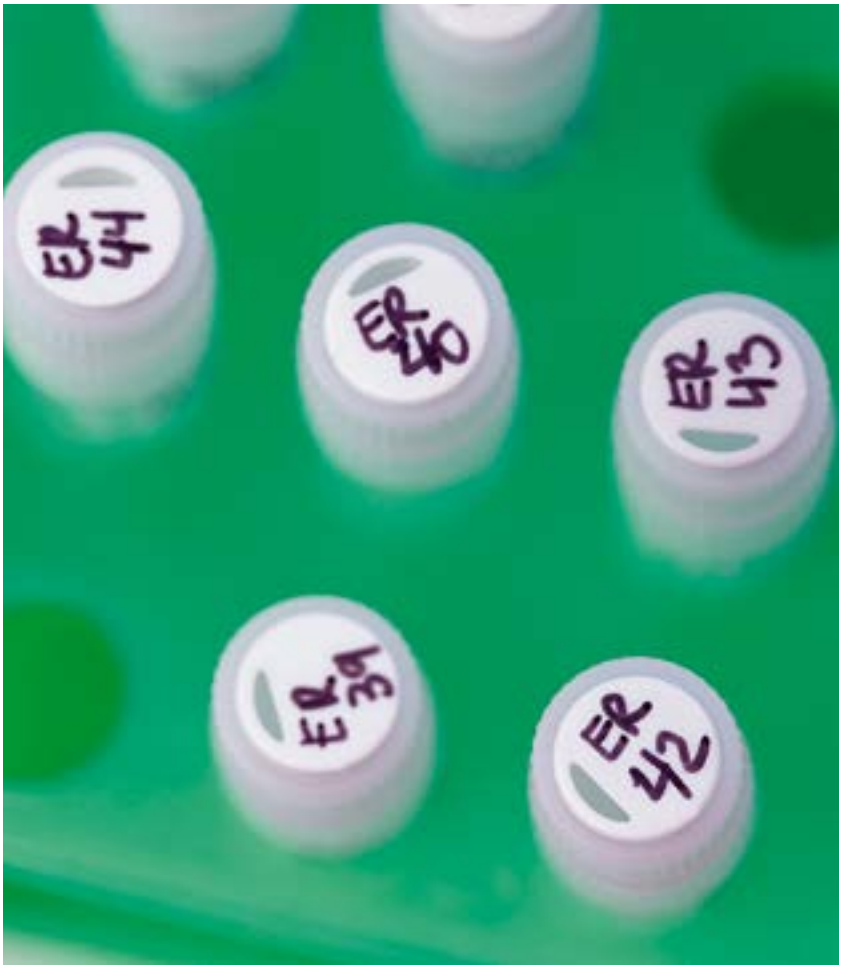
5,487
consultations for allergies

Major progress was made on hidradenitis suppurativa in 2014. The team improved understanding of the microbial component of this disease by identifying a characteristic microbial flora that varies according to the stage of skin lesions, which helps explain the progress of patients undergoing current therapeutic strategies based on long-term antibiotherapy. These strategies will be tested in therapeutic trials in the next few years.

The new knowledge generated by these projects underscores the vital role of the Medical Center as part of the Center for Translational Science, illustrating the valuable support that it can provide for clinicians.

Clinical research

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



The clinical research department: From scientific to translational research

In 2014, the Clinical Research Department became part of the Center for Translational Science. It supports the projects run by this center, providing the expertise needed for the entire clinical research cycle, from project start-up to business development.

The Institut Pasteur as sponsor

As a sponsor[1] of research projects, the Institut Pasteur helps bridge the gap between fundamental research and clinical research. The Clinical Research Department represents the Institut Pasteur as a sponsor. In 2014, the Clinical Research Committee examined the regulatory, legal, and ethical compliance of 31 new clinical research projects. The Institut Pasteur was the sponsor/legal representative for half of these projects (48%). Thirty-five percent of the projects involved the Institut Pasteur International Network.

Alongside these projects, support was also provided for more than 30 new projects, some of which had already been mooted in 2013, so that the ethical and regulatory aspects could be dealt with in advance, thereby guaranteeing the projects' feasibility and helping speed up the implementation process.

Developing innovative therapies: from preclinical to clinical trials

In 2014, major advances were made in the clinical trials led by the Clinical Research Department. In the immunotherapy trial with vaccine candidate MAG-Tn3, the formulation of the vaccine candidate was finalized, and following batch release the clearances required to start recruiting patients were secured. Recruitment of the first patient was due early 2015. The phase I trial for the Sanfilippo B gene therapy project, which began in September 2013, was conducted with the four patients planned. Although it is far too early to draw conclusions from the trial (the follow-up period has been extended by 18 months), the first results appear to be promising and are awaited with great interest by the international community in 2015.

In 2014, the Clinical Research Department also continued to coordinate the production of batches for regulatory toxicology studies for other projects that are still in the pharmaceutical development and preclinical stages. One example is the FP7-funded Stopenterics project. For some vaccine candidates, planning is under way for the first administration in humans.

Training... and informing

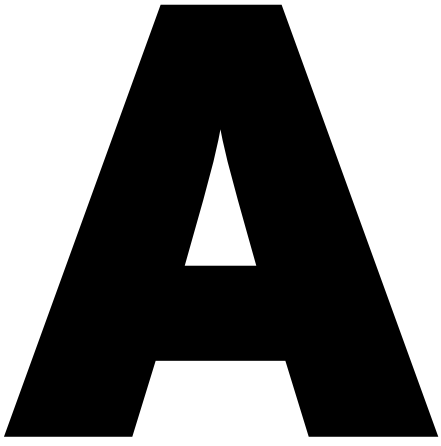
The fifth season of Clinical Research Department Workshops again proved extremely popular, catering to a wide audience from the research community and the general public. The discussion sessions focused on issues in the field of clinical research, including innovative and important themes related to research on humans such as genetic research, the patient's role in the research process, GMOs as health products, pharmacovigilance, and research ethics.

1. In legal terms, the sponsor is the body that initiates the project and takes responsibility for the research.

EXPERTISE AND RESOURCES

Research applications

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



As emphasized in the Institut Pasteur's strategic plan, *"The valorization of scientific research in connection with the international academic and industrial communities has always been part of the vocation of the Institut Pasteur. It is also a critical element of its future: academic and industrial partnerships can provide patients with the benefit of discoveries made on campus, represent essential self-generating resources for the institute, and are also a means to finance ever more penetrating research to the benefit of all."*

An outstanding year for industrial relations

Taken as a whole, direct and indirect income from industrial activities in 2014 came to nearly €60 million, a sum which will help fund future research activities carried out on campus. This achievement once again confirms the Institut Pasteur's position as one of the top research institutions in terms of technology transfer.

Increasing numbers of invention disclosures

With 64 invention disclosures submitted – an increase of 25% over last year – the target laid down for the year in the strategic plan was clearly exceeded. This growth reflects the quality of the Institut Pasteur's scientific activities and also the development of a closer relationship with the community of scientists, who are becoming increasingly aware of the positive impact of innovation.

64
invention disclosures

30
priority patent applications

12
license agreements

Proactive intellectual property management

The number of priority patent applications also rose by 25%, with 30 applications filed. The annuities budget was effectively managed again this year, with a 12% decrease in expenditure compared with 2013.

A key patent on cell reprogramming using our "DNA Flap" technology, which enables genes to be inserted and expressed in optimal conditions, was granted in the United States. This patent covers cells used in gene therapy or adoptive immunotherapy. It puts us in a strong position to negotiate or renegotiate agreements with current or new partners.

An intellectual property strategy was devised and implemented to protect the Institut Pasteur's rights in the area of diagnostics for neurological complications associated with AIDS. This places the Institut Pasteur in a promising position for a potential industrial partnership.

Several patents were granted by the relevant authorities during the year, and license agreements for some of these patents have already been concluded with industrial partners, strengthening the potential of these partnerships. These include the patents licensed to Cellectis (genome engineering), Stragen (analgesics), and Genticel (cervical cancer). For three priority applications in the field of Alzheimer's diagnostics (partnership with Roche) international extensions were also filed.

New framework agreements were signed between the Institut Pasteur and some of its academic partners, including the CNRS and AP-HP, offering greater flexibility in managing patents owned jointly with these institutions.

10
collaborative research agreements

A busy year for contracts, with several strategic partnerships at all stages of negotiation

The renewal of our intellectual property in the area of AIDS diagnostics enabled us to conclude a major contract with Grifols, a company that recently took over the diagnostics assets of Novartis. Discussions are being held with other stakeholders in this field with a view to securing further large-scale contracts.

The Institut Pasteur renewed its framework agreement with Biomérieux, and new contracts with Roche, Stragen, and Ferring were mooted. Terms were laid down for a partnership with a major Japanese imaging firm, and various promising new partnerships were negotiated, including with AIT, a Technion spin-off, and Moderna, which is developing an innovative, highly original approach to vaccination.

Some partners that hold license agreements with the Institut Pasteur achieved noteworthy results this year. These include Themis, which has had extremely promising results from the phase 1 trial of a chikungunya vaccine, and Bluebird Bio, whose beta-thalassemia treatment based on Institut Pasteur technology was awarded Breakthrough Therapy status by the FDA.

Development of spin-offs and a thriving entrepreneurial ecosystem

In April 2014, two Institut Pasteur spin-offs enjoyed highly successful IPOs: Genticel (which raised €34.50 million) and Genomic Vision (which raised €23 million). In June, another Institut Pasteur spin-off, Cellectis, sealed a major agreement with the Pfizer laboratory on a promising new anticancer therapeutic approach.

These developments reflect the success of the Institut Pasteur's technology transfer activities, via the creation of new companies.

Two companies based on technologies developed on the Institut Pasteur campus were set up this year: Diaccurate and DNA Script.

The Institut Pasteur is encouraging business start-up, as laid down in its strategic plan, by offering training courses in entrepreneurship for potential company founders and initiatives to facilitate access to the funding needed for young companies. It initiated negotiations with French and foreign investors to co-found investment funds that enjoy the combined support of the French Banque publique d'investissement and the European Investment Fund. An initial fund, combined with an innovative diagnostic project enabler that will provide professional project development management, is set to raise around €35 million, and a more general second fund is aiming to raise €45 million.

Promoting business development in the Institut Pasteur International Network

The strategic plan contains a series of objectives designed to consolidate the role of the Institut Pasteur International Network as a major asset for the Institut Pasteur. Following the proposals discussed at the meeting of the directors of the International Network institutes in September, a program comprising training courses for scientists and potentially also for business development staff, together with the provision of expertise based on a standard agreement, will be gradually introduced to help optimize business development within the network.

Human resources

In 2014, in line with the vision set out in the strategic plan to place people at the heart of its activities, the Human Resources Department adopted initiatives and measures to promote and support the Institut Pasteur's development.

Developing skills, supporting and facilitating career management

In 2014, the Institut Pasteur pursued its ambitious recruitment policy – a vital strategy that will equip it to meet new scientific challenges –, taking on 442 new staff members, 53 on permanent contracts and 389 on fixed-term contracts. By offering competitive packages, it has attracted experienced scientists and new talents, particularly in key areas such as bioinformatics (a first wave of seven bioinformaticians was recruited in 2014).

In addition to these strategic recruitments, the Institut Pasteur has been working to improve the development potential, flexibility, and attractiveness of its careers in response to the constantly changing demands of today's research environment. To this end, the Human Resources Department has launched a strategy for forward-looking management of jobs and skills, involving a new jobs and skills framework, as part of a major overhaul of the career profile structure. This new approach applies to technical and administrative staff as well as engineers and scientists. This reflection process, launched in 2014, should be completed by the end of 2015.

From now on, mobility is strongly encouraged in the International Network. Starting this year, all scientists recruited by the Institut Pasteur on a permanent basis will spend at least three months in an institute of the International Network during the first two years of their contract.

Efforts have also been stepped up this year to improve the welcome and support facilities for scientists. In February 2014, more than 250 postdoctoral fellows, recently recruited young scientists, and international staff members attended days of meetings and discussions that were organized to help them settle in and get to know each other. In March 2014, a structure in charge of integration and career guidance for contract scientists was set up in the HR Department, to help foreign scientists with all the paperwork and administrative procedures they need to complete and also to offer career support for scientists on fixed-term contracts. As well as offering one-to-one meetings and tailored career guidance, the team also puts on events (including the Beyond the PhD round tables) to help scientists develop their career plans.

In 2014, the HR Department continued to work in collaboration with the other departments on campus to examine the possibility of merging and optimizing core activities such as administrative support services for research and the activities carried out by preparation labs. Starting this year, special platforms have been set up in some buildings on campus for media production, equipment preparation, and waste management.

Support, simplification, and modernization

Following the reorganization of the HR Department in 2013 to establish closer links between its teams and the rest of the campus, this year the department consolidated its mission to provide services, advice, and support for Institut Pasteur staff. It has also pursued its strategy to optimize its organizational structure and processes. A portal offering various HR services was brought online in autumn 2014. This reflects the general strategy to modernize the campus by improving IT tools and adopting an enterprise resource planning (ERP) system. This portal helps simplify and improve the services offered by the HR Department (features include an annual leave management system and a tool for updating personal administrative data). Other portals and services related to the support structures will be introduced in the first quarter of 2015.

Significant efforts have also been made in the area of training. Bioinformatics training programs have been set up in conjunction with the scientific community and the Information Systems Department (including an intensive bioinformatics summer school for biologists).

In 2014, new arrangements were also introduced to welcome new staff members and help them settle in to the Institut Pasteur. Starting in April 2014, regular Welcome Day sessions have been held to welcome newcomers as soon as they arrive and help them get used to life on campus.

The commitments made in 2013 via the "generation contract" between the management and trade unions were also upheld this year. Targets for the recruitment of young people and older employees were exceeded, with 29 employees under the age of 31 recruited on permanent contracts and seven new employees over the age of 55. The Human Resources Department has also focused on promoting training and employment among older employees; mid-career interviews were carried out with 39 employees aged 45 or over.

Finally, the dialog between management and unions was particularly effective this year; the annual negotiations held at the end of 2014 led to the signing of a memorandum of understanding concerning the future development of the Institut Pasteur, which included a series of significant measures: in addition to payroll measures and measures relating to labor relations (with the proposed introduction of an electronic voting system for staff representative and Works Council member elections), the MoU includes the strategy for forward-looking management of jobs and skills and the establishment of a profit-sharing scheme (finalized in early 2015). This profit-sharing scheme is a new compensation tool that recognizes collective and individual efforts, encouraging and rewarding the dedication of each and every employee to the development of the Institut Pasteur.

Key figures*

2,493
staff members on campus

2,013 Institut Pasteur employees (70.5% on permanent contracts)

424 employees from external research organizations

56
interns and students

Of the
2,437
people working on campus (excluding interns and students)

51.5%
scientific managers

33.3%
non-managerial staff

15.2% administrative and technical managerial posts

442
recruitments in 2014:

269
women

45.93%
scientists

13.57%
of those recruited under the age of 25

Average age: **43**

60.76%
of scientists have fewer than five years' service

60.61%
of Institut Pasteur employees are women

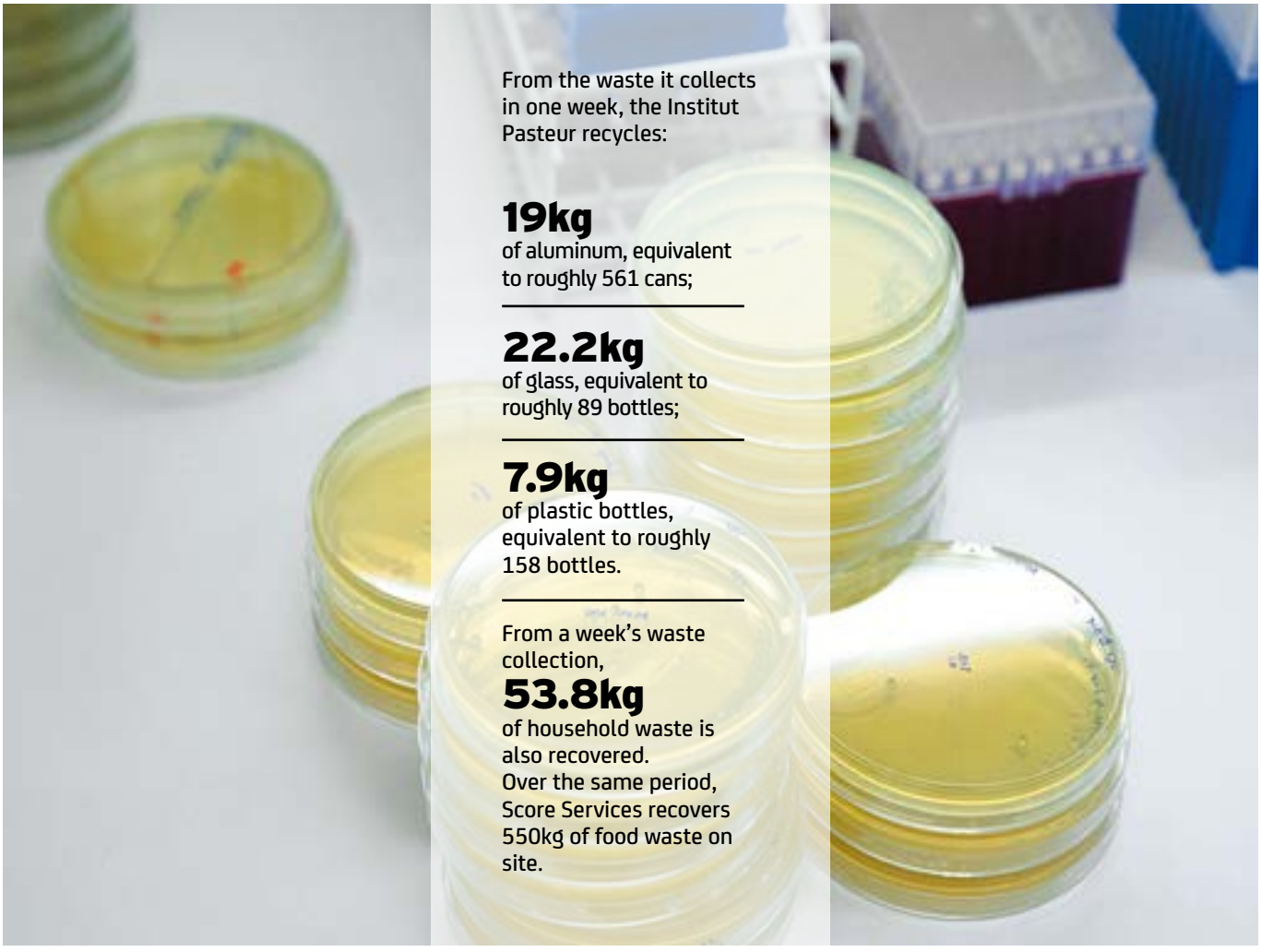
More than **67** nationalities on campus

220
new staff members attended Welcome Days

* As of December 31, 2014

Sustainable development

Following his appointment, new President Christian Bréchot reaffirmed the Institut Pasteur's membership of the United Nations Global Compact. He also confirmed that the Institut Pasteur would be pursuing its "Green Campus, Responsible Campus" program, in line with the 2014-2018 strategic plan.



From the waste it collects in one week, the Institut Pasteur recycles:

19kg
of aluminum, equivalent to roughly 561 cans;

22.2kg
of glass, equivalent to roughly 89 bottles;

7.9kg
of plastic bottles, equivalent to roughly 158 bottles.

From a week's waste collection,
53.8kg
of household waste is also recovered.
Over the same period, Score Services recovers 550kg of food waste on site.

Improving waste recycling and recovery

For several years now, the Institut Pasteur has been committed to improving waste recycling and recovery. In January 2014, a system to separate food waste was introduced at the Institut Pasteur staff restaurant, in accordance with article 204 of the "Grenelle 2" environment act. Around 47 tonnes of organic waste will be collected and dehydrated on site each year to produce an organic substrate, which will then be packaged by an organic-mineral fertilizer producer and distributed to farmers. This dehydration system also helps optimize the waste collection cycle – instead of the previous daily collection, the campus now only needs a monthly collection, reducing disruption for local residents.

In connection with this waste separation scheme, a series of eco-designed, fully recyclable bins have been installed at the door of the staff restaurant. These bins are divided into organic waste and non-organic waste, such as cans, plastic bottles and glass bottles, which are now recycled. To promote this new scheme, the Quality, Environment and Sustainable Development Department launched a communications campaign and provided support for the first few days after the bins were installed to encourage people to separate their waste.

A grant for more eco-friendly equipment

The Institutional Communications and Image Department, in cooperation with the Quality, Environment and Sustainable Development Department, has been awarded a grant from the Seine-Normandy Water Agency. This grant covers 20% of the purchase cost for new photo printing equipment, which offers the following advantages:

- elimination of the chemical run-off, which previously represented 360 liters a year;
- use of a solvent-free water-based ink;
- improved energy efficiency with the use of a cold process;
- an eco-friendly design that reduces the frequency of replacement of consumables.

Significant reduction in noise disturbance

A new noise map was drawn up in 2014. Noise emissions in regulated areas were analyzed at 15 reference points around the Paris campus, similar to those used in 2009 to draw up the first noise map. This new map demonstrates how effective the €4 million action plan launched in 2009 has been. During the day, no noise exceeding the regulatory threshold was recorded, and during the night, only one of the 12 points observed in 2009 was still non-compliant with regulations in 2014. Additional action will be taken to remedy this final point, and a further map will be drawn up in 2015.

Communications and fundraising

In view of the strategic challenges facing our foundation as it seeks to develop its research activities, the support of our donors – whether individuals or companies – remains a vital source of funding.

In 2014, we received €28 million in donations, an impressive increase of 13% over 2013. These funds mean that our scientists can pursue their ongoing research projects and also implement and lead new projects, in line with the Institut Pasteur's recently published strategic plan. Donations from individuals continued to rise, reaching €17 million, up from €14.8 million in 2013. Once again, this remarkable outpouring of generosity reflects a strong relationship of trust with our donors that will have long-term benefits for public health. In addition to our loyal donors who give generously year after year, more than 55,000 people made a first-time gift last year, particularly during our major fundraising operation, Pasteurdon, in October 2014. More and more people are also using races or personal challenges (such as the Paris marathon and half marathon, as well as the "Etape du Tour" cycling challenge) to raise money for our research.

In 2014, corporate sponsorship rose significantly, totaling €9.7 million (compared with €8.7 million in 2013), particularly thanks to new partners (GeoPost, Chronopost, Assu 2000, and Onet) and to some of our existing sponsors extending their support.

Sanofi was one of those to renew its partnership; in 2014, the third edition of the Sanofi-Institut Pasteur Awards recognized the outstanding work of four world-class scientists, with two young scientists receiving awards for the first time.

The EDF Foundation once again pledged its commitment to the work of the Institut Pasteur's scientists. Following its previous support for a project on cryptococcosis, a severe fungal infection believed to affect around a million people each year worldwide, the Foundation is now supporting a project that aims to develop the use of bacteriophages – viruses that only infect bacteria and are their "natural enemies" – to fight bacterial infections which have developed resistance to antibiotics.

> "A strong relationship of trust with our donors that will have long-term benefits for public health."

Pasteurdon takes to the airwaves

The 2014 edition of Pasteurdon, the Institut Pasteur's annual campaign to raise funds and awareness, was held from October 9 to 12. For the fourth year in a row, actress Alexandra Lamy showed her support to the Institut Pasteur's scientists as Pasteurdon patron. This year, for the first time, 9 radio stations rallied alongside the 19 French TV channels and various partner companies for the eighth edition of this unique event. In 2014, Nostalgie, Chérie FM, Rires et Chansons, NRJ, Radio Classique, RMC, Virgin Radio, RFM, and Europe 1 joined the ranks of those generously supporting the research carried out at the Institut Pasteur.

The stellar efforts of AG2R La Mondiale's cycling team in 2014's Tour de France were mirrored in the group's generosity during the Tour: it repeated and extended its "Roulons solidaires" ("Riding in solidarity") campaign for Institut Pasteur research into neurodegenerative diseases.

The Le Roch-Les Mousquetaires Foundation, a partner since 2008, renewed its commitment to supporting the Institut Pasteur in its efforts to tackle foodborne infectious diseases. Apprenticeship tax, the only source of funding for our Teaching Center, remained stable this year at €1.3 million.

Given the difficult economic climate in recent years, we would particularly like to extend our thanks to all our donors and sponsors, all of those who enable Pasteurian research to find applications and whose generous support means that we can continue the work of Louis Pasteur by extending its reach internationally and laying the foundations for the medicine of the future.

Legacies and donations

Significant upward trend. In 2014, although the number of new legacies and gifts received remained stable (around 110), they represented an overall increase in value of 30% compared with 2013. The legacies bequeathed to the Institut Pasteur are increasingly shared with other institutions, which obviously affects the sums received by the Institut Pasteur itself. Overall the legacies and gifts recorded in 2014 totaled €36.6 million, up from €34.6 million in 2013 (an increase of 5%). Life insurance policies again represented a major source of recurring income, amounting to almost €5.6 million. These policies, like legacies and gifts, offer favorable tax arrangements in that they are exempt from transfer duties.

Quality policy: Unique certification confirmed in 2014 – The Institut Pasteur's Legacies and Real Estate Assets Management Office is the

only department of its kind in France to have applied quality procedures to all its activities, recognized by an external certification body. This certification was successfully renewed for three years following an audit conducted by AFNOR Certification in 2014.

Communications activities. More and more people are contacting the Legacies Office every year to find out how to give a legacy, gift or life insurance policy to the Institut Pasteur, or to learn more about innovative schemes such as the temporary transfer of usufruct rights and posthumous gifts. Since 2012, the office has employed a dedicated staff member in charge of legator relations; those interested in giving to the Institut Pasteur can request advice and guidance or speak to one of the office's legal experts. In 2014, a promotional campaign was launched in both the mainstream and trade press to raise awareness of legacies and gifts – two major sources of funding which have played a fundamental role in the development of the Institut Pasteur over the years.

The think tank Fiducie philanthropique (philanthropic trust), which was set up by the Institut Pasteur following the success of its first Conference on Philanthropic Trusts in 2009, developed its activities and issued a series of opinions. The experts in this think tank include notaries, lawyers, and bankers.

To date, it is the only platform where experts from a variety of disciplines can share their thoughts and ideas on questions relating to generosity and philanthropy.

Financing structure

€296.4 M
Current income
in 2014

REVENUE FROM OWN ACTIVITIES

Industrial royalties (€39.6 M accounting for 13.4% of income) are essential for the Institut Pasteur. They are a direct result of the research carried out on campus. They rose significantly in 2014 owing to the resolution of a litigation with a pharmaceutical company and the implementation of a new license for HIV patents.
Research contracts and agreements (€88.2 M accounting for 29.8% of income) remained stable, following two years of significant growth as a result of the Institut Pasteur's success in tenders funded by the French National Research Agency (particularly under the Investing in the Future program) and the European Union (particularly with the European Research Council).
External services (€18.1 M accounting for 6.1% of income) comprise activities linked to business development (expert assessments, advice for industrialists, etc.), public health activities carried out at the Medical Center, and services provided, particularly to institutes in the network. This income rose by €1.5 M compared with 2013.

PUBLIC GIFTS & DONATIONS AND REVENUES FROM ASSETS

Revenues from assets (€35.3 M accounting for 11.9% of income) include current financial revenue, rent from income property, and agricultural revenue from estates registered among the Institut Pasteur's assets. They rose significantly (by €4.4 M) compared with 2013, with €1.9 M additional income from financial revenue and €2.5 M from rent and dividends from rental properties (the income from four properties sold in 2012 was reinvested in late 2013 in an income property).
Public gifts & donations (€51.8 M accounting for 17.5% of income) include all donations and legacies recorded as operating income, and apprenticeship tax. The contribution of public gifts and donations to the Institut Pasteur's current income is up by €1.8 M from 2013.

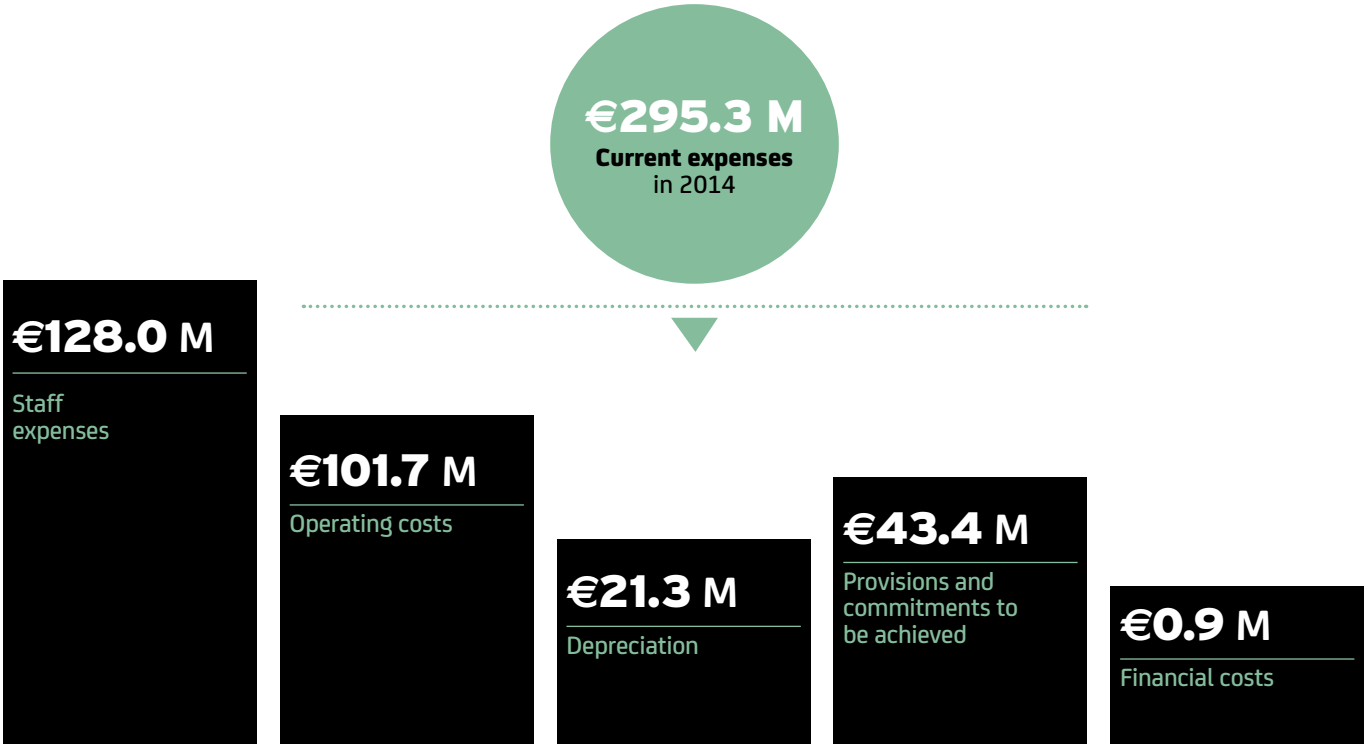
GOVERNMENT CONTRIBUTIONS

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

OTHER INCOME

This item includes recovery of provisions and transfer of charges.

1. The values and percentages include the carry-over of unused income from previous years.



The structure of research spending shows that 80% of our budget is earmarked for infectious diseases (viral, bacterial and parasitic diseases).

Financial statements

In 2014, the operating deficit grew slightly compared with 2013, reaching -€25.4 M. The financial result (€26.6 M), comprising income from short- and long-term investments, enabled us to balance the current result for the financial year (+€1.2 M). Exceptional items bring the Institut Pasteur's net result to €26.0 M.

Current operations

Current revenue increased by 4.9% compared with 2013.

The highest rises were recorded on royalties and support from our donors. Ongoing government grants, which remain key to balancing the Institut Pasteur's current result, fell by a further €2.4 M after a decrease of €1.3 M in 2013. Research contracts and agreements remained stable, despite the difficult economic climate in France and at international level.

Current expenditure was up by 4.8% from 2013, owing to the development of research contracts and agreements and to the implementation of the 2015-2018 strategic plan. This plan is designed to increase the Institut Pasteur's attractiveness by strengthening and developing its technological platforms, its bioinformatics activities, cooperation with the 32 institutes in the Institut Pasteur International Network and with clinicians, and business development. Finally, the modernization program for buildings and IT facilities on campus continued this year, with a new campus master plan for 2015-2018 and the introduction of integrated SAP software in the support departments in early 2015. In terms of the Institut Pasteur's activities, research accounts for the majority of current expenditure, while the rest is allocated to public health and teaching.

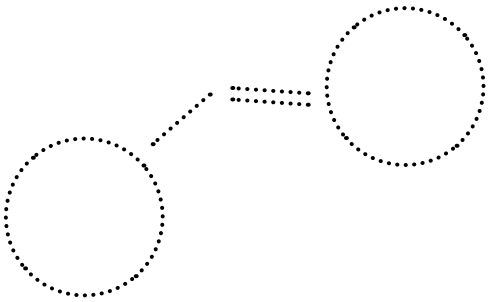
Exceptional items

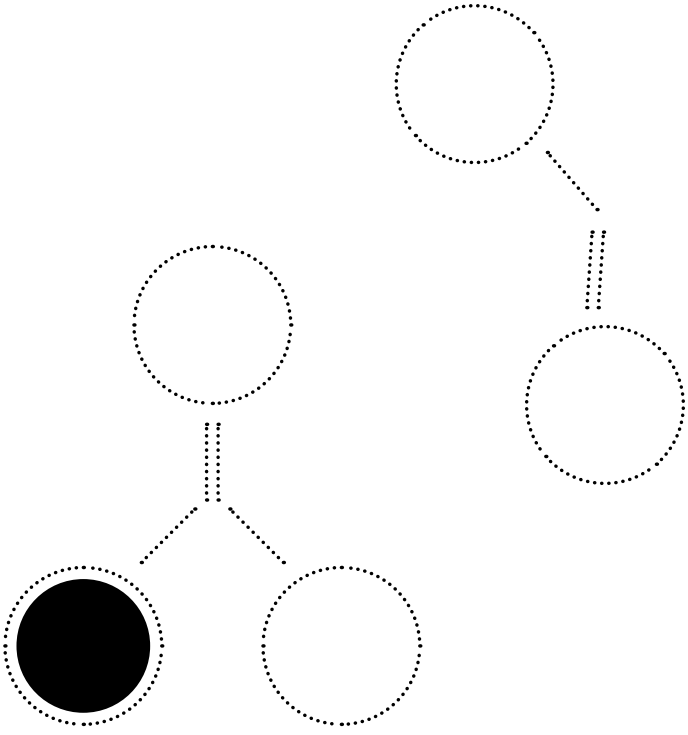
Exceptional operations comprise both a gift component (donations and legacies for the share exceeding €300,000) and a financial component (net valuation of financial assets resulting from capital gains or losses, realized or latent, based on the performance of the portfolio, with the balance of capital gains generated always exceeding the capital losses realized).

In 2014, the donations and legacies recorded as exceptional income amounted to €19.5 M, up by €4.6 M compared with 2013. The financial component showed a positive balance of €0.7 M, down by €17.6 M from 2013 because of the poor performance of the financial markets.

In addition to these two recurring items, exceptional income for 2014 also includes €4.6 M of various expenses and capital gains resulting from the sale of assets.

These exceptional items therefore bring the Institut Pasteur's net result to €26.0 M.

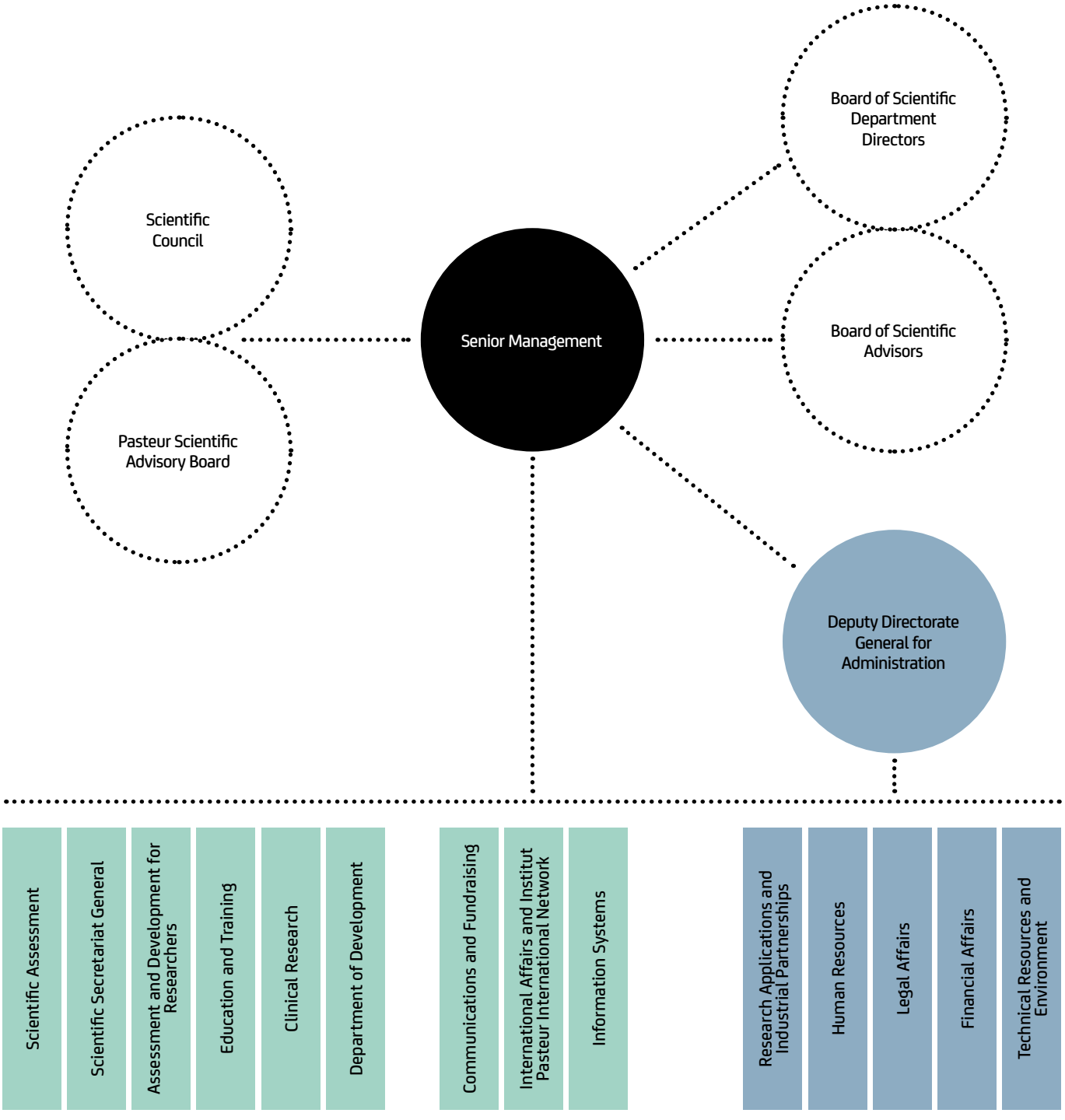




The Institut Pasteur is governed by the Board of Directors, Management, and General Meeting. The President, appointed by the Board of Directors, is responsible for overall policy and the smooth running of the institute.

ORGANIZATION

Departments and governing bodies



Board of Directors

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

April 2015

Board of Directors Bureau

Chair

ROSE-MARIE VAN LERBERGHE
Corporate Board Member

Vice-Chairman

BERNARD GUIRKINGER
Regional Delegate for Eastern France at Groupe SOS, Member of the French Economic, Social and Environmental Council

Vice-Chairman

LAURENT DEGOS
Professor of Hematology, Saint-Louis Hospital

Treasurer

SOPHIE MANTEL
Head of Department in the Budget Division, French Budget Ministry

Secretary

ALAIN JACQUIER
Head of the Macromolecular Interaction Genetics Unit, Institut Pasteur

Chairman of the Finance and Audit Committee

MICHÈLE FROMENT-VEDRINE
Chief Advisor French Government's Accounting Office

Other members

STEWART COLE
Director of the Infectiology Research Institute, École polytechnique fédérale de Lausanne (EPFL)

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

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

ALAIN FUCHS
President of the CNRS (French National Center for Scientific Research)

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

JEAN-BERNARD LÉVY
Chairman and Chief Executive Officer of EDF

YVES LÉVY
Chairman and Chief Executive Officer of Inserm (French National Institute for Health and Medical Research)

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

ARMELLE PHALIPON
Director of Research in the Molecular Microbial Pathogenesis Unit, Institut Pasteur

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

ODILE PUIJALON
Institut Pasteur

KORY SORENSON
Corporate Board Member

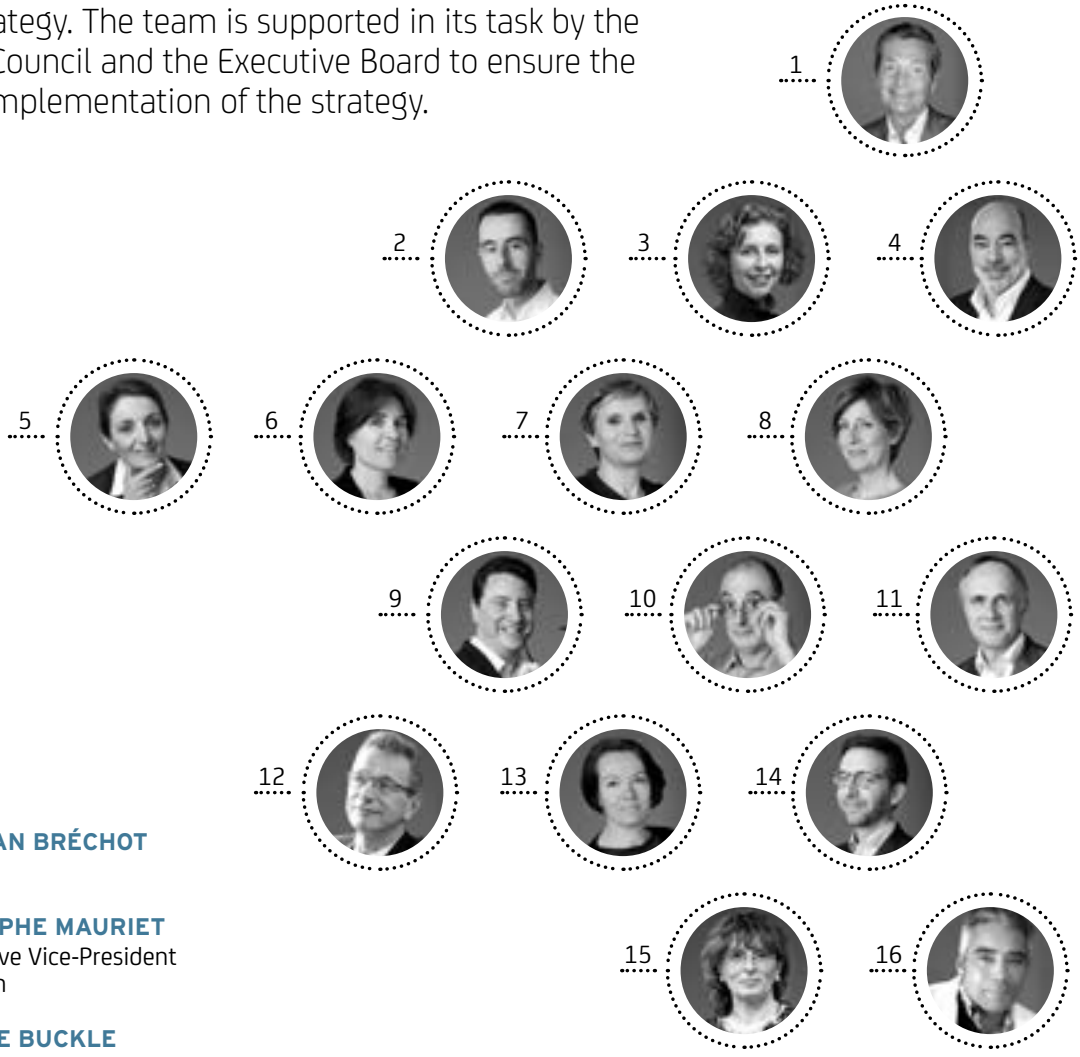
FRANÇOIS TADDEI
Director of the Center for Research and Interdisciplinarity (CRI)
Head of Research Team 1 in laboratory U1001 (Inserm)

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

LIONEL ZINSOU
Chairman and Chief Executive Officer of PAI Partners

Management of the Institut Pasteur

The management team sets the Institut Pasteur's overall strategy. The team is supported in its task by the Scientific Council and the Executive Board to ensure the effective implementation of the strategy.



1 – **CHRISTIAN BRÉCHOT**
President

2 – **CHRISTOPHE MAURIET**
Senior Executive Vice-President Administration

3 – **ISABELLE BUCKLE**
Vice-President Research Applications and Industrial Relations

4 – **JEAN-FRANÇOIS CHAMBON**
Vice-President Communications and Fundraising

5 – **NATHALIE DENOYÉS**
Vice-President Technical Resources and Environment

6 – **CORINNE FORTIN**
Vice-President Financial Affairs

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Vice-President Scientific Assessment

11 – **MARC JOUAN**
Vice-President International Affairs and International Network

12 – **PIERRE LEGRAIN**
Vice-President Development

13 – **NATHALIE DE PARSEVAL**
Scientific Secretary General

14 – **MICHAËL PRESSIGOUT**
Vice-President Information Systems

15 – **MONICA SALA**
Executive Director for Education

16 – **PATRICK TRIEU-CUOT**
Vice-President Scientific Careers

Scientific Council

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

April 2015

Elected Pasteurian Members

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

AZIZ EL AMRAOUI
Head of Laboratory in the Genetics & Physiology of Hearing Unit

JEAN-PAUL LATGÉ
Head of the *Aspergillus* Unit

FRÉDÉRIC TANGY
Head of the Viral Genomics and Vaccination Unit

Appointed Pasteurian Members

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

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

LLUIS QUINTANA-MURCI
Head of the Human Evolutionary Genetics Unit

CHRISTOPHE ROGIER
Director of the Institut Pasteur in Madagascar

External Members

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

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

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

RICHARD MOXON
Professor at the Weatherall Institute of Molecular Medicine

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

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

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

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

THANKS TO OUR SPONSORS

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Fondation Daniel & Nina Carasso
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