

2019

Institut Pasteur
Annual Report

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The French edition of this Annual Report was completed between January and April 2020, and the English edition between March and June 2020, during the unprecedented COVID-19 pandemic. Efforts to fight SARS-CoV-2 resulted in a workload increase for a great many Institut Pasteur teams. We wish to extend our heartfelt thanks to all contributors for their commitment in these difficult times and to the readers of this Annual Report for their understanding when reading these pages.

SCIENCE & ART

SCIENTISTS AND ARTISTS: A MEETING OF MINDS – AND DRESS CODES

Louis Pasteur always looked at the world as if through a microscope, with a curious mind and endless questions, whether he was seeking to understand and explain it from his laboratory or create a likeness of it with his watercolors.

Regardless of the hat he was wearing – scientist or painter –, his outlook was the same.

Today, artists and Pasteurians share so much more than just a “uniform” – the ubiquitous smock or lab coat. Whether skillfully manipulating a brush or scientific instruments, working with paint or biological samples, producing an artwork or a scientific publication, they share the same ambition: representing the visible and translating the invisible. Their mission is to push back the limits of knowledge and go beyond mere appearances.

United through the centuries by a common approach, artists and scientists help create a new portrait of society and the individuals that compose it. They provide a better understanding of life, and encourage us to celebrate and protect it.

#MetsTaBlouse
(PutOnYourLabCoat)



PHOTOS:

● PAOLA ARIMONDO, WHO IS EXPLORING SOLUTIONS TO OVERCOME DRUG RESISTANCE IN MALARIA PARASITES, ALONGSIDE JEAN-MARC GHIGO WHO IS STUDYING A PARTICULAR BACTERIAL LIFE FORM – BIOFILMS. ANTIMICROBIAL RESISTANCE, A KEY COMPONENT OF THE 2019-2023 STRATEGIC PLAN, WAS SHOWCASED BY THE INSTITUT PASTEUR IN 2019 TO HIGHLIGHT THE IMPORTANCE OF THIS PUBLIC HEALTH ISSUE (SEE P. 9) AND THE WORK OF 60 OF ITS RESEARCH TEAMS ON THE SUBJECT.

● THE HEARING INSTITUTE, WHOSE INAUGURAL SCIENTIFIC CONFERENCE WAS HELD IN SEPTEMBER 2019 (SEE P. 8).

● LAB COAT GRAFFITIED BY ARTIST BISHOP PARIGO, ONE OF THE WORKS PRODUCED FOR PASTEURDON 2019 (SEE P. 10). #METSTABLOUSE (PUTONYOURLABCOAT)

PROFILE

The Institut Pasteur is a non-profit foundation with recognized charitable status. Its missions are to help prevent and treat diseases, mainly those of infectious origin, through research, public health, education and training, and the development of research applications.



€297.8 M
budget



2,780
staff members (as at 12/31/2019)



74
nationalities (as at 12/31/2019)



144
research units (as at 01/01/2020, including Hearing Institute teams)



24
research support services, hosting technological platforms



32
member institutes of the Institut Pasteur International Network

Institut Pasteur researchers strive year on year to advance science and improve human health

NOBEL PRIZES

1 NOBEL LAUREATE
(10 laureates since 1907)



CNRS MEDALS

**2 GOLD MEDALS
6 SILVER MEDALS
7 BRONZE MEDALS
AWARDED BY THE CNRS**



OTHER FRENCH AWARDS



3 GRAND PRIX FOR MEDICAL RESEARCH
awarded by Inserm

6 RESEARCH PRIZES
awarded by the Allianz/
Institut de France Foundation

1 Émile Jungfleisch GRAND PRIX

1 Inria GRAND PRIX

2 CANCER RESEARCH AWARDS
from the Simone et Cino del Duca
Foundation-Institut de France

2 Mémain-Pelletier AWARDS

11 PRIZES awarded by the Schlumberger
Foundation for Education and Research

INTERNATIONAL AWARDS



1 Gairdner AWARD

1 Kavli PRIZE in neuroscience

1 Sjöberg PRIZE from the Royal Swedish Academy

1 Balzan PRIZE

1 Brain PRIZE

3 Robert Koch PRIZES

3 L'Oréal-UNESCO For Women in Science AWARDS

4 Louis-Jeantet PRIZES

EUROPEAN GRANTS



FUNDING FROM THE EUROPEAN RESEARCH COUNCIL (ERC)

25 ERC STARTING GRANTS

19 ERC ADVANCED GRANTS

9 ERC CONSOLIDATOR GRANTS

2 ERC PROOF OF CONCEPT GRANTS

APPOINTMENTS



5 MEMBERS of the US National
Academy of Sciences, Washington (USA)

4 MEMBERS of the British Royal Society

38 MEMBERS of EMBO (European Molecular
Biology Organization)

22 MEMBERS of the French Academy of Sciences

INTERVIEW WITH

CHRISTIAN VIGOUROUX CHAIRMAN OF THE BOARD OF GOVERNORS

If you had to choose two highlights for the Institut Pasteur from 2019, what would they be?

Pasteur always delivers more than we expect. You asked for two highlights; I'll give you three: the year was once again characterized by scientific excellence, public generosity and a universalist approach. The Institut Pasteur and all its staff focused their efforts on implementing the Strategic Plan and realizing their shared ambition of combating infectious diseases – a key component of the plan and a long-standing aspiration for the Institut Pasteur. The devastating reality of COVID-19 in this first half of 2020 makes us realize just how vital the fight against infectious diseases is and always will be. Even aside from COVID-19, I am struck by how the Institut Pasteur is always there on the front line to respond to threats to public health, from HIV to malaria and tuberculosis. We are always pursuing victory in these health battles, and the efforts of our scientists are producing results. The opening of the Hearing Institute shows that we are willing to invent new formulas to advance science. As well as its scientific presence in *Nature*, the Institut Pasteur can be found on the pages of French TV guides for its annual fundraising campaign. In 2019, Pasteurdon consolidated its position in the media landscape. It goes without saying that Pasteurdon is crucial for the Institut Pasteur's resources, but it also plays an important role in raising awareness of our areas of expertise. The generosity of the public is as remarkable as ever, as illustrated by the overwhelming success of the "Z Event" charity marathon and the many donations received from young gamers. That said, we are equally proud of each and every gift, including those that remain out of the media spotlight – each one a show of the continued support of our donors and the strong reputation of the Institut Pasteur. Picking up on the idea of science without borders, a concept encapsulated by the name "Pasteur," the Board of Governors is keen to further boost the Institut Pasteur's international reach. The meeting of the Council of Directors of the Institut Pasteur International Network

in Yaoundé in November 2019 was a resounding success and demonstrated a collective determination to harness the dynamism of this global network. We held discussions with Africa's rising talents, one month after the superb inaugural lecture at the Collège de France by Professor François-Xavier Fauvelle about the eternity of Africa.

In 2019, work to implement the Strategic Plan continued apace. How is the Board of Governors supporting these efforts?

After lengthy discussions and a seminar, we adopted the 2019-2023 Strategic Plan proposed by Institut Pasteur President Stewart Cole. We are supporting the implementation of the plan day by day, as it guides our methods and inspires us in every area – scientific, financial, social, media

"THE OPENING OF THE HEARING INSTITUTE SHOWS THAT WE ARE WILLING TO INVENT NEW FORMULAS TO ADVANCE SCIENCE."

and health – and at international level. The Board – whose composition was renewed in 2019 and is now gender equal –, its Bureau and its financial and social committees regularly contribute their expertise by asking the right questions, discussing the right answers and keeping the Institut Pasteur on the right track. The Strategic Plan marshals our efforts in what has become a dangerous, competitive world. It provides us with a compass, but we constantly need to make sure it underpins our day-to-day decisions and the principles for which the Board serves as guarantor. This involves ongoing dialog with the senior management team and the other statutory bodies such as the General Meeting Board and the Scientific Council, with the help of internal audits. It also requires a shared resolve with the President, Stewart Cole, and the excellent united team that he has built around him. The senior management team now has its full complement of staff, following the recruitment of Professor Bruno Hoen as Medical Research Director. The action of the two successive Scientific Directors, Olivier Schwartz and Christophe d'Enfert, has been decisive. Finally, none of the Institut Pasteur's work would be possible without the efforts of all its staff and scientists. They are its strength, they maintain its ambition and reputation, and we are proud of them. Together we are constantly striving to develop our resources and capabilities so that we can push back the boundaries of research and invention. The Board of Governors is committed to consolidating the foundations for the Institut Pasteur's continued development.

What specific areas will the Board of Governors focus on in 2020?

The long-term development of the Institut Pasteur, its independence – which means keeping a constant eye on its resources and funding –, and constantly increasing the quality of its scientific research and achievements. These three areas are our barometers, they drive our work. Our efforts will only come to fruition with an active policy of cohesion, providing the Institut Pasteur with a solid base and creating the best possible conditions for each and every member to champion the cause of science. We want to continue attracting young talent and creating new research entities. At the scientific level, this cohesion has been in evidence with the Institut Pasteur's rapid response to the COVID-19 pandemic. It was also pivotal to the successful implementation of new staff representative bodies, where there has been a particular focus on the challenging question of how to effectively address occupational risks. Moreover, it underpins the new recruitment and appointment policy that the President is gradually introducing. Our cohesion serves our ambition, namely to further develop the extraordinary scientific spirit that drives the Institut Pasteur. As we see the growing problem of antibiotic resistance moving to the forefront of public attention, we know that we are on the right track.

As well as cohesion and ambition, what other areas are commanding the Board's attention?

We will continue to pay close attention to the Institut Pasteur's presence in society. The public need to be able to put their trust in us, and it is up to us to make sure that they can do so.



This applies both to institutions – we need to continue working closely with the CNRS, Inserm and universities – but also to the public at large. We need to be active in public debates and put forward our ideas and expertise on global health, highlighting the need for constant innovation. Finally, we need to be on our guard when it comes to safety and security issues. The health and well-being of society depends on it – as does our reputation. These issues range from highly pathogenic microorganisms and toxins (MOTs) and the recommendations of the French National Agency for the Safety of Medicines and Health Products (ANSM) to questions of information security and the specific action plan (PPI) developed with our local neighborhood in Paris' 15th *arrondissement*. Our sound ethics contribute powerfully to our credibility and reassure our stakeholders and the public. This is essential to another area where we need to be constantly on our guard, namely our resources and finances. Every day we confound the pessimistic forecasts thanks to the ongoing generosity and support of the public. We will soon be making a number of major decisions on real estate programs and the acquisition of new technologies. The unfailing support of the public is a source of real strength for the Institut Pasteur. It is clear that the efforts requested by our Board of Governors are starting to bear fruit, thanks to the commitment of the President and the Senior Executive Vice President, François Romaneix.

Do you have a message for the future?

The film shot in 2019 on the Institut Pasteur campus with Patrick Bruel and Fabrice Luchini caught our imagination. It was both lighthearted and serious; it spoke of friendship and love, life and death – and also research and health in France and worldwide. The film is called "The Best is Yet to Come." Let's make sure that this title reflects our course of action, in the hope that, in years to come, when the current crisis and emergency health situation have passed, the Institut Pasteur might host another film shoot, this time for a picture entitled "The Best Just Got Even Better."

INTERVIEW WITH

STEWART COLE PRESIDENT

What projects were successfully completed in 2019 to advance the Institut Pasteur's research?

We have just come to the end of the first year of implementation of the Strategic Plan. The aim of the plan is to give new impetus to basic research and increase its impact on health challenges. In that respect, much has been achieved. The scientific departments have been reorganized, with the creation of the Department of Global Health, reflecting the need for a worldwide approach to health – as the COVID-19 pandemic in early 2020 has unfortunately demonstrated. We have also set up a Department of Computational Biology, providing a long-term basis for the Institut Pasteur's investments in the field of bioinformatics. The department's teams have been particularly busy in the past few months analyzing and processing scientific data related to the SARS-CoV-2 coronavirus. In neuroscience, the Hearing Institute was officially opened after an inaugural scientific conference in September 2019. I am also very pleased that we have reached the second stage of the NanoImaging project, enabling us to optimize our use of the Titan Krios™ microscope. A series of atomic-resolution protein structures were produced last year. My congratulations to the scientists responsible for the logistics of the project. The next stage is to position the Institut Pasteur as a world leader in cryo-electron tomography imaging of host-pathogen interactions. We have also made major investments in our information systems, strengthening our storage capabilities and installing an ultra-high-speed network for all our laboratories.

Were any new laboratories created in 2019?

Yes indeed, there were a number of new five-year groups (G5s), including one in the field of bioinformatics in 2019

and three others due to be launched in 2020. There will be one G5 for each area of the Strategic Plan. Five-year units (U5s), a new entity type created in 2020, are designed to develop the careers of permanent scientists by giving them the resources they need to conduct ambitious scientific projects. With these new entities, we have delivered on our gender equality commitments, with a better representation of women in senior scientific positions. Twice as many women as men were promoted to the rank of professor in 2019.

How have research applications benefited from the impetus of the Strategic Plan?

The development of research applications is a key component of our scientific policy. Our business development activities are hindered by the fact that our inventions are at a low level of maturity compared with the expectations of industry partners and the level needed to create startups. To overcome this challenge, we have set up an Institut Pasteur Innovation Accelerator. In five years' time, we hope to have a portfolio of products under development to meet public health needs. This accelerator will help bring projects to maturity with the injection of human and financial resources.

On that topic, how are the Institut Pasteur's finances looking?

The financial situation of the Institut Pasteur improved in 2019. We reduced our operating deficit by prudently managing our expenditures and capitalizing on a number of opportunities. But we need to remain cautious, especially given the exceptional circumstances brought about by the COVID-19 pandemic, such as the forced reduction in activity



of some entities and the expenses incurred to ensure that campus could be operated safely during the lockdown period. The impact is all the more acute because 2019 was a particularly good year – a record year, even – in terms of public donations and legacies. The Institut Pasteur was chosen as the partner for the 2019 Z Event, a charity project that harnesses the contributions of the French gaming community. This event particularly boosted the Institut Pasteur's popularity with young people. Back in December, the Chairman of the Board of Governors*, Christian Vigouroux, and myself were delighted to be able to thank the promoter of the Z Event, Adrien Nougaret (alias ZeratoR), in person. Pasteurdon 2019 was also a resounding success, with this year's slogan #MetsTaBlouse (PutOnYourLabCoat!). We decided to make the most of the momentum generated by the slogan and keep it as a running theme for all our communication and fundraising activities. Finally, I would take this opportunity to express my hope that there will be no more cuts to public funding, despite the progressive decline in the French research effort in recent years. The constant reductions represent a major obstacle for our projects and investments.

What investments are planned for 2020?

I will be monitoring particularly the progress in the building projects set out in the Strategic Plan. These include building a research center on vector-borne diseases (such as those spread by mosquitoes) on our campus and the renovation of a historical building. We are also planning an extension to the Institut Pasteur Medical Center, with funding granted by the Mairie de Paris, partly to gain more space and also to house the Hearing Institute's Center for Research and Innovation in Human Audiology (CERIAH). It is vital that the Institut Pasteur campus should remain a state-of-the-art

environment that continues to offer outstanding working conditions. Its attractiveness and scientific competitiveness depend on it. In relation with these projects, I would like to see the Institut Pasteur step up its efforts to become a leader in terms of environmental protection and sustainable development. We are already taking action to reduce the greenhouse gas emissions produced by our activities and facilities. These measures will be extended in 2020 to ensure that the Institut Pasteur remains a role model in this area. We need to further reduce our use of plastics, for example, and increase our use of recyclable materials.

The Institut Pasteur renewed many of its partnerships in 2019. Why are they so important?

Indeed, the framework agreement with the CNRS was extended, and our very close links with Inserm have been further boosted with the creation of the Hearing Institute. The Institut Pasteur also has the advantage of being a member of the Institut Pasteur International Network. Collaboration with other institutes in the network is crucial. At the Council of Directors of the Institut Pasteur International Network in Yaoundé in November 2019, we launched a period of shared reflection on the governance of the network, in accordance with our Strategic Plan. I hope that this will continue in 2020. Finally, we are working with hospital partners. Bruno Hoen, who took on the role of Medical Research Director in 2019, will be supervising medical research and strengthening links with the aim of facilitating new translational research projects and boosting the synergies between basic and clinical research. This strategy resulted in the launch of a number of outstanding clinical projects on COVID-19 in a short space of time in early 2020.

What is your message for 2020?

In 2020, I hope that we can continue to advance the priorities identified in our Strategic Plan. I am convinced that with a concerted, determined approach, we can further strengthen the Institut Pasteur's position as one of the world's leading research centers.

* The Board of Governors was previously referred to as the Board of Directors.

**"I AM CONVINCED THAT WITH A
CONCERTED, DETERMINED APPROACH,
WE CAN FURTHER STRENGTHEN THE
INSTITUT PASTEUR'S POSITION AS ONE
OF THE WORLD'S LEADING RESEARCH
CENTERS."**

2019 HIGHLIGHTS

144

The number of research units at the Institut Pasteur as of January 1, 2020, including seven at the Hearing Institute

INSTITUTIONAL

INTERNATIONAL INAUGURATION MEETING OF THE HEARING INSTITUTE

The Hearing Institute (an Institut Pasteur center) is a center for basic and translational research in neuroscience, with a focus on hearing. It was set up at the initiative of the Fondation Pour l'Audition and the Institut Pasteur. To mark the opening of the Hearing Institute, Professor Christine Petit organized an inaugural scientific meeting at the Collège de France on September 16 and 17, 2019, in partnership with the Fondation Pour l'Audition and Inserm. The aim of the Hearing Institute is to promote an integrative approach to auditory neuroscience and develop innovative diagnostic tools and curative therapies to treat those with hearing loss.



THE HEARING INSTITUTE BUILDING.



€290 million

The annual excess cost of resistant bacterial infections in France. The scientists* estimated not only the direct economic cost but also the number of new cases: in 2016, there were nearly 140,000 new cases of resistant bacterial infection, representing 12% of all bacterial infections requiring hospitalization. The research was based on hospital admissions during 2015 and 2016.

* University of Versailles Saint-Quentin-en-Yvelines (UVSQ), Inserm and Institut Pasteur.

INSTITUTIONAL

HIGH-LEVEL MEETING ON ANTIMICROBIAL RESISTANCE

Research on antimicrobial resistance is a priority area of the Institut Pasteur's 2019-2023 Strategic Plan and a key issue for human health. Approximately 700,000 people die each year worldwide as a result of resistance to existing antimicrobial treatments. To mark the visit of former British minister Jim O'Neill, the Institut Pasteur held a round table on the question of antimicrobial resistance on Thursday September 26, 2019. The discussions particularly focused on economic challenges and funding for the development of new therapeutic strategies. Lord Jim O'Neill is

an economist and the author of the landmark Review on Antimicrobial Resistance, which raised international awareness of this important issue.

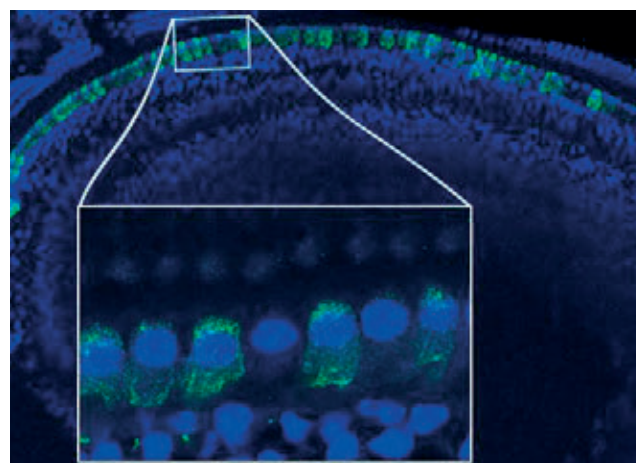


ECONOMIST LORD JIM O'NEILL AT THE ROUND TABLE ON ANTIMICROBIAL RESISTANCE AT THE INSTITUT PASTEUR ON SEPTEMBER 26, 2019.

EFFECTIVE GENE THERAPY FOR CONGENITAL HEARING LOSS

Scientists* restored hearing in an adult mouse model of DFN9 deafness, one of the most frequent forms of genetic hearing loss. Individuals with this condition are profoundly deaf as they are deficient in the gene coding for otoferlin, a protein which is essential for transmitting sound information at the auditory sensory cell synapses. By giving the mouse an intracochlear injection of the gene, the scientists restored auditory synapse function and auditory thresholds to near-normal level. This paves the way for future gene therapy trials in patients.

* Institut Pasteur, Inserm, CNRS, Collège de France, Sorbonne University, University of Clermont Auvergne, Universities of Miami, Columbia and San Francisco.



IMMUNOFLUORESCENCE IMAGING OF THE COCHLEAR SENSORY EPITHELIUM IN A MOUSE TREATED WITH GENE THERAPY.

A NEW BACTERIA-KILLING WEAPON

When the first antibiotics were discovered in the early 20th century, the rate of death from infectious diseases fell dramatically. Nonetheless, the emergence of multidrug-resistant bacteria as a result of antibiotic misuse is raising fears that by 2050, these same diseases will once again become the leading cause of death worldwide. To tackle this threat, scientists successfully programmed a bacterial genetic structure to make it capable of specifically killing multiple antibiotic-resistant bacteria without destroying bacteria that are beneficial to the body. Unlike other approaches under development, this novel tool is associated with a minimal rate of emergence of new resistance.

OBSERVING THE CULTURE OF A BACTERIAL STRAIN.



2019 HIGHLIGHTS

2,780

The number of staff working at the Institut Pasteur in Paris. #MetsTaBlouse (PutOnYourLabCoat)



ARTISTIC INTERPRETATIONS OF THE LAB COAT IN HONOR OF THE 2019 PASTEURDON, FROM TOP LEFT: BISHOP PARIGO, JO BER, JEAN-PHILIPPE GOURNAY, KEKLI, KRSN, MR POES AND BASILA, SUN 7, ZDEY, L'ATLAS, BEBAR, JULIA KREMER, PANAR OBITZ, AND ETIENNE BARDELLI (SCULPTURE).



THE WEEKEND AFTER THE LAUNCH OF PASTEURDON, INSTITUT PASTEUR LABORATORIES OPENED THEIR DOORS TO THE PUBLIC, AND TWO OF THE ARTISTS LED WORKSHOPS WITH STREET ART MATERIALS.

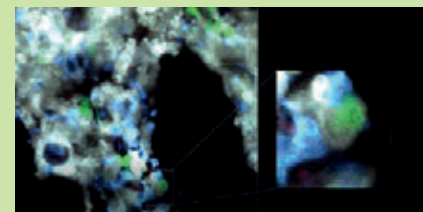
INSTITUTIONAL

#METSTABLOUSE (PUTONYOURLABCOAT): CONTEMPORARY ARTISTS GIVE THE SCIENTIST'S LAB COAT A MAKEOVER

White lab coats, that ubiquitous scientific symbol, were given a new look by contemporary urban artists, who transformed them with colors and striking motifs. For the 2019 edition of Pasteurdon – the Institut Pasteur's campaign to raise funds, improve awareness and celebrate French research –, a dozen contemporary urban artists agreed to customize a lab coat. Bebar, Bishop Parigo, Etienne Bardelli, Jean-Philippe Gournay, Jo BeR, Julia Kremer, Kekli, KRSN, L'Atlas, Mr POES & Basila, Panar Obitz, SUN7 and ZDEY all took on the challenge. Before they started they were given a glimpse behind the scenes of biomedical research as they met Institut Pasteur scientists.

Each artist offered a unique interpretation of the universal scientific "uniform." The resulting creations were unveiled at the Pasteurdon launch event on October 9, 2019 by the Institut Pasteur scientists themselves, who took to the stage wearing the colorful coats. They then handed the floor to the artists, who demonstrated their creative talents to the sound of vigorously shaken spray paint cans. The following weekend, the Institut Pasteur's laboratories opened to the public for a Discovery Day, and one of the artists led a workshop giving participants the opportunity to test out street art materials.

For the public, the incredible transformation of this scientific emblem was also a chance to consider science from a dynamic, modern perspective.



VISUALIZATION OF CAR T CELLS IN ACTION. CAR T CELLS (GREEN) INFILTRATING THE TUMOR (WHITE). THE CANCER CELLS KILLED BY CAR T CELLS ARE IN BLUE.

IMMUNE CELLS FIGHTING BLOOD CANCER VISUALIZED FOR THE FIRST TIME

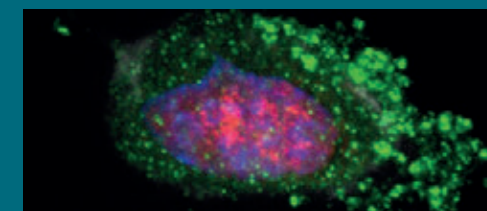
When cancer escapes the immune system, our defenses are rendered powerless and unable to fight the disease. Chimeric antigen receptor T cells (CAR T cells) represent a promising immunotherapy strategy, developed with the aim of tackling tumors head-on. But the occurrence of relapse in some patients remains a challenge. Scientists at the Institut Pasteur elucidated the precise function of CAR T cells in a bid to optimize future therapies.

GASTRIC CANCER SUSCEPTIBILITY MARKER DISCOVERED

Gastric cancer, the third most common cause of cancer-related deaths, is often associated with a poor prognosis because it tends to be diagnosed at an advanced stage and is therefore difficult to treat. To reduce the death rate, it is essential to identify a biomarker enabling early diagnosis of this cancer. In pursuit of this goal, scientists* analyzed the mechanisms involved in the development of gastric cancer during infection with the bacterial pathogen *Helicobacter pylori*.

Their research led to the identification of a potential susceptibility marker.

* Institut Pasteur, CNRS, University of Rennes 1, IMSS (Mexico), University of Florence (Italy).



GASTRIC EPITHELIAL CELLS INFECTED WITH *H. PYLORI*.

CERVICAL CANCER: NEW TEST ENHANCES ABILITY TO PREDICT RISK

In 2019, *The Journal of Molecular Diagnostics* and the Institut Pasteur announced the development of a new test that helps predict the risk of developing cervical cancer in human papillomavirus (HPV)-positive women. The twofold test is capable of detecting and determining the type of HPV infection, and predicting the likelihood that it will progress to cancer.

GUT MICROBIOTA IMBALANCE PROMOTES THE ONSET OF COLORECTAL CANCER

Two French teams, led by Professor Philippe Sansonetti* and Professor Iradj Sobhani** (operating as the "Oncomix" group since April 2016), in collaboration with the US team led by Professor Khashayarsha Khazaie*** showed that an imbalance in the gut microbiota, also known as dysbiosis, promotes the onset of colorectal cancer. The scientists demonstrated that transplanting fecal flora from patients with colon cancer into mice caused lesions and epigenetic changes characteristic of the development of a malignant tumor. The study led to the development of a non-invasive blood test which identifies the epigenetic phenomenon associated with dysbiosis. The test was validated in 1,000 individuals.

* Inserm, Institut Pasteur. ** Henri-Mondor Hospital (AP-HP), University Paris-Est Créteil. *** Mayo Clinic.



INTESTINAL MICROVILLI.

2019 HIGHLIGHTS



INSTITUTIONAL

LOUIS PASTEUR'S SCIENTIFIC ACHIEVEMENTS ON GOOGLE ARTS & CULTURE

Thanks to a collaboration between the Institut Pasteur and several French and international institutions, people around the world can now explore humanity's greatest inventions and discoveries in the new interactive online project Google Arts & Culture. The new exhibition, entitled *Once Upon a Try. A Journey of Invention and Discovery*, was launched in March 2019.

As one of the project partners, the Institut Pasteur is offering the public the opportunity to learn more about the day-to-day life of its founder, Louis Pasteur, by going on a virtual tour of the Pasteur Museum, housed in the former apartment on the Institut Pasteur campus where the illustrious scientist spent the last seven years of his life. This is a great chance to find out more about Louis Pasteur, a keen painter in his youth before he went on to make some of the 19th century's most revolutionary discoveries, which today still serve as founding principles for modern science.

To make this virtual tour possible, a Street View team digitized the rooms in the museum so that online visitors can explore Louis Pasteur's private apartments and the Byzantine-style crypt where he is buried alongside his wife – extraordinary sites that are not usually accessible to the public.

Visitors are guided through four virtual exhibitions, discovering Louis Pasteur's scientific achievements, especially how he came to work on rabies and develop the vaccine that brought him global recognition.

Learn more: <https://artsandculture.google.com/partner/institut-pasteur>

1889

The year that the first microbiology course was taught by Émile Roux. Ever since, the Institut Pasteur has played a key role in teaching life sciences internationally (read more in the Education section).



SCIENTIFIC SOUVENIR ROOM IN THE PASTEUR MUSEUM AT THE INSTITUT PASTEUR, PARIS.

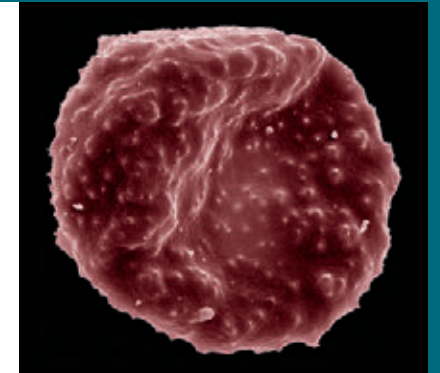


ENTRANCE OF THE CRYPT WHERE LOUIS PASTEUR IS BURIED. PASTEUR MUSEUM, INSTITUT PASTEUR, PARIS.

MALARIA: A NEW BREAKTHROUGH IN DEVELOPING EFFECTIVE ANTIMALARIAL DRUGS

Parasites of the genus *Plasmodium*, which cause malaria, are transmitted to humans through bites from infected mosquitoes. The parasites manage to acclimatize to these two completely different hosts because the plasticity of their genome enables them to adapt as necessary. A group of scientists* decided to investigate the epigenetic mechanisms behind this plasticity, in particular DNA methylation. They identified molecules capable of inhibiting DNA methylation and effectively killing even the most resistant *Plasmodium falciparum* parasites.

* Institut Pasteur, CNRS.



RED BLOOD CELL INFECTED BY *PLASMODIUM FALCIPARUM*.

IN FRANCE, *Aedes albopictus* MOSQUITOES TRANSMIT AFRICAN ZIKA BETTER THAN ASIAN ZIKA

Scientists at the Institut Pasteur described the vector competence of the *Aedes albopictus* mosquito in southern France in relation to various Zika virus genotypes. They demonstrated that the French *Aedes albopictus* transmits the African Zika virus better than the Asian Zika virus. This discovery by the Institut Pasteur reveals what type of Zika virus French people may soon be exposed to. In October 2019, although there were relatively few areas of active Zika

transmission worldwide, indigenous cases of Zika virus were reported in the Var, in France.



HEAD OF A FEMALE *Aedes albopictus* MOSQUITO, THE VECTOR FOR DENGUE AND CHIKUNGUNYA.

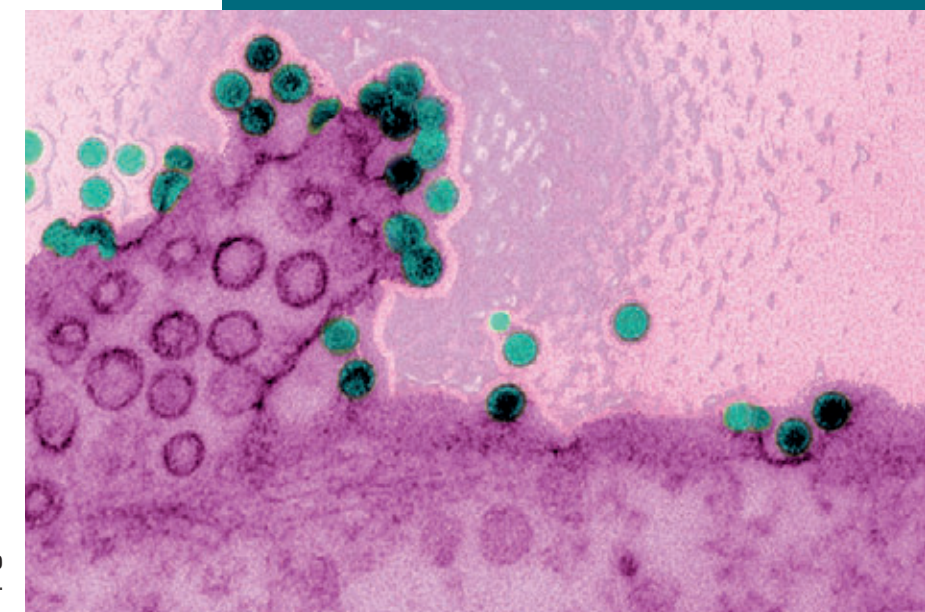
MALARIA IN AFRICA, A 20,000-YEAR-OLD STORY...

It appears that malaria emerged in Africa at least 20,000 years ago – and not at the same time as the adoption of agriculture 4,000 to 5,000 years ago. This discovery by the Institut Pasteur and the CNRS was based on extensive research into the β S mutation, full sequencing of the HBB gene and a large-scale genomic study on 479 individuals from 13 Sub-Saharan African populations.

CHIKUNGUNYA: IDENTIFICATION OF AN ESSENTIAL PROTEIN FOR VIRUS REPLICATION

Scientists* identified a protein that plays a crucial role in chikungunya virus replication in target cells. This research opens up new therapeutic possibilities to tackle chikungunya, an infectious disease caused by a virus transmitted to humans by mosquitoes. The mechanisms of infection of human cells with the chikungunya virus still remain very poorly understood.

* Institut Pasteur, Inserm, CNRS, Université de Paris, Saint-Louis Hospital (AP-HP), Necker-Enfants Malades Hospital (AP-HP).



FIBROBLAST INFECTED BY THE CHIKUNGUNYA VIRUS.

2019 HIGHLIGHTS

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A NEW DISCOVERY

A team* researching graft-versus-host disease (GVHD) used liquid chromatography and mass spectrometry to monitor allogeneic patients at Saint-Louis Hospital, Paris. The results show major changes in the human metabolome after an allograft, associated with impairments to the patient's metabolism and microbiota. These findings could represent potential new therapeutic targets for GVHD prevention or treatment.

* Saint-Louis Hospital (AP-HP), Université de Paris, Inserm, Institut Pasteur.

INSTITUTIONAL

98 out of 100

The Institut Pasteur's excellent score (98%) in the 2019 French Gender Equality Index, as required by French law since March 1, 2019. In 2018, the Institute scored 93 out of 100. This excellent score reflects the Institut Pasteur's ongoing commitment to gender parity in the areas of pay rises, promotions and salary increases after maternity leave. All these issues require constant vigilance.

INSTITUTIONAL

THE BEST IS YET TO COME, A FILM PARTLY SHOT AT THE INSTITUT PASTEUR

The Best is Yet to Come, a feature film directed by Matthieu Delaporte and Alexandre de La Patellière, was released in cinemas on December 4, 2019. Starring Patrick Bruel and Fabrice Luchini, the film was partly filmed at the Institut Pasteur. Fabrice Luchini and Patrick Bruel play two friends who somehow, following a huge misunderstanding, both believe that the other has just months to live and decide to drop everything to make up for lost time. Fabrice Luchini plays Arthur, who works at the Institut Pasteur as an infectious disease scientist. Some of the film's scenes were shot at the Institut Pasteur in January 2019, involving more than 150 Institut Pasteur staff, including nearly 90 extras played by scientists and PhD students.



DEPRESSION: THE KEY ROLE OF NEUROINFLAMMATION

Depression is a complex multifactorial condition whose underlying mechanisms have still not been elucidated. As a result, available treatments are far from effective and an estimated 30% of patients are resistant to conventional treatment. Scientists from the Institut Pasteur, in collaboration with teams from Sainte-Anne Hospital, shed light on the role of brain inflammation as a mechanism that may lead to depression. This is an important discovery in our understanding of the condition, paving the way for new treatment possibilities.



INSTITUTIONAL

AUTISM: A UNIQUE EVENT AT THE INSTITUT PASTEUR

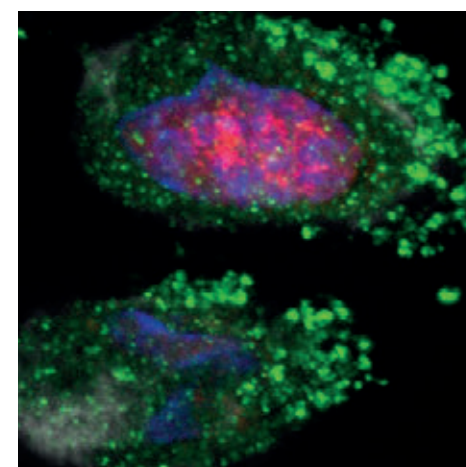
On Saturday March 30, 2019, nearly 550 people came to the Institut Pasteur for a day focusing on the latest progress in research by the Institut Pasteur and Robert Debré Hospital (AP-HP) on autism and

autism spectrum disorder. The initiative was in line with the objective in the Institut Pasteur's Strategic Plan to develop interactions between the Institut Pasteur and civil society.



HIV: REPROGRAMMING CELLS TO CONTROL INFECTION

Cells from the rare individuals who naturally control HIV infection have been the focus of investigation for nearly 15 years with the aim of elucidating their specific features. Scientists from the Institut Pasteur have described the characteristics of CD8 immune cells in these "HIV controller" subjects. Their unique antiviral power can be attributed to an optimal metabolic program that confers persistence and the ability to react effectively against infected cells. Working ex vivo, the scientists successfully reprogrammed cells from infected non-controller individuals to give them the same antiviral potency as controllers' cells.



CD8 CELLS OF HIV CONTROLLER PATIENTS IN CONTACT WITH CD4 CELLS INFECTED WITH HIV.

THE BENEFICIAL EFFECTS OF LITHIUM ON THE BRAIN IN BIPOLAR DISORDER

Collaborative research* led to new findings on the action of lithium in bipolar disorder. A model-based technique measured by diffusion MRI was used to analyze the brain microstructure of patients with bipolar disorder. The results indicate that dendritic density in the frontal cortex is higher in patients treated with lithium. This supports the theory that improved brain plasticity and interneuronal communication in this brain region may underlie the beneficial effects of lithium in bipolar disorder.

* CEA, Inserm, Institut Pasteur, Fondation FondaMental, Mondor University Hospitals (AP-HP), Grenoble University Hospital.



PRAIRIE PROJECT SELECTED AS AN INTERDISCIPLINARY INSTITUTE OF ARTIFICIAL INTELLIGENCE

The French Ministry of Higher Education, Research and Innovation announced the creation of PRAIRIE, an Interdisciplinary Institute of Artificial Intelligence (3IA). The aim of the project is to create a center of excellence in artificial intelligence in Paris. It is led by the CNRS, Inria, the Institut Pasteur, Université de Paris and Université PSL. The companies Amazon, DeepMind, Engie, Facebook, Faurecia, GE Healthcare, Google, Idemia, Microsoft, NAVER LABS, Nokia Bell Labs, Pfizer, PSA Group, Sanofi, SUEZ and Valeo are also participating in the institute.

2019 HIGHLIGHTS

HIGH-RISK PREGNANCY: THE INTERFERON EFFECT

Scientists* identified a cellular mechanism that alters placental development, potentially causing serious complications during pregnancy. The mechanism is linked with the production of interferon, a molecule produced in response to infection, especially viral infection. High-risk pregnancies occur frequently and may be caused by various factors. It is estimated that 10 to 20% of pregnant women miscarry during their first trimester of pregnancy.

* Institut Pasteur, CNRS, Inserm, Necker-Enfants Malades Hospital (AP-HP), Université de Paris.

4 MISSIONS

In early 2019, in accordance with the articles of association, the Board of Governors approved the Institut Pasteur's missions:

- research,
- public health,
- education and training,
- development of research applications.

DYSENTERY: *SHIGELLA*, A BACTERIUM THAT CAN ADAPT ITS BREATHING

Bacillary dysentery, caused by *Shigella* bacteria in the gut, is a major health problem in tropical regions and developing countries. Complications lead to hundreds of thousands of deaths every year, mainly among young children. Scientists at Inserm and the Institut Pasteur are investigating the virulence mechanisms employed by *Shigella*. They observed that the bacterium is capable not only of consuming oxygen from tissues in the colon to develop and create infectious foci, but also of adapting the way it breathes so that it can continue

INSTITUTIONAL

A DEPARTMENT FOR INTERNAL AUDIT AND CONTROL

Although the Institut Pasteur has pursued an internal audit policy for the past five years, it had not previously set up a dedicated structure responsible for internal audit and control. To consolidate efforts in this area, the Institut Pasteur decided to create a Department for Internal Audit and Control, a small-scale coordination structure responsible for the following tasks: leading the risk mapping process; consolidating existing internal control mechanisms; and drawing up annual internal audit plans to be submitted to the Board of Governors, conducting these audits and monitoring action plans.

SEX DETERMINATION: DISCOVERY OF A NEW RIBOSOMOPATHY IN HUMANS

Sex determination is the process whereby a gendered organism becomes male or female. A multinational consortium, led by Institut Pasteur scientists, discovered a new ribosomopathy in humans that may result in sex reversal or testicular regression syndrome. DHX37, a gene highly conserved during evolution and until now only known for its role in ribosome biogenesis, is involved in both determining and maintaining the identity of testicular tissue. It is the first genetic cause to be identified for testicular regression.

developing once the oxygen in the foci has run out. These findings, published in *Nature Microbiology*, open up new avenues for the development

of antibiotics and vaccines for *Shigella*, which features on WHO's list of 12 priority pathogens.

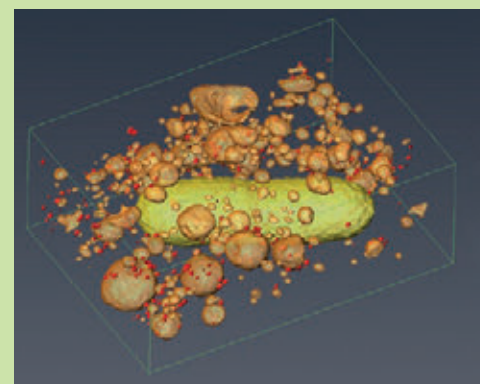


IMAGE OF A *SHIGELLA FLEXNERI* BACTERIUM AT THE INFECTION SITE.

2019-2023 STRATEGIC PLAN

NEW STRUCTURES TO REALIZE A SHARED AMBITION

The aim of the Institut Pasteur's 2019-2023 Strategic Plan is to "provide new impetus to basic research and increase its impact on health challenges." In 2019, the Institut Pasteur set out to achieve some of the plan's main scientific objectives, such as responding to public health challenges, providing a favorable technological environment, introducing an organizational structure for scientific activities that reflects its priority areas, developing research applications and increasing the impact of research on health.

OPPORTUNITY INNOVATION

CREATION OF THE HEARING INSTITUTE

● **Hearing Institute**, which is associated with senior management for administrative and operational purposes and with the Department of Neuroscience for scientific matters (Director: Christine Petit)

ORGANIZATION SCIENCE

CREATION OF SCIENTIFIC DEPARTMENTS

● **Department of Global Health**, created from the merger of the Center for Global Health and the Department of Infection and Epidemiology (Director: Arnaud Fontanet)
 ● **Department of Computational Biology**, conversion of the Center for Bioinformatics, Biostatistics and Integrative Biology into a scientific department (Director: Olivier Gascuel)

OPPORTUNITY RESPONSIBILITY

CREATION OF FIVE-YEAR UNITS (U5S)

● **Anthropology and Ecology of Disease Emergence** – Department of Global Health (Head: Tamara Giles-Vernick)
 ● **Archaeal Virology** – Department of Microbiology (Head: Mart Krupovic)
 ● **Malaria Genetics and Resistance** – Department of Parasites and Insect Vectors (Head: Didier Ménard)
 ● **RNA Biology of Influenza Viruses** – Department of Virology (Head: Nadia Naffakh)

JUNIOR RESEARCHERS

CREATION OF FIVE-YEAR GROUPS (G5S)

● **Sequence Bioinformatics** – Department of Computational Biology (Head: Rayan Chikhi)

JUNIOR RESEARCHERS

CONVERSION OF G5S INTO UNITS

● **Dynamic Regulation of Morphogenesis** – Department of Developmental and Stem Cell Biology (Head: Jérôme Gros)
 ● **Membrane Protein Mechanisms** – Department of Structural Biology and Chemistry (Head: Nicolas Reyes)
 ● **Insect-Virus Interactions** – Department of Genomes and Genetics (Head: Louis Lambrechts)
 ● **Epigenomics, Proliferation and the Identity of Cells** – Department of Developmental and Stem Cell Biology (Head: Pablo Navarro-Gil)
 ● **Humoral Immunology** – Department of Immunology (Head: Hugo Mouquet)

NEW THEMES

CREATION OF UNITS

● **Progressive Sensory Disorders, Pathophysiology and Therapy** – Department of Neuroscience (Head: Aziz El Amraoui)
 ● **Structural Image Analysis** – Department of Structural Biology and Chemistry (Head: Niels Volkmann)

INNOVATION ADAPTATION

CREATION OF INNOVATIVE LABORATORIES

Laboratories supported by the Institut Pasteur Innovation Accelerator (AIIP) that develop innovative programs within this framework.
 ● **Bacteriophage, Bacterium, Host** – Department of Microbiology (Head: Laurent Debarbieux)
 ● **Pathogen Discovery** – Department of Virology (Head: Marc Eloit)
 ● **Innovation Lab: Vaccines** – Department of Virology (Head: Frédéric Tangy)

INNOVATION ADAPTATION

CREATION OF TECHNOLOGICAL PLATFORMS

● **HPC Core Facility** – Information Systems Department, C2RT (Head: Youssef Ghorbal)
 ● **Research Support Center** – Hearing Institute (Head: Danuta Oficjalska). The center comprises:
 – the Hearing Institute Animal and Auditory Phenotyping Core Facility;
 – the Hearing Institute Bioimaging Core Facility.

RECOGNITION EXPERTISE

AND AN OIE COLLABORATING CENTER (OIECC)

OIE (World Organization for Animal Health) Collaborating Center (OIECC) for the detection and identification in humans of emerging animal pathogens and the development of tools for their diagnosis.

Set up in May 2019 following a decision from the World Assembly of Delegates of the World Organization for Animal Health (OIE) (Heads: Jean-Claude Manuguerra and Marc Eloit).



INSTITUT PASTEUR

Jacques Dermagne Prize awarded by the Société d'Encouragement pour l'Industrie Nationale (Society for the Encouragement of National Industry) to associations that help increase the profile and influence of France internationally.

AWARDS AND APPOINTMENTS IN 2019

APPOINTMENTS

1/ Anu Bashamboo

Human Developmental Genetics Unit
Henning-Andersen Prize in Pediatric Endocrinology

2/ Roland Brosch

Head of the Integrated Mycobacterial Pathogenomics Unit
Elected to Fellowship in the American Academy of Microbiology

3/ Gérard Eberl

Head of the Microenvironment and Immunity Unit
Elected member of Academia Europaea

4/ Aziz El Amraoui

Head of the Progressive Sensory Disorders, Pathophysiology and Therapy Unit
Elected member of the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum

5/ Thomas Gregor

Head of the Physics of Biological Functions Unit
Elected member of EMBO

6/ Simonetta Gribaldo

Head of the Evolutionary Biology of the Microbial Cell Unit
Elected to Fellowship in the American Academy of Microbiology

7/ Marc Lecuit

Head of the Biology of Infection Unit
Elected member of Academia Europaea

8/ Javier Pizarro-Cerda

Head of the Yersinia Unit
Elected member of Academia Europaea

9/ Lluís Quintana-Murci

Head of the Human Evolutionary Genetics Unit
Appointed to the Human Genomics and Evolution Chair at the Collège de France

HONORS AND PRIZES

10/ Rogerio Amino

Head of the Malaria Infection and Immunity Unit
Pasteur Vallery-Radot Prize

11/ Laure Bally-Cuif

Head of the Zebrafish Neurogenetics Unit
François Jacob Award

12/ Frédéric Barras

Head of the Stress Adaptation and Metabolism in Enterobacteria Unit
Visiting Professor at Sapienza University (Rome)

13/ David Bikard

Head of the Synthetic Biology five-year group
EMBO Young Investigator Award

14/ Carmen Buchrieser

Biology of Intracellular Bacteria
Jacques Piraud Award

15/ Daria Bonazzi

Pathogenesis of Vascular Infections Unit
French Academy of Sciences' "Major advances in French biology research" award (endowed by the Mergier Bourdeix Foundation)

16/ Simon Cauchemez

Head of the Mathematical Modeling of Infectious Diseases Unit
Louis-Daniel Beaupérthuy Prize

17/ Guillaume Dumenil

Head of the Pathogenesis of Vascular Infections Unit
Pasteur Vallery-Radot Prize

18/ Simonetta Gribaldo

Head of the Evolutionary Biology of the Microbial Cell Unit
Visiting Miller Research Professor at the University of California, Berkeley (60 days)

19/ Philippe Glaser

Head of the Ecology and Evolution of Antibiotic Resistance Unit
Louis Pasteur Medal from the André-Romain Prévot Foundation

20/ Romain Levayer

Head of the Cell Death and Epithelial Homeostasis Unit
Laureate of the Schlumberger Foundation for Education and Research Prize

21/ Nadia Naffakh

Head of the RNA Biology of Influenza Virus Unit
Human Frontier Science Program (HFSP) grant award

22/ Jean-Christophe Olivo-Marin

Head of the Bioimage Analysis Unit
Engineering in Medicine and Biology Society (EMBS) Distinguished Service Award

23/ Lluís Quintana-Murci

Head of the Human Evolutionary Genetics Unit
René & Andrée Duquesne Award
Allianz/Institut de France Foundation Prize

24/ Eduardo Rocha

Head of the Microbial Evolutionary Genomics Unit
"FRM Team" (French Foundation for Medical Research) award

25/ Cosmin Saveanu

Group Leader in the Genetics of Macromolecular Interactions Unit

Thérèse Lebrasseur Award of the Fondation de France

26/ Gerald Spaeth

Head of the Molecular Parasitology and Signaling Unit
Georges Zermati Prize

27/ Ludovic Tailleux

Leader of the Host Response to Bacterial Infection Group
Georges, Jacques and Elias Canetti Prize

28/ Sven van Teeffelen

Head of the Microbial Morphogenesis and Growth Unit
EMBO Young Investigator Award

ERC FUNDING

29/ Jérôme Gros

Head of the Dynamic Regulation of Morphogenesis Unit
ERC Consolidator Grant (Role of Tissue Mechanics in Embryonic Self-Organization and Cell Fate Plasticity)

30/ Aurèle Piazza

Spatial Regulation of Genomes Unit
ERC Starting Grant (Mechanism of homology search and the logic of homologous chromosome pairing in meiosis), sponsored by the CNRS

31/ Michael White

Malaria: Parasites and Hosts Unit
ERC Starting Grant (Algorithms and multiplex assays for integrated serological surveillance of malaria and neglected tropical diseases)

IP YOUNG SCIENTIST PRIZE

POST-DOC CATEGORY

32/ Daria Bonazzi

Pathogenesis of Vascular Infections Unit

33/ Pascale Vonaesch

Molecular Microbial Pathogenesis Unit

PHD CATEGORY

34/ Meryem Baghdadi

Stem Cells and Development Unit

35/ Wei Ouyang

Imaging and Modeling Unit

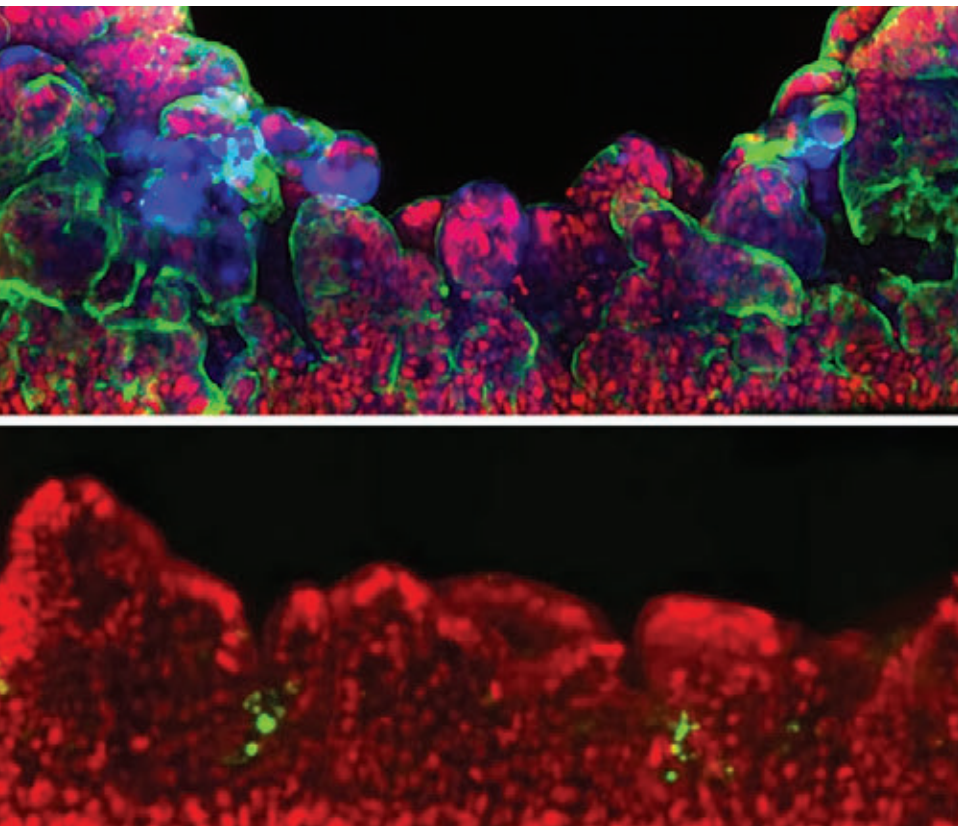




1. RESEARCH MISSION

The Institut Pasteur is committed to conducting outstanding research to benefit human health the world over. Its ongoing ambition is to provide fresh impetus to basic research and increase the impact of this research on health issues.

ÉLIETTE TOUATI
HEAD OF THE INFECTION, GENOTOXICITY AND CANCER GROUP IN THE *HELICOBACTER* PATHOGENESIS UNIT
SEE PAGE 35 TO READ ABOUT ONE OF ÉLIETTE TOUATI'S 2019 PUBLICATIONS.
LEARN MORE ABOUT THE PICTURES ABOVE ON PAGE 96.



INTESTINE-ON-CHIP. TOP: STITCHED IMAGES SHOWING INTESTINAL CRYPTS FROM A FRONTAL CROSS SECTIONING (CONFOCAL MICROSCOPE AND Z PROJECTION). CELLS FIXED, PERMEABILIZED AND STAINED FOR ACTIN (PHALLOIDIN-ALEXA647, BLUE), WITH ANTI VILLIN-1 (GREEN) AND NUCLEI WITH DAPI (RED). BOTTOM: STITCHED IMAGES SHOWING A CROSS SECTIONING OF AN INTESTINE-ON-CHIP INFECTED BY *SHIGELLA-WT-GFP* (GREEN) FOR ONE HOUR. NUCLEI STAINED WITH DAPI (RED).

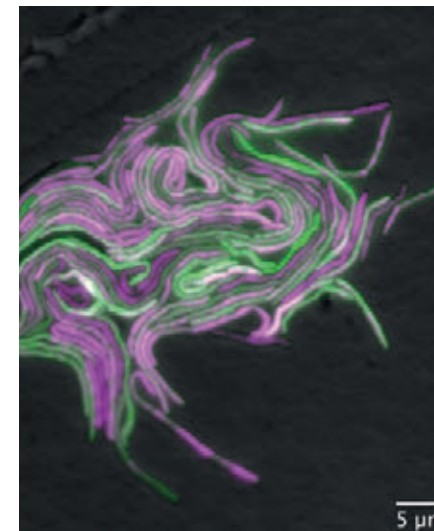
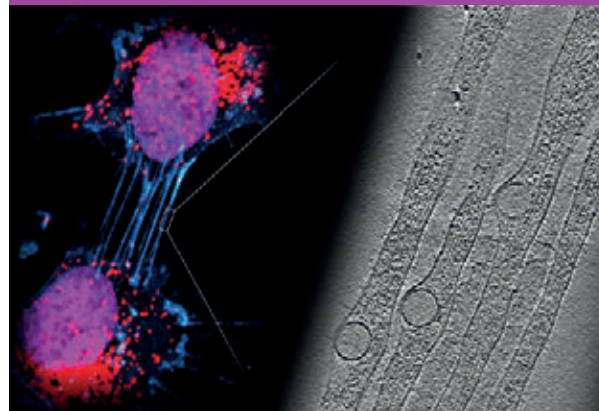
DEPARTMENT OF CELL BIOLOGY AND INFECTION

The Cell Biology and Infection Department (BCI) develops an integrated understanding of the cell, the fundamental unit of life, in physiological conditions, during infection and in other cellular-based pathologies such as cancer and neurodegenerative diseases. Its research programs are highly interdisciplinary; they use and develop quantitative tools and innovative techniques to improve understanding of the molecular mechanisms at work in cells. The department fosters strong links with quantitative disciplines, such as mathematics and physics. BCI teams develop new cellular, tissue and animal models for studying infections and other diseases. The department is led by Marc Lecuit.

NEW DISCOVERIES ABOUT NANOTUBES (TNTs), TRANSPORTERS OF TOXIC PROTEINS

The laboratory coordinated by Chiara Zurzolo discovered that tunneling nanotubes (TNTs), thin connections between cells, allow the transfer of different amyloid aggregates involved in the progression of neurodegenerative diseases. By combining advanced fluorescent microscopy and cryo-electron tomography, they clarified the anatomy of TNTs and showed that they are unique structures made of a bundle of tubes that braid around each other. Inside each individual tube are vesicles, organelles, and actin filaments that serve as railways for cargo exchange. They also showed that TNT formation is specifically regulated by the Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), and that specific inhibitors reduce the transfer of amyloids between neurons. These data suggest that the Wnt/Ca²⁺-CaMKII pathway could be a promising target for therapies designed to impair TNT-mediated propagation of amyloid aggregates. Together, this work is an essential step towards understanding TNT-mediated cell-to-cell communication and its role in neurodegenerative diseases.

Sources: Anna Sartori-Rupp, Diégo Cordero Cervantes, Anna Pope et al., Nature Communications, January 21, 2019. Jessica Y. Vargas, Frida Loria, Yuan-Ju Wu & al., The EMBO Journal, October 18, 2019.



PREEXISTING VARIATION IN DNA DAMAGE RESPONSE PREDICTS THE FATE OF SINGLE MYCOBACTERIA UNDER STRESS.

WHEN DNA DAMAGE RESPONSE PREDICTS SINGLE-CELL FATE UNDER STRESS

Phenotypic variation is the ability of clonal cells to diversify both under optimal, and even more under stressful conditions, and conceivably contributes to the ability of microbes to endure protracted antibiotic therapy, as in tuberculosis drug-persistence. This phenomenon is also likely to contribute to the development of genetic drug resistance. The laboratory of Giulia Manina has shown that both non-pathogenic and pathogenic mycobacteria exhibit differential drug susceptibility at the subpopulation level, depending on their phenotypic state. In particular,

by using fluorescent reporters for DNA damage response and time-lapse microfluidic microscopy, Giulia Manina's laboratory showed that more than 50% of bacilli within a clonal population experience transient DNA damage events, which solve spontaneously. Remarkably, cells experiencing DNA damage are more susceptible to treatment with a quinolone drug, as opposed to genetically healthier cells, which persist more. These findings suggest that preexisting variation in DNA damage is predictive of single-cell fate during drug treatment, paving the way for new opportunities in drug discovery.

Source: Manina G. et al., The EMBO Journal, November 15, 2019.

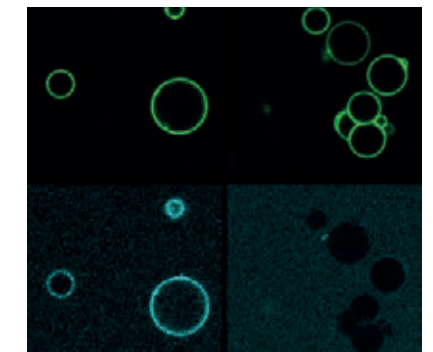
ORGAN-ON-CHIP TO INVESTIGATE HOST-PATHOGEN INTERACTION AT THE TISSUE SCALE

A collaborative work between the team of Nathalie Sauvonnet (Molecular Microbial Pathogenesis, BCI), the Biomaterials & Microfluidics and the Ultrastructural Bioimaging core facilities (BCI), shows the first successful implementation of the Organ-on-Chip technology in the field of infectious disease. Practically, researchers revealed that the intestinal architecture, organized in 3D, and the mechanical forces play critical roles during *Shigella* infection. The organ-on-chip allows reproduction of the high infectivity of *Shigella*, observed only in humans. These results highlight the importance of employing physiologically relevant assays when trying to better understand host pathogen interactions at the tissue level.

Source: Grassart A. & al., Cell Host Microbe, September 11, 2019.

ATG11 TETHERS ATG9 VESICLES TO INITIATE SELECTIVE AUTOPHAGY

Autophagy is a major waste disposal system that allows cells to degrade damaged or unwanted cytoplasmic components. A tight regulation of this pathway ensures that under normal conditions such material is efficiently removed to protect the cells from toxic effects. If cells experience any type of stress or starvation, the pathway starts to degrade bulk cytoplasm. Although this also destroys functional proteins and other cellular components, it allows cells to survive adverse conditions by freeing resources to maintain vital functions. The unit Membrane Biochemistry and Transport led by Thomas Wollert revealed the molecular mechanism of this important cellular switch. They found that two molecules that function either in one or the other type of autophagy perform seemingly identical functions. Moreover, the team found that starvation induces the rapid degradation of the factor that



promotes selective autophagy. This allows the non-selective factor to take over. Selective autophagy is important for maintaining cellular homeostasis and dysfunctions promote the onset of neurodegenerative diseases. By contrast, non-selective autophagy is essential for cells to cope with stress but the pathway is abused by cancer cells during proliferation. Understanding how the cell switches between the two pathways is key to developing new strategies to treat cancer or neurodegeneration.

Source: Matscheko N. et al., PLoS Biol., July 29, 2019.

DEPARTMENT OF COMPUTATIONAL BIOLOGY

The Center for Bioinformatics, Biostatistics and Integrative Biology (C3BI), one of the largest bioinformatics centers in France, is now a department at the Institut Pasteur. The Department of Computational Biology hosts 18 research units (5 with primary affiliation) with expertise in areas ranging from mathematical modeling to algorithms, statistics and machine learning. The Bioinformatics and Biostatistics Hub performs analyses, develops applications and data processing pipelines. It also provides training for units and platforms on the Paris campus and in the Institut Pasteur International Network. In 2019 the Hub dealt with more than a hundred new projects. The department is led by Olivier Gascuel who was recently elected to the French Académie des sciences.

A FAST METHOD TO RECONSTRUCT AND VISUALIZE ANCESTRAL SCENARIOS

The Evolutionary Bioinformatics Unit has developed the PastML program. This tool, based on decision-theory concepts, reconstructs “ancestral scenarios” that describe the evolution of traits or characters along phylogenetic trees. The characters can be highly varied and represent the morphology of species studied, biochemical properties of proteins, the geographical origin of an outbreak and its global spread, or the emergence and spread of resistance to treatments. In mere minutes, PastML analyzes vast reams of data suggesting the most likely hypotheses. PastML is available to the international scientific community, as Phylogeny.fr has been since 2008. NGPhylogeny.fr, a new version entirely rebuilt by the same teams in 2019 with the help of the Bioinformatics and Biostatistics Hub, is also available. NGPhylogeny.fr is consulted nearly a hundred times a day by scientists worldwide.

Source: Sohta A. Ishikawa et al., Mol. Biol. Evol., May 24, 2019. NGPhylogeny.fr: Frédéric Lemoine et al., Nuc. Acid Res., July 2, 2019.



FOR DENGUE (DENV2), THE SCIENTISTS RECONSTRUCTED THE PHYLOGEOGRAPHY SCENARIO EXPLAINING THE EMERGENCE OF THIS PANDEMIC IN HUMANS AND ITS GLOBAL SPREAD.

RISK OF CHRONIC DISORDERS: UNDERSTANDING THE INTERPLAY BETWEEN INDIVIDUAL'S GENOME AND THE ENVIRONMENT

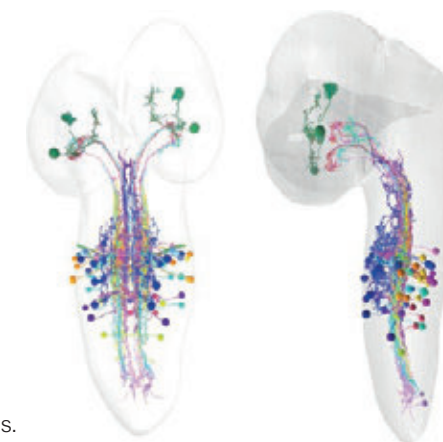
An individual's environment in a broad sense, from pollutant exposure to unhealthy lifestyle, has been linked to a range of chronic disorders, including cardiovascular disease, obesity, type 2 diabetes, cancers, and autoimmune diseases. Most of these conditions have also a complex genetic component and thousands of at-risk genetic mutations have now been identified. Conversely, our knowledge of the interplay between an individual's genome and the environment remains limited. The Statistical Genetics group

has developed new innovative methodologies and publicly available software to characterize the role of gene-environment interactions in human phenotypes when using large multidimensional human cohorts. It has also contributed to several international initiatives that explored changes in genetic risk on blood pressure, dyslipidemia, and pulmonary phenotypes, conditional on factors such as smoking, alcohol consumption, age and drug treatment.

Source: Gallois et al., Nature Communications, 2019, PMID=31636271.

LEARNING FROM INSECT NEURAL CIRCUITS

The Decision and Bayesian Computation group is developing computational approaches for modeling and understanding the neural activities of primitive animals. Small insects are able to perform complex probabilistic choices, navigate ambiguous environments, learn and survive predators using neural circuits considerably smaller than the ones found in mammals or in most machine learning applications. The group aims to identify biological neural circuits involved in complex computations in order to understand the evolutionary pressure that optimized them and to draw inspiration for the design of small efficient and robust artificial neural circuits as part of the Prairie Institute for Artificial Intelligence project. In a recent work, they combined high throughput behavioral assay, single neuron inactivation, connectomics (the study of neural connections in the brain) and active learning



DORSAL AND LATERAL VIEWS OF ONE OF THE PUTATIVE MECHANOSENSORY BIOLOGICAL NEURAL NETWORKS OF THE DROSOPHILA LARVA REVEALED BY MACHINE LEARNING.

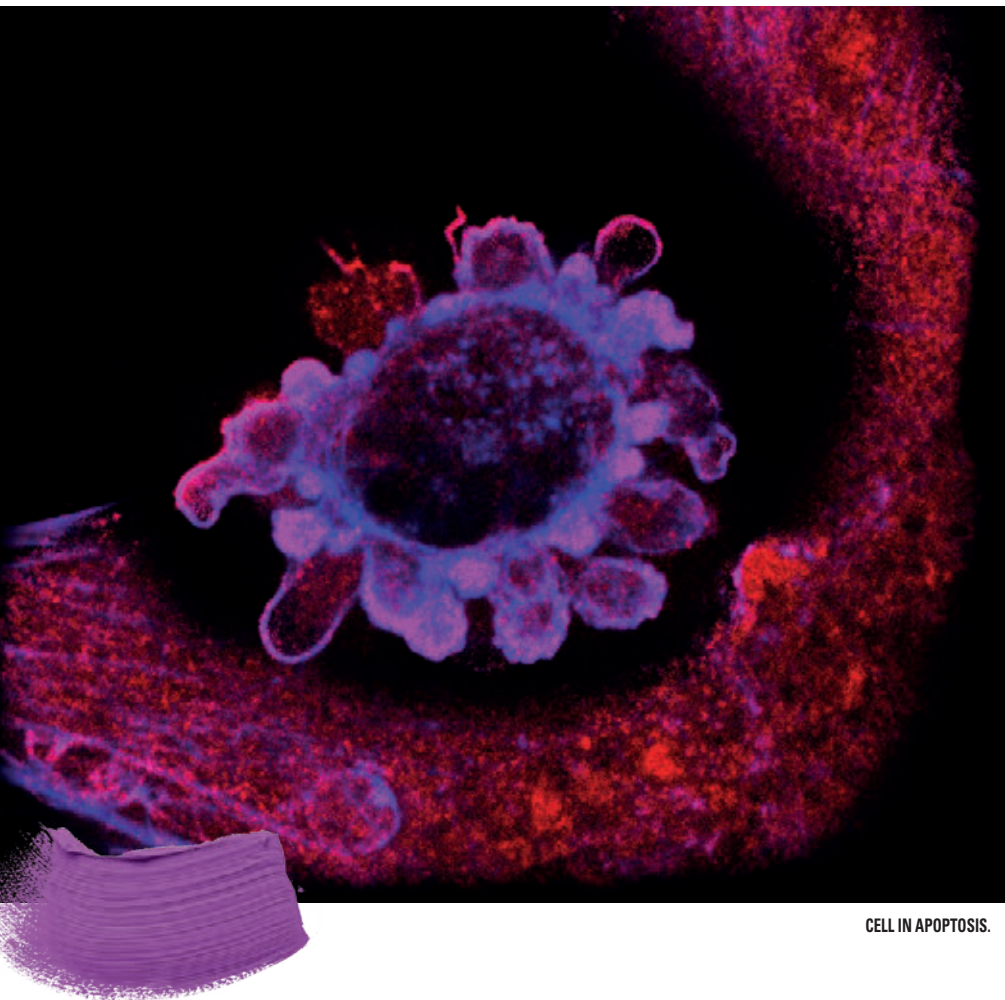
to identify neurons involved in competitive interactions within the nervous system of the drosophila larva. These results are coupled with the simulation of the neural circuits' dynamics where these neurons are involved.

Source: Jean-Baptiste Masson et al., PLoS Genetics, February 14, 2020 [epub December 30, 2019].



TEACHING COMPUTATIONAL BIOLOGY ON CAMPUS AND IN THE INTERNATIONAL NETWORK

To train future biology researchers in computational methods, the Bioinformatics and Biostatistics Hub has joined forces with the rest of the department and the Image Analysis Hub to develop training in programming, data analysis, bioinformatics and imaging. The course is divided into 17 modules and aimed primarily at PhD students (70 per year). Several of these modules have already been taught at institutes in the Institut Pasteur International Network (Hanoi, Montevideo and Tunis in 2019), and young scientists from the International Network have completed training courses in the department. The training material and internships will also be available in France's prestigious grandes écoles (ENS and Centrale-Supélec) via the INCEPTION program.



CELL IN APOPTOSIS.

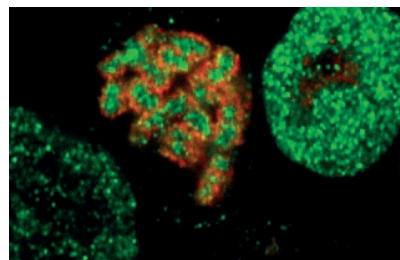
DEPARTMENT OF DEVELOPMENTAL AND STEM CELL BIOLOGY

The Department of Developmental and Stem Cell Biology covers a broad spectrum of research, ranging from individual cells to whole organisms and from embryos to adults. How do cells acquire their identity, and how are organs formed? The department's work in the field of developmental biology has given rise to research on stem cells and their potential role in tissue regeneration. The department is led by François Schweisguth.

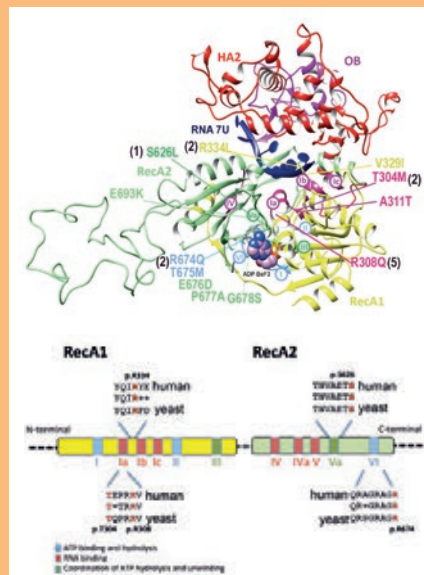
NUCLEOSOMAL RESILIENCY, OR HOW SOME TRANSCRIPTION FACTORS CONTRIBUTE TO GENE REGULATORY INHERITANCE

Transcription factors (TFs) have long been recognized as key players in the establishment of specific gene expression patterns. However, TFs were traditionally thought to be evicted from their target genes during DNA duplication – when the replication fork profoundly alters the chromatin – and during mitosis – when the chromosomes fully condense to enable the equal partition of the genetic information between the daughter cells. A team led by Pablo Navarro at the Institut Pasteur has shown that certain TFs, such as Esrrb and CTCF, display the rare capacity of surviving replication and mitosis. In doing so, they preserve the local structure of the nucleosomes under the form of regular and well-ordered “beads on a string”. This new mechanism of gene regulatory inheritance during replication and mitosis has important consequences regarding the understanding of cellular processes involving proliferation, such as stem cell self-renewal, development and tumorigenesis.

Source: Owens N. & al. *Elife*. October 10, 2019.



MITOTIC CHROMOSOMES (IDENTIFIED BY K167, RED SIGNAL) DECORATED BY THE TF ESRRB (GREEN).



MUTATIONS CAUSING HIGHLY PRESERVED FUNCTIONAL RESIDUES WITH IMPACT ON HUMAN SEX INVERSION.

PATHOGENIC VARIANTS IN THE RNA HELICASE DHX37 ARE A FREQUENT CAUSE OF DISORDERS OF SEXUAL DEVELOPMENT

Sex determination is a classic paradigm for understanding fundamental processes of cell fate choice and organogenesis. The process by which a progenitor cell decides to form either a testis or an ovary is poorly understood in vertebrates. Unbiased genomic screens of rare human individuals, who have errors in sex-determination, termed disorders of sex development (DSD), are a powerful approach to understand this process. In a large multinational study, the unit of Ken McElreavey discovered that a highly conserved RNA helicase DHX37, which is essential for ribosome biogenesis in eukaryotes, is specifically required for human testis-determination and maintenance

of testis tissue (risk of 46,XY gonadal dysgenesis and 46,XY testicular regression syndrome). Human diseases associated with ribosome biogenesis are an emerging and poorly understood branch of medicine. These results force a shift in our understanding of vertebrate sex-determining mechanisms. More generally, they pave the way for a new understanding into the relationship between the ribosome and human disease.

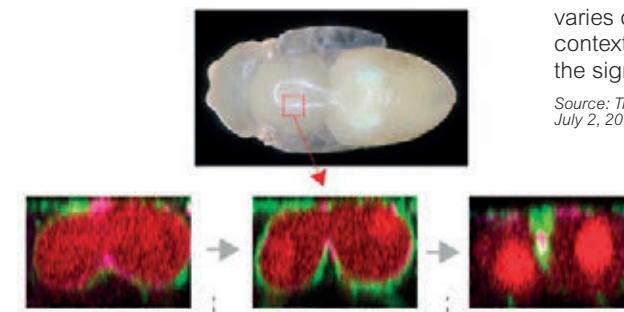
Source: McElreavey K. & al. *Genet Med*. July 24, 2019.

KEY STAGE IN NOTCH RECEPTOR ACTIVATION ASSOCIATED WITH THE DYNAMICS OF CELL DIVISION

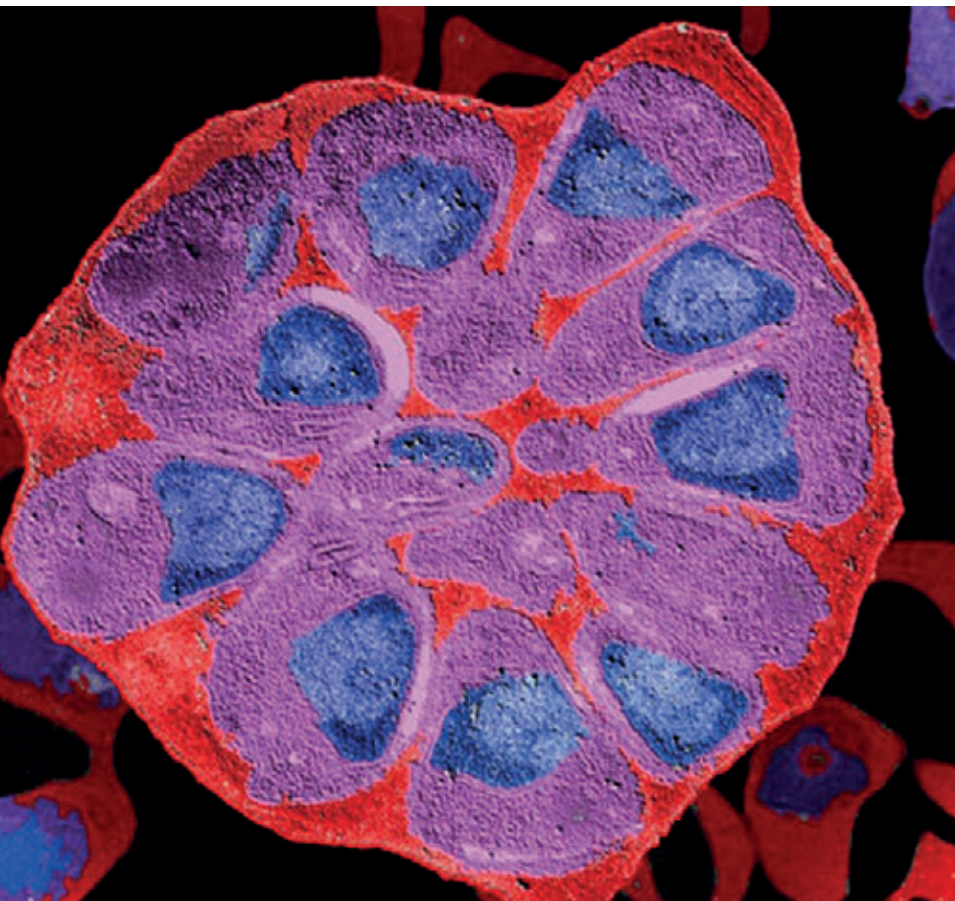
During embryo development and throughout adult life, cells are permanently exchanging information with their neighbors on their state of differentiation. These exchanges involve the membrane receptor Notch, and any disruption in the activation of the receptor can lead to various medical conditions in adults. Notch is activated by a membrane ligand which, when internalized by

endocytosis, produces a force that exposes a receptor cleavage site. This stage is critical in Notch activation. Analysis of the lineage of sensory organs in *Drosophila* revealed that the polymerization dynamics of actin filaments are needed for effective internalization of the Notch ligand in a precise time window after mitosis. This suggests that the actin cytoskeleton helps produce the force needed to activate Notch. It also suggests that this force varies depending on the mechanical context of the cells receiving the signal.

Source: Trylinski M., Schweisguth F. *Cell Rep*. July 2, 2019.



THE ACTINE CYTOSKELETON CONTRIBUTES TO PRODUCING THE FORCE NECESSARY TO ACTIVATE NOTCH.



RED BLOOD CELL PARASITIZED BY *PLASMODIUM FALCIPARUM*.

DEPARTMENT OF STRUCTURAL BIOLOGY AND CHEMISTRY

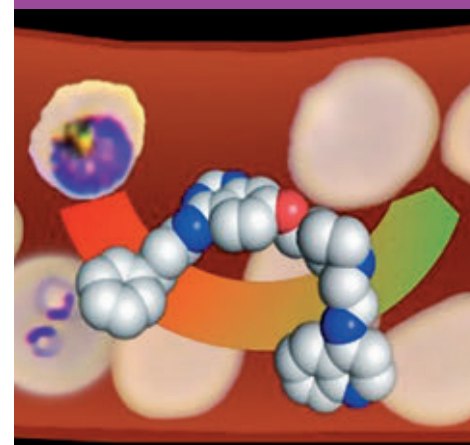
The structure of a molecule is intricately linked to its function. The units and technological platforms in the Department of Structural Biology and Chemistry focus their research on the three-dimensional organization, properties and synthesis of molecules of biological interest, especially those that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



NEW BREAKTHROUGH IN DEVELOPING EFFECTIVE ANTIMALARIAL DRUGS

In the context of the rapidly increasing resistance to antimalarial treatments, we showed that inhibitors of DNA methylation effectively and quickly kill parasites in human blood. The rationale resides in the chemical targeting of the epigenetic regulation of the parasite that allows it to adapt to the different environments in the human host. In addition, the compounds remain active against the resistant parasite strains, including the artemisinin resistant ones, paving avenues for new drugs that could eliminate resistant parasites. These findings result from the collaboration between the Unit of Paola B. Arimondo (Department of Structural Biology and Chemistry), that of Artur Scherf (Department of Parasites and Insect Vectors) and the team of Benoit Witkowski (Institut Pasteur du Cambodge).

Source: Nardella F et al., ACS Central Science, November 27, 2019.



THE PARASITES (IN PURPLE) PROLIFERATING IN THE HUMAN BLOOD CELLS (PINK) ARE KILLED BY THE COMPOUND.

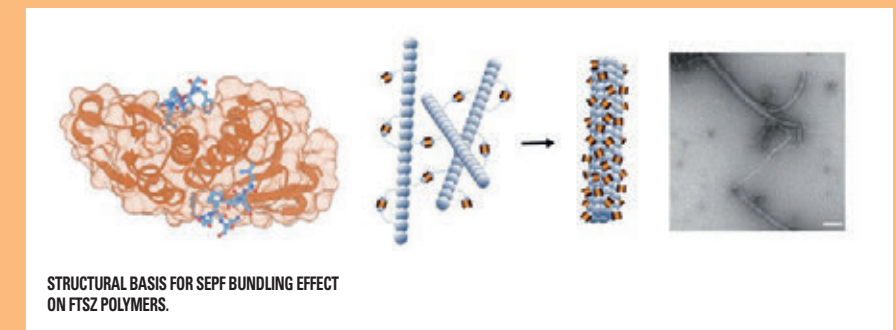
MECHANISTIC MICROBIOLOGY: UNDERSTANDING CELL DIVISION IN ACTINOBACTERIA

The bacterial cytoskeleton formed by the FtsZ protein – the prokaryotic tubulin – lies at the heart of cell division. FtsZ activity in the cell is essential and thus highly regulated via many interactors, notably those that bring and attach the cytoskeleton to the membrane. In contrast to well-studied bacteria such as *Escherichia coli* or *Bacillus subtilis*, the detailed molecular mechanism of how this occurs is poorly understood in *Actinobacteria*, a large bacterial phylum that contains important human pathogens such as *Mycobacterium tuberculosis*. The work of Sogues and colleagues sheds new light on the dynamic interplay between FtsZ and its

membrane anchor, SepF. Combining structural biophysics with genetics and cell biology, this work demonstrates that the FtsZ-SepF interdependence is crucial for Z-ring assembly, membrane

remodeling and septum formation in the actinobacterial model organism, *Corynebacterium glutamicum*.

Source: Sogues A et al., Nature Comm., 2020 (in press).



STRUCTURAL BASIS FOR SEPF BUNDLING EFFECT ON FTSZ POLYMERS.

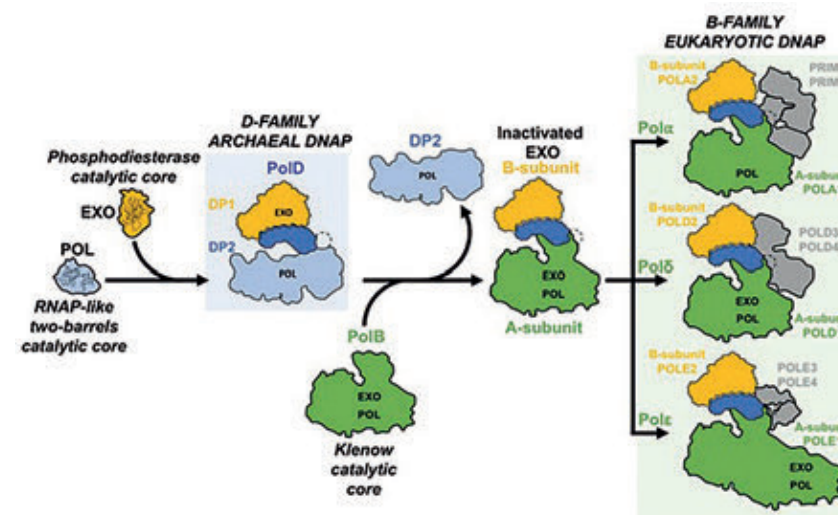
STRUCTURE OF THE ARCHAEL POLD DNA POLYMERASE: THE MISSING LINK BETWEEN AN RNA WORLD AND THE CONTEMPORARY EUKARYOTIC REPLICATIVE DNA POLYMERASES

PolD is an archaeal replicative DNA polymerase (DNAP). Archaeaea is one of the three main areas of the living world. PolD is made of a proofreading

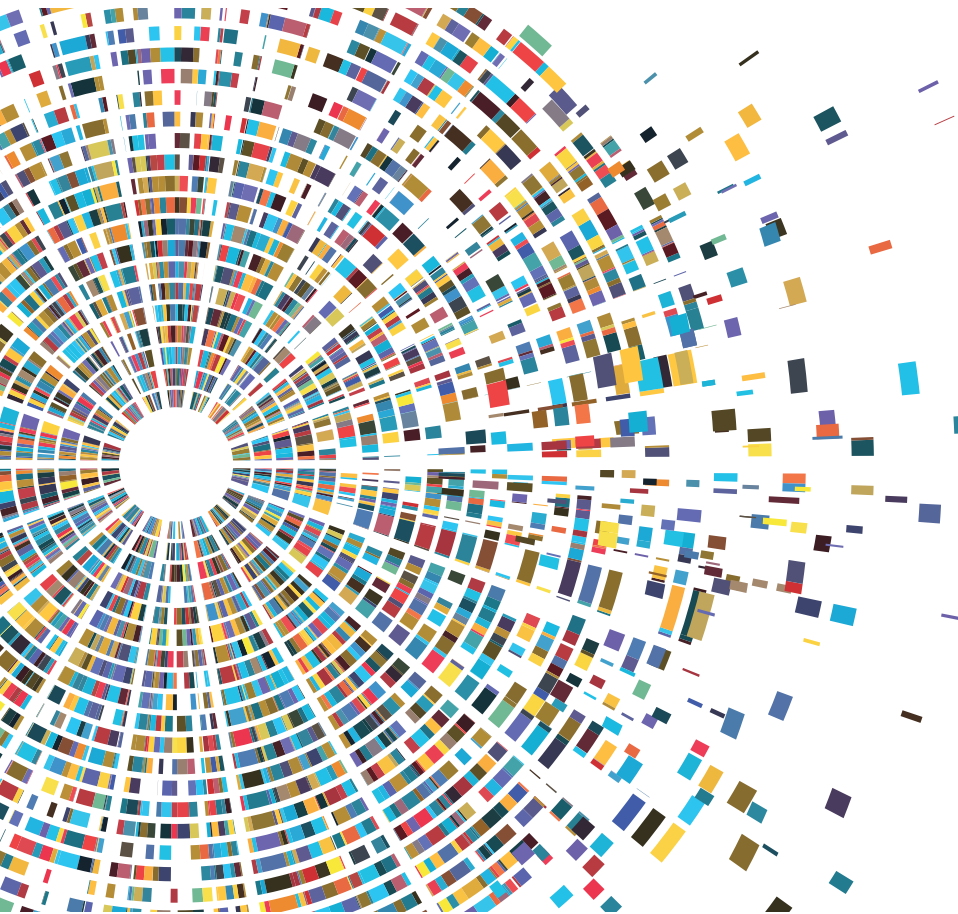
exonuclease subunit (DP1) and a larger polymerase catalytic subunit (DP2). Recently, an Institut Pasteur research team reported the individual

crystal structures of the DP1 and DP2 catalytic cores, thereby revealing that PolD is an atypical DNAP that has all functional properties of a replicative DNAP but with the catalytic core of an RNA polymerase (RNAP). They now report the DNA-bound cryo-electron microscopy (cryo-EM) structure of the heterodimeric DP1–DP2 PolD complex from *Pyrococcus abyssi*, revealing a unique DNA-binding site. Comparison of PolD and RNAPs extends their structural similarities and brings to light the minimal catalytic core shared by all cellular transcriptases. Finally, elucidating the structure of the PolD DP1–DP2 interface, which is conserved in all eukaryotic replicative DNAPs, clarifies their evolutionary relationships with PolD and sheds light on the domain acquisition and exchange mechanism that occurred during the evolution of the eukaryotic replisome.

HYPOTHETICAL SCENARIO ACCOUNTING FOR THE ORIGINS OF ARCHAEL POLD AND ITS EVOLUTIONARY RELATIONSHIPS WITH THE EUKARYOTIC REPLICATIVE DNAPS.



Source: Raia P. et al., PLoS Biol., January 18, 2019.



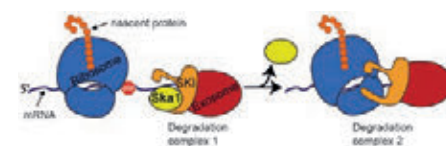
DEPARTMENT OF GENOMES AND GENETICS

Decoding the architecture, expression and evolution of genomes sheds light on new biological functions and offers a vast array of research possibilities for scientists in the Genomes and Genetics Department. The department explores the genetic information of microorganisms such as yeast and bacteria, as well as that of humans and mice. It investigates how this information is organized in the genome and is shaped by cellular processes. This helps clarify how the evolution of genomes reflects selection for adaptation, notably in terms of quality control of cellular processes and antibiotic resistance in microbes as well as humans' immune response. The progress of these research programs is largely based on sequencing, genotyping, and microfluidics approaches. The department is led by Eduardo Rocha.

A NOVEL CELLULAR TOOL FOR QUALITY CONTROL OF GENE EXPRESSION

In both yeast and mammals, messenger RNA is translated into protein by the ribosomes in the cytoplasm. After several translation cycles, these RNAs are degraded. Moreover, some defective mRNAs need to be detected and eliminated. In both cases, degradation is co-translational and takes place at both extremities. The exosome assisted by the SKI complex degrades RNA from the 3' extremity (downstream). Recent research by the Macromolecular Interaction Genetics team showed that SKI needs to be associated with the ribosome to be active. However, this raises a paradox because the extremity of mRNA is not translated and therefore has no ribosome. The team recently demonstrated the existence of a new SKI complex associated with the Ska1 protein that is specifically required for the degradation of ribosome-free regions. This discovery resolves an important question for our understanding of a fundamental mechanism in cell function.

Source: Zhang et al, EMBO Journal, June 2019.



DURING THE 3' TO 5' DEGRADATION OF RNAs, THE SKI-EXOSOME COMPLEX IS FIRST ASSISTED BY SKA1; THEN WHEN THE COMPLEX ARRIVES NEAR THE CODING REGION, A RIBOSOME TAKES THE PLACE OF SKA1 FOR ITS ASSOCIATION WITH SKI AND ITS ACTIVATION.

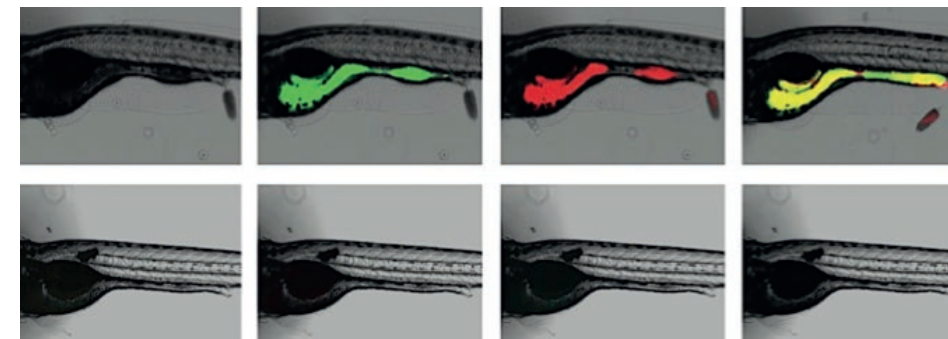
A NEW WEAPON TO KILL ANTIBIOTIC-RESISTANT BACTERIA

Antibiotic resistance in bacteria is growing at such a rate that it threatens the efficacy of treatments for some infectious diseases. There is now an urgent need to propose alternatives to "conventional" antibiotics. The Bacterial Genome Plasticity Unit has built a genetic weapon capable of killing specific types of pathogenic bacteria that are resistant to antibiotics. This weapon is based

on the specific expression of a highly potent antibacterial toxin, delivered by a natural genetic transfer mechanism, plasmid conjugation, from inoffensive bacteria such as those found naturally in the gut microbiota. Bacteria appear not to develop a mechanism of resistance to tackle this arsenal. But one of the challenges of this method is how to control the sheer power of the toxin. The scientists

verified the specific nature of the approach by targeting the cholera agent, *Vibrio cholerae*, a marine bacterium, and demonstrating that it could be specifically eliminated from the microbiota of its natural hosts, a fish and a shellfish.

Source: Lopez-Igual et al, Nature Biotechnology, July 2019.



THE WEAPON FOR KILLING ANTIBIOTIC-RESISTANT BACTERIA IS BASED ON THE SPECIFIC EXPRESSION OF AN ANTIBACTERIAL TOXIN THAT IS EXTREMELY POWERFUL.

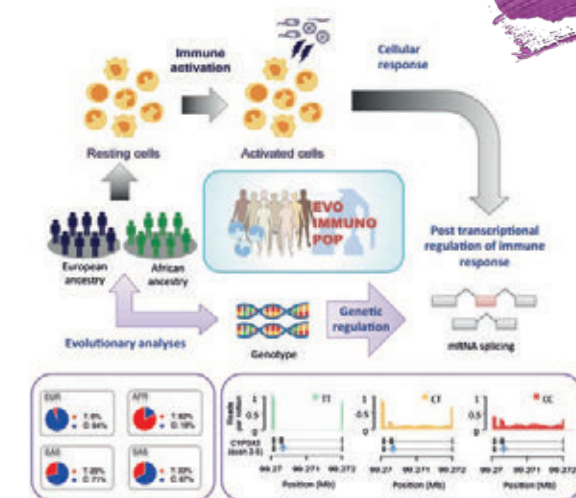
CHARACTERIZING THE GENETIC AND EVOLUTIONARY BASIS OF THE SPLICING RESPONSE TO INFECTION

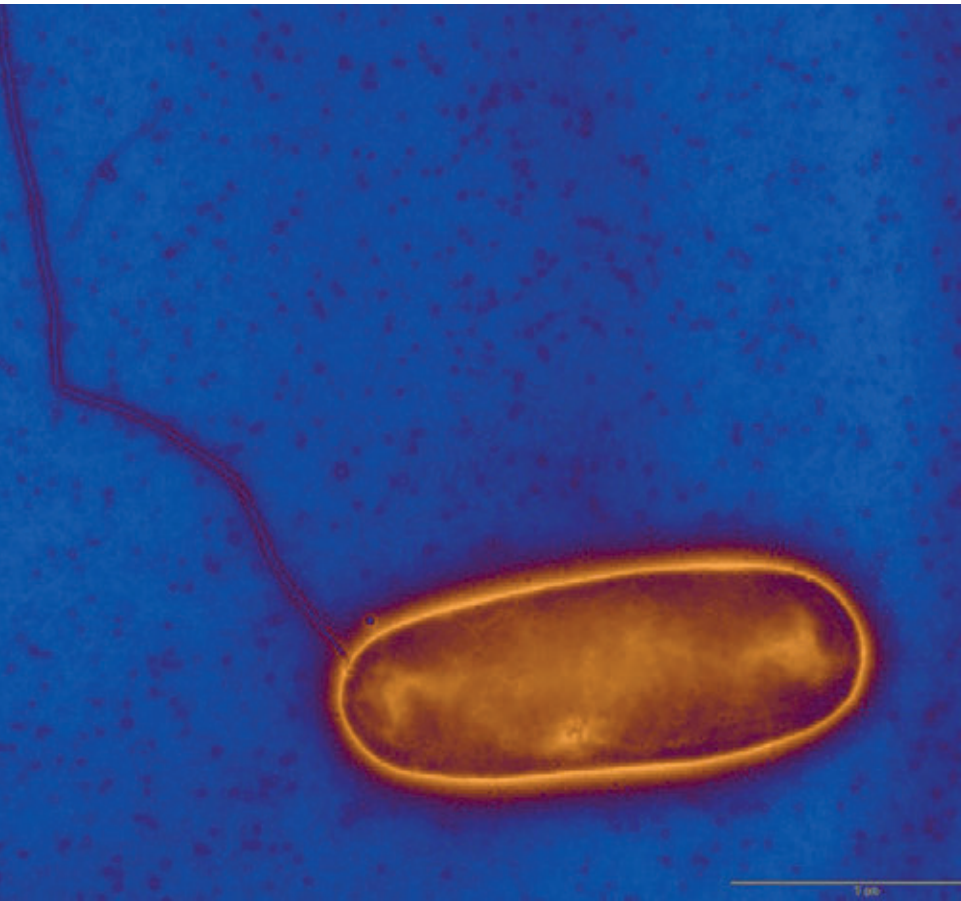
In humans, alternative splicing is widely observed in response to infection. Yet the evolutionary importance of such an alternative splicing response to infection and its variability across human populations has remained largely uncharacterized. The Human Evolutionary Genetics team profiled the messenger RNAs from resting and stimulated monocytes, a type of white-blood cell, from 200 individuals of African and European descent. The team showed that immune activation deeply alters the splicing of mRNAs produced by the cell. In particular, it leads to a drastic increase in usage of cryptic splice sites that is largely attributable to a reduced activity of the nonsense mediated decay pathway, a surveillance pathway whose function is to reduce errors in gene expression. The researchers identified over a thousand genetic variants associated with changes in isoform usage

(isoforms are different forms a protein takes when it comes from the same gene), often leading to increased susceptibility to auto-immune diseases. Finally, they showed that both past admixture with archaic hominins (a sub-tribe of hominids that includes the genus *Homo* and the related extinct genera) and positive selection have

contributed towards diversifying the splicing landscape across human populations. This increases our understanding of the mechanisms that contribute to population differences in susceptibility to immune-related diseases.

Source: Rotival et al, Nature Communications, April 2019.

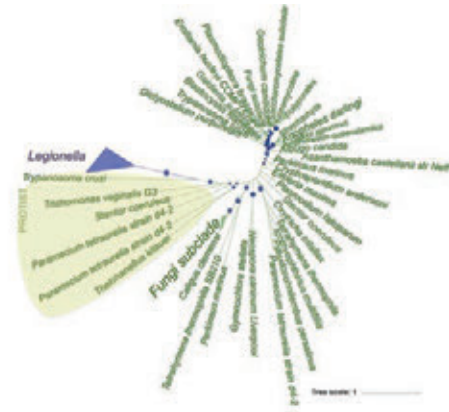




LEGIONELLA PNEUMOPHILA THE BACTERIUM RESPONSIBLE FOR SEVERE ACUTE LUNG DISEASE.

DEPARTMENT OF MICROBIOLOGY

The scientists of the Department of Microbiology study fundamental biological processes of bacteria and archaea (and their viruses) using genomics, genetics, metabolism, molecular and cellular biology approaches, etc. They also focus on the mechanisms that render some of these microorganisms virulent and enable them to evade the host immune system or to develop resistance to antibiotics. These studies improve our understanding of these microorganisms, and contribute to the development of new therapies or diagnostic tools to treat or prevent bacterial infections. The department is led by Frédéric Barras.



HYLOGENETIC ANALYSES OF *LEGIONELLA* RAB PROTEIN SUGGEST EUKARYOTIC ORIGIN.

HORIZONTAL GENE TRANSFER BETWEEN DOMAINS OF LIFE SHAPED THE VIRULENCE OF *LEGIONELLAE*

The genus *Legionella* comprises 65 species for which aquatic amoebae are the natural reservoir. Using functional and comparative genomics to deconstruct the entire bacterial genus we revealed the surprising parallel evolutionary trajectories that have led to the emergence of human pathogenic *Legionella*. Researchers identified an unexpectedly large repository of more than 18,000 secreted proteins many of which were acquired by HGT (Horizontal Gene Transfer) from all domains of life. Eukaryotic Rab-GTPase domains are found nearly exclusively in eukaryotes and *Legionella*. This study revealed the surprising extent to which *legionellae* have co-opted genes and thus cellular functions from their eukaryotic hosts and identified an unprecedented environmental reservoir of bacterial virulence factors. It provided a new understanding of how reshuffling and gene-acquisition from environmental eukaryotic hosts may allow for the emergence of human pathogens.

Source: Laura Gomez-Valero, et al., Proc Natl Acad Sci USA, February 5, 2019.

DISCOVERING NEW METABOLISMS AND THEIR EVOLUTION BY ANALYZING THE GENOMES OF UNCULTIVATED MICROORGANISMS

The vast majority of microbial biodiversity currently remains uncultivated. But the rise in high-throughput sequencing techniques in recent years has given us unprecedented access to the genomic data of this hidden majority in a wide range of environments. Recent research by the team led by Simonetta Gribaldo in the Evolutionary Biology of the Microbial Cell Unit has made use of these data to shed new light on the diversity and evolution of significant metabolisms in archaea and bacteria.

The first study explored the diversity and evolution of methanogenic and methanotrophic archaea, microorganisms that play a key role in climate change, the production of biogas and the degradation of organic matter in anoxic environments, including the digestive systems of animals and humans. The scientists used vast quantities of published metagenomic data to reconstruct ten genomes of previously unknown archaea. Their analysis demonstrated new methanogenic pathways, some of which will now be studied in the laboratory. The second study looked

at the evolutionary history of one of the oldest metabolic pathways for carbon fixation, the Wood-Ljungdahl pathway. It demonstrated that this pathway can be found in several lines of uncultivated microorganisms and that it is highly likely to have originated in archaea. The analysis also indicates a possible scenario in which this metabolic pathway evolved over billions of years, and gave rise

to methylotrophy in bacteria. The research sheds new light on diversity and the historical evolution of metabolisms, opening up multiple potential avenues of investigation with considerable environmental, industrial and medical interest.

Sources: Borrel G, et al., Nat Microbiol., March 4, 2019; 4:603-613.
Adam P, et al., Nat Microbiol., August 26, 2019; 4:2155-2163.



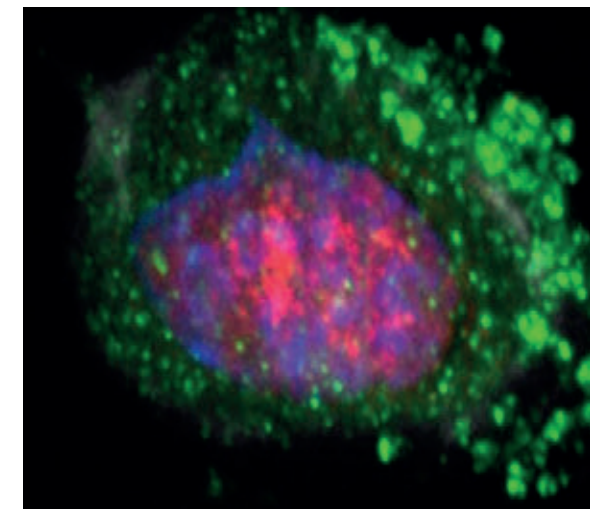
EXAMPLE OF AN ENVIRONMENT IN WHICH THE GENOMES OF NEW ARCHAEA LINES WERE IDENTIFIED (WASHBURN HOT SPRINGS, UNITED STATES).

THE DEPLETION OF TRANSCRIPTION FACTOR USF1 AND ITS CELLULAR DELOCALIZATION BY *HELICOBACTER PYLORI* BACTERIA ENCOURAGE GASTRIC CARCINOGENESIS

The bacterium *Helicobacter pylori* is responsible for the development of gastric cancer (GC). *H. pylori* induces genetic instabilities which play a key role in the carcinogenesis process. Studies developed by Eliette Touati (*Helicobacter pathogenesis*), in collaboration with Marie-Dominique Galibert at the University of Rennes and teams from Mexico and Italy, showed that *H. pylori* inhibits the expression of the transcription factor USF1 and leads to its delocalization at the periphery of cells. This deregulation is associated

with the degradation of the tumor suppressor p53 and the induction of genetic instabilities, thus promoting the oncogenic activity of the infection. Indeed, USF1-deficient mice show a higher severity of the *H. pylori*-induced lesions. Furthermore, in GC patients, low expression of both USF1 and p53 is associated with a worse prognosis. Thus, USF1 has tumor suppressive functions and should be considered as a new biomarker of GC susceptibility.

Source: Costa, et al., Gut., December 10, 2019.



GASTRIC EPITHELIAL CELLS INFECTED BY THE *H. PYLORI* BACTERIUM, SHOWING THE FORMATION OF USF1 FOCI (GREEN).



A PASTEUR MEDICAL MYCOLOGY COURSE PRACTICAL SESSION ON MARCH 22, 2019.

DEPARTMENT OF MYCOLOGY

Over the last thirty years, fungal infections have become a major public health concern. The Department of Mycology focuses its research on the three main fungi responsible for invasive infections: *Aspergillus fumigatus*, *Candida albicans* and *Cryptococcus neoformans*. The aim is to shed light on the biology of these pathogenic fungi, identify their virulence mechanisms and develop new strategies for diagnosis, prevention and treatment. The department is led by Guilhem Janbon.

GENES & IMMUNITY SHOWCASES THE INSTITUT PASTEUR'S EXPERTISE IN FUNGAL INFECTIONS

Following on from the celebrations marking the Institut Pasteur's 130th anniversary, four members of the Department of Mycology produced a literature review on fungal pathogens that was published in both *Microbes & Infection* and *Genes & Immunity*. The authors of the review of recent literature on the subject began by looking back at the history of mycology and its close links with Louis Pasteur's own story. They then outlined various issues associated with epidemiology and challenges in treating diseases caused by fungal pathogens. According to the latest estimates, more than a million people worldwide die every year as a result of these all too often neglected diseases. While considerable progress has been made in terms of knowledge about both the biology of these pathogens and the immunology and pathophysiology of infection, many challenges remain. The development of new diagnostic tools, the discovery of new antifungal treatments and vaccines, and the improvement of knowledge about the epidemiology of fungal infections, the genetics of host susceptibility and the influence of the mycobiota on the immune response represent future avenues for research in the field of medical mycology.

Sources: Janbon G. & al., *Microbes & Infect.*, June 27, 2019.
Janbon G. & al., *Genes & Immun.*, June 25, 2019.



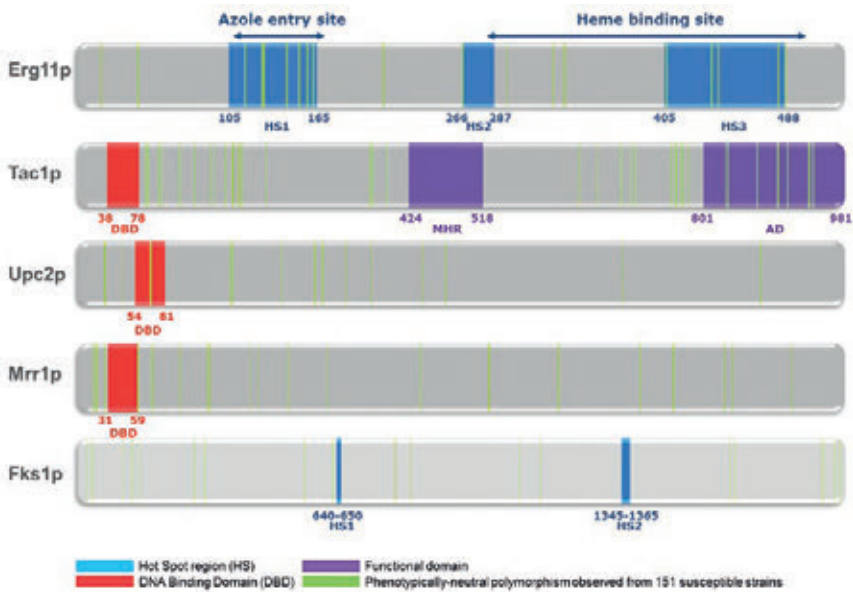
PHOTO OF A CANDIDA ALBICANS COLONY ON RPMI MEDIUM.

CANDIDA ALBICANS: LARGE-SCALE GENOME EXTRACTION TO UNDERSTAND RESISTANCE TO TREATMENT

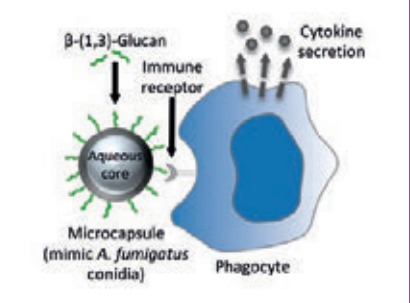
Azoles and echinocandins are the main antifungal agents used for the treatment of invasive candidiasis. The resistance of clinical isolates of *Candida albicans* is a major cause of treatment failure. *C. albicans* is a yeast with considerable genetic polymorphism. Mutations in the genes involved in resistance to antifungal agents may simply be the result of natural polymorphism, or they may induce phenotypic resistance. In this study, we described a repertoire of mutations associated with natural polymorphism observed in the genes

involved in antifungal resistance, using data from the whole genome sequences of 151 antifungal-sensitive strains. We confirmed that this repertoire is an effective tool for the rapid selection of potential mutations of interest in ten *C. albicans* strains with resistance *in vitro* to these antifungal agents. The repertoire is now available for the scientific community, for the rapid identification of mutations that may be responsible for resistance in *C. albicans*.

Source: Sitterlé E. & al., *J Antimicrob. Chemother.*, January 10, 2020.



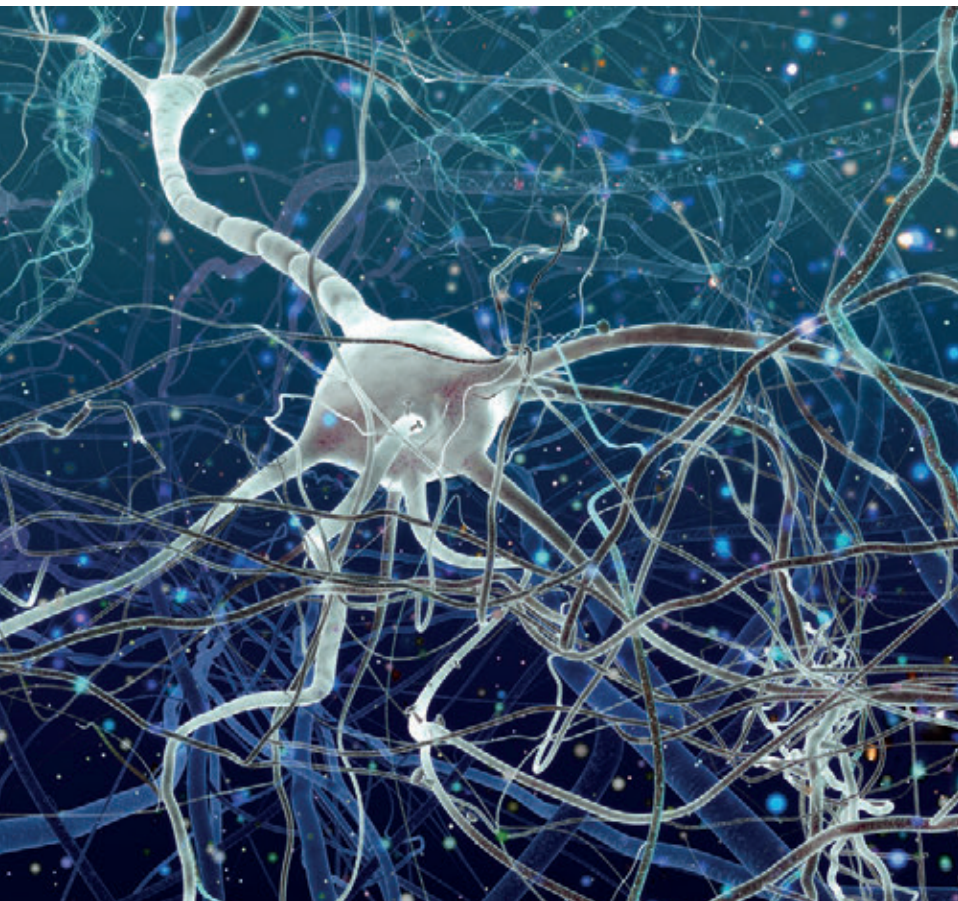
SCHEMATIC MAPPING OF THE PHENOTYPICALLY-NEUTRAL AMINO-ACID SUBSTITUTIONS IN ERG11P, TAC1P, UPC2, MRR1P AND FKS1P OBTAINED FROM DATA OF THE 151 *C. ALBICANS* SUSCEPTIBLE CLINICAL STRAINS.



A TOOL FOR STUDYING THE IMMUNOMODULATORY EFFECT OF MICROBIAL CELL WALL POLYSACCHARIDES

The fungal cell wall is composed mainly of different polysaccharides that are the first components to interact with a host system. In this study, researchers fabricated microcapsules (MCs) with aqueous fluorescent core upon controlled emulsification-condensation between diethylenetriamine and diacyl-chloride. They chemically ligated β -(1,3)-glucan (BG), a major polysaccharide present in the fungal cell wall, on MCs. These BG grafted MCs (BG-MCs) mimicked conidia, the asexual spores produced by *Aspergillus fumigatus*, an airborne opportunistic fungal pathogen. BG-MCs were then used as a tool to study immunomodulatory effect of β -(1,3)-glucan. Researchers successfully showed that the MC-grafted BG elicits better pro-inflammatory response compared to BG alone. MC-grafted BG resembles its arrangement in the conidial cell wall, whereas BG alone in solution aggregates forming particles, suggesting that the organization of BG plays a role in the immune response. Further, the aqueous fluorescent core of the BG-MCs effectively tracked them inside the immune cells, facilitating the identification of immune cell surface receptors involved in the recognition of β -(1,3)-glucan.

Source: Bouchemal K. & al., *Bioconjugate Chemistry*, June 7, 2019.



3D ILLUSTRATION OF NEURONS IN THE HUMAN BRAIN.

DEPARTMENT OF NEUROSCIENCE

The Department of Neuroscience investigates the organization and function of the central nervous system across scales, from the molecules to animal behavior. These studies form the fundamental basis for translational research focused on the mechanisms, pathophysiology, and clinical implications of neurological and psychiatric disorders. These include: hearing loss, developmental disorders (autistic spectrum disorders and dyslexia), addiction, mood disorders and neurodegenerative disease, all of which represent major health challenges for developed countries. The Department is led by David DiGregorio. In 2019, Prof. Christine Petit, a long-time principal investigator in the Neuroscience Department, launched the Hearing Institute, an Institut Pasteur center that maintains a scientific affiliation with the Department. Its inauguration was marked by a speech from the French Prime Minister and an international symposium, with lectures from world experts in the fundamental and translational research in hearing (see pp. 8 and 17).

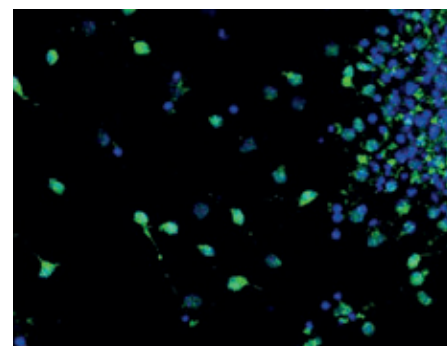
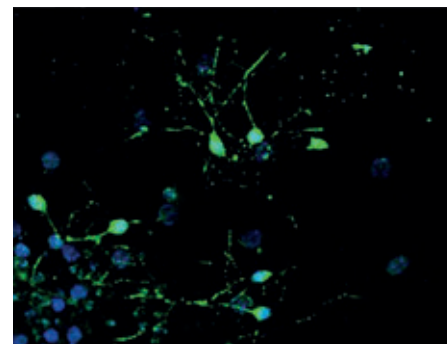


A BLOOD FACTOR INVOLVED IN WEIGHT LOSS AND AGING

Aging is a process that affects all functions of the human body, particularly brain function. It can be delayed, though, with lifestyle changes (physical exercise, restricting calorie intake, etc.). Researchers in the Perception and Memory Unit (Institut Pasteur/CNRS) have elucidated the properties of a molecule in the blood – GDF11 – whose mechanisms were previously unknown. In a mouse model, they showed that this molecule could mimic the benefits of certain calorie restrictions – dietary regimens that have proven effective in reducing cardiovascular disease, preventing cancer and increasing neurogenesis in the brain.

Source: Katsimpardi L. & al., Aging Cell, October 22, 2019.

TOP: NEUROGENESIS INDUCED BY GDF11 SUPPLEMENTATION IN AGED BLOOD.
BOTTOM: ABSENCE OF NEUROGENESIS WITH AGED BLOOD.



EXPLORING THE SOCIAL BEHAVIOR OF MICE TO UNDERSTAND THE BIOLOGICAL BASES OF AUTISM

Autism affects more than one person in every hundred. It is characterized by anomalies in social communication and repetitive behaviors. The first genes associated with this disorder were identified by the Human Genetics and Cognitive Functions team. To investigate their mechanisms, the team generated mice carrying these mutations, but their social behavior proved difficult to analyze. Consequently, the team partnered up with the Bioimage Analysis Unit to develop a monitoring system that combines 3D images, artificial intelligence and radio-frequency identification to automatically and comprehensively characterize the behavior of the mice in small groups of four animals over long periods (several days). The system, known as the Live Mouse Tracker, revealed previously unexplored behavioral differences in mice lacking two genes, Shank2 and Shank3, that are already

associated with autism. The two models presented opposing activity profiles for object exploration and atypical interactions in complex social situations in comparison with non-mutant control mice (*Nature Biomedical Engineering*, 2019). The Live Mouse Tracker improves the reliability and efficacy of behavioral analyses of several mouse models and facilitates the implementation of drug trials. A database (<https://livemousetracker.org/>) has been set up to share these results with scientific colleagues in several countries. The Live Mouse Tracker is free to use and open source, allowing some 29 different teams (from France, the Netherlands, Germany, Japan, South Korea, Switzerland, Austria and the USA) to develop a total of 38 systems in just a year since its publication.

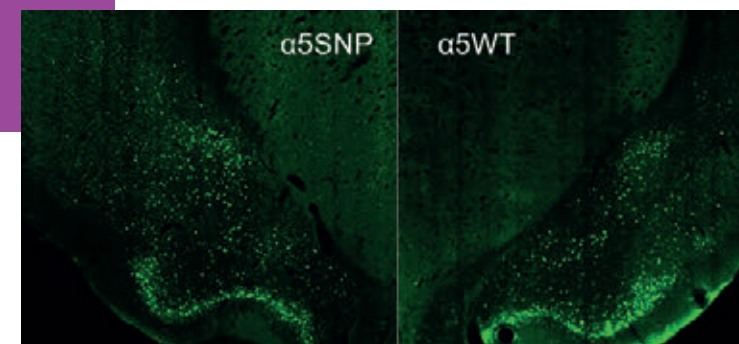
Source: Fabrice de Chaumont & al., Nature Biomedical Engineering, May 20, 2019.

A TOBACCO-DEPENDENCE GENE RESPONSIBLE FOR ALCOHOL DEPENDENCE

Nicotine, which is responsible for most of the addictive properties of tobacco, alters brain function by binding to nicotinic acetylcholine receptors. These receptors are transmembrane channel proteins made up of subunits designated α and β , which can assemble in multiple combinations. A series of human genome-wide studies have revealed a strong correlation between a locus on chromosome 15 (15q25), containing nicotinic subunit genes $\alpha 5$, $\alpha 3$ and $\beta 4$,

and the risk of developing tobacco dependence. One mutation has been identified in particular (rs16969968, or SNP $\alpha 5$). Given the known high comorbidity between tobacco and alcohol addiction, scientists have investigated whether this mutation is also associated with alcoholism. A team from the Institut Pasteur's Integrative Neurobiology of Cholinergic Systems laboratory and the CNRS observed that rats carrying the SNP $\alpha 5$ mutation have a more marked appetite for alcohol and exhibit a greater tendency to relapse to alcohol consumption after abstinence, in association with hyperactivation of the insular cortex, a crucial region for interoception. Molecules that specifically target the activity of nicotinic receptors containing the $\alpha 5$ subunit could be a new therapeutic target of interest in individuals carrying this mutation.

Source: Morgane Besson & al., Neuropsychopharmacology, July 9, 2019.



REPRESENTATION BY IMMUNOFLUORESCENCE OF THE ANTERIOR PART OF THE INSULAR CORTEX AND THE CLAUSTRUM, A THIN LAYER OF GRAY MATTER IN THE BRAIN.



TSÉ TSÉ FLY (*GLOSSINA MORSITANS*).

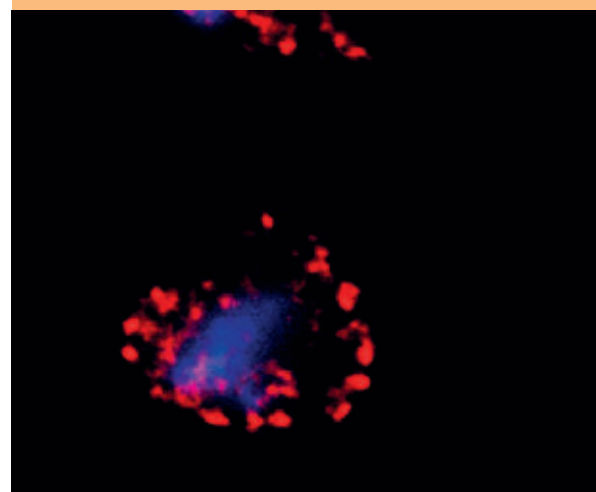
DEPARTMENT OF PARASITES AND INSECT VECTORS

The Department of Parasites and Insect Vectors conducts research on the three key eukaryotic parasites responsible for severe diseases of major public health concern that generate an important economic burden in the world's most populous regions. These are: *Plasmodium*, which causes malaria; *Leishmania*, the agent of leishmaniasis; and *Trypanosoma brucei*, responsible for sleeping sickness. The Anopheles mosquito, which is the vector of *Plasmodium* and other viruses, is also studied, as well as the tsetse fly, the vector for *Trypanosoma brucei*. The department is led by Gerald Spaeth.

TARGETING A PHOSPHOLIPASE TO BLOCK MALARIA TRANSMISSION

Plasmodium falciparum gametocytes ingested by Anopheline mosquitoes are activated in the midgut and transform into gametes. The process of gametogenesis involves the rounding up of activated gametocytes, transformation into gametes and egress from red blood cells. We have used a genetic approach to explore the role of a novel patatin-like phospholipase, PfPATPL1, in this process. We demonstrated that deletion of the gene encoding PfPATPL1 results in reduced efficiency of gametocyte rounding up and reduced secretion of perforin-like protein, PfPLP2, which ruptures peripheral membranes to enable egress. Importantly, we also demonstrated that genetic deletion of PfPATPL1 reduces the efficiency of transmission of malaria parasites in mosquitoes. Our study thus identifies PfPATPL1 as a key player in the process of gametogenesis and identifies this phospholipase as a potential target to inhibit malaria transmission.

Source: Singh P. et al., Proc Natl Acad Sci USA, August 27, 2019.



SECRETION OF PERFORIN-LIKE PROTEIN, PFPLP2, DURING EGRESS OF *P. FALCIPARUM* GAMETES.

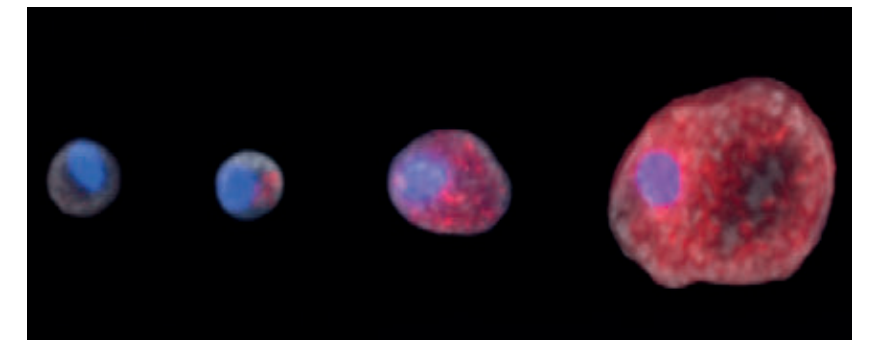
NUCLEAR ATTACK: *LEISHMANIA* INTERFERES WITH THE EPIGENETIC PROFILE OF ITS MACROPHAGE HOST CELL

Leishmania parasites have evolved molecular strategies to exploit mammalian macrophages as host cells, often with devastating consequences for infected individuals. Analyzing *Leishmania* infection in murine macrophages *in vitro* and *in vivo*, Gerald Spaeth's team established the first experimental proof that this dominant human pathogen remodels the host cell chromatin during infection to establish permissive conditions for persistent, intracellular parasite survival. The team showed that the strong reduction of two distinct histone H3 activation marks, i.e. H3K9/K14 acetylation and H3K4 trimethylation, at host pro-inflammatory promoter genes correlates with decreased expression of crucial NF-κB and inflammasome activators.

This finding uncovers a major novel mechanism underlying the strong anti-inflammatory and immune subversive properties *Leishmania*

exerts on its host cell, and opens interesting new venues for host-directed, anti-microbial drug discovery.

Source: Lecoecur et al., Cell Reports, February 11, 2020.



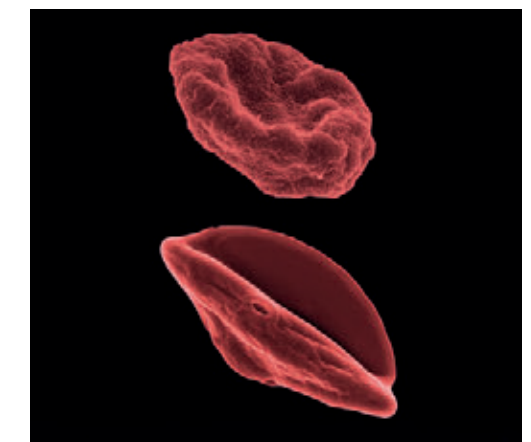
MACROPHAGES ISOLATED FROM *LEISHMANIA AMAZONENSIS* INFECTED SKIN LESIONS SHOWING DIFFERENT INFECTION LEVELS. RED, MCHERRY TRANSGENIC PARASITES; BLUE, MACROPHAGE NUCLEUS.

MULTIPLE EPIGENETIC LAYERS CONTROL MALARIA PARASITE DEVELOPMENT DURING THE LIFE CYCLE

Malaria parasite virulence and transmission are controlled by a particular gene activation control system (called variegated gene expression) that enables chronic infection via immune evasion (antigenic variation) and commitment to sexual stages. By studying the underlying epigenetic basis, the Scherf team made several key discoveries in 2019. They identified a non-canonical DNA cytosine modification that is linked to gene activity. Furthermore, dynamic methylation of the messenger RNA (N⁶-methyladenosine, m6A) modulates the expression of parasite proteins most likely via m6A specific reader proteins, demonstrating the presence

of a posttranscriptional layer of epigenetics. In collaboration with a medicinal chemist (Paola Arimondo), the team identified several novel compounds that target epigenetic factors with a robust killing effect on multidrug-resistant *P. falciparum* parasites. This work opens new avenues into so far unknown parasite biological processes and identifies new targets for intervention strategies.

Sources: Nardella F. et al., ACS Cent Sci., January 22, 2020. Baumgarten S. et al., Nat Microbiol., August 5, 2019. Hammam E. et al., Nucleic Acids Res., January 10, 2020.



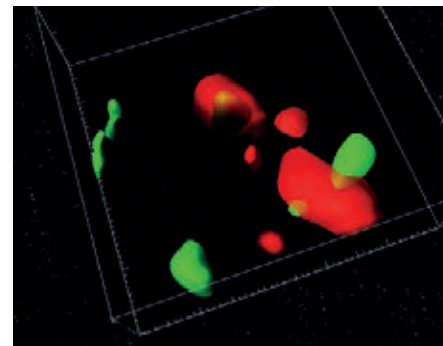
P. FALCIPARUM VIRULENCE AND DEVELOPMENTAL SWITCHES TO TRANSMISSION STAGES DEPEND ON VARIEGATED GENE EXPRESSION.



HEPATITIS B VIRUS (HBV).

DEPARTMENT OF VIROLOGY

The Virology Department focuses its research on viruses – their molecular organization, pathogenicity determinants, multiplication and interactions with host defense mechanisms. The viruses under study include respiratory viruses such as influenza and the novel coronavirus (SARS-CoV-2); 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, microcephaly caused by the Zika virus, and Rift Valley fever; and viruses causing hemorrhagic fever (such as the Lassa fever and Ebola viruses). The department is led by Sylvie van der Werf, also Head of the National Reference Center for Respiratory Viruses (Including Influenza), which is actively involved in surveillance and research on the novel coronavirus (SARS-CoV-2).



ASSEMBLED HEPATITIS B VIRUS (GREEN) ENCAPSIDATING THE RESTRICTION FACTOR DNASE I (RED). IN THE BACKGROUND, THE WHITE DOTS ARE SINGLE HBV VIRAL PARTICLES, WHICH TOGETHER RESEMBLE HUNDREDS OF STARS.

DNASE I, A NOVEL RESTRICTION FACTOR FOR HEPATITIS B VIRUS

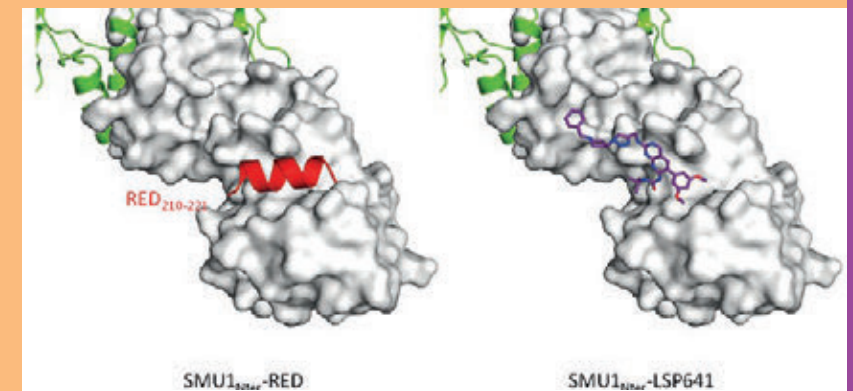
Hepatitis B virus (HBV) infects the liver cells and is responsible for acute and chronic infection. Although several antiviral treatments can effectively inhibit HBV replication, they are not curative and do not fully eliminate the virus. The virus needs to be eliminated in chronic carriers to prevent the disease from developing into cancer. In this study, the Institut Pasteur's Molecular Retrovirology Unit and scientists from the Montpellier Infectious Disease Research Institute demonstrated that DNase I, a cellular protein capable of degrading DNA, is incorporated into viral particles and induces degradation of the HBV genome. This protein, considered as a novel antiviral restriction factor, is expressed *in vitro* in a hypoxic (oxygen-depleted) environment, and also in patients infected with HBV. The aim of the research is to use this protein to produce viral particles containing DNase I that can act as "Trojan horses", targeting infected liver cells and inducing the degradation of the viral and cellular DNA in them.

Source: Hallez C. & al, Nat Microbiol., April 1, 2019.



TARGETING HOST PROTEINS TO TACKLE INFLUENZA VIRUSES

The Influenza Virus-Host Cell Interactions group, in cooperation with scientists from the Structural Biology Institute (IBS) and Paris Descartes University, set out to target a cell component that plays a vital role in influenza virus replication, the RED-SMU1 splicing complex. Using crystallography, modeling and molecular virology approaches, they identified synthetic molecules that interfere with RED-SMU1 complex assembly (see figure). The scientists

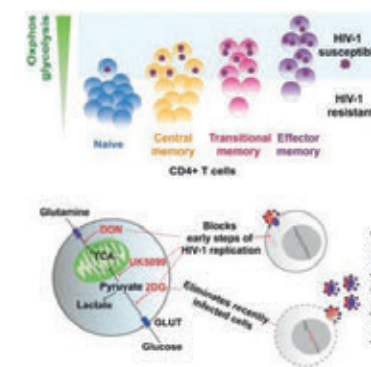


N-TERMINAL DOMAIN OF THE SMU1 PROTEIN IN COMPLEX WITH A SHORT ALPHA-HELIX OF THE RED PROTEIN (ON THE LEFT) OR WITH THE LSP641 MOLECULE THAT INHIBITS THE ASSEMBLY OF RED-SMU1 COMPLEX (ON THE RIGHT).

demonstrated that these molecules reduce the intracellular rate of RED-SMU1 complex and inhibit viral mRNA splicing and viral multiplication, while preserving cell viability. These data pave the way for the development of a new antiviral strategy that is

potentially effective against a broad spectrum of influenza viruses and less likely to be affected by the development of drug resistance than the antiviral drugs currently in use.

Source: Ashraf U. & al., Proc Natl Acad Sci USA., May 28, 2019.



SUSCEPTIBILITY TO HIV INFECTION IN A SUBPOPULATION OF CD4 CELLS WITH HIGH METABOLIC ACTIVITY AND INHIBITORS USED TO BLOCK THESE PATHWAYS.

CELLULAR METABOLISM, A MAJOR DETERMINANT IN HIV-1 INFECTION IN CD4+ T CELLS

The antiretroviral therapy currently in use is designed to block HIV infection but is not capable of eliminating the virus from the body. The virus persists in reservoir cells, CD4 T lymphocytes, which are the main targets of HIV. In this study, scientists from the Institut Pasteur's HIV, Inflammation and Persistence Unit and their colleagues identified the characteristics of the various subpopulations of CD4 cells associated with HIV infection. Experiments have shown that it is the metabolic activity of the cell,

and in particular its glucose consumption, which plays a key role in susceptibility to HIV infection. The virus mainly targets cells with high metabolic activity, and to multiply it, hijacks the energy and products provided by the cell. This requirement represents a weakness for the virus that could be exploited to target infected cells. The scientists successfully blocked infection *ex vivo* using metabolic activity inhibitors that have already been investigated in cancer research.

Source: Valle-Casuso JC & al., Cell metabolism, March 5, 2019.



GROUP OF CHILDREN IN SENEGAL IN 2008.

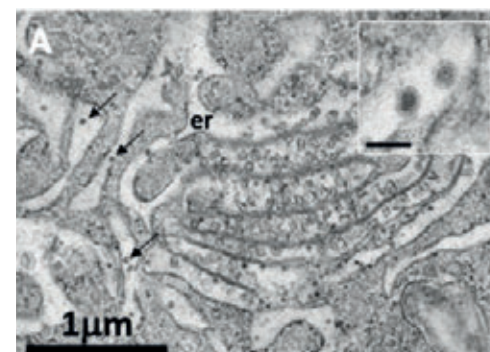
DEPARTMENT OF GLOBAL HEALTH

The Department of Global Health adopts an interdisciplinary approach for the investigation of global public health issues. The department's work ranges from basic science to clinical research, and it also aims to consolidate the actions of Institut Pasteur teams worldwide in the interdependent fields of human, animal and environmental health (the One Health approach). It works in close collaboration with institutions around the world, especially those in the Institut Pasteur International Network, with the support of National Reference Centers (CNRs) and WHO Collaborating Centers (WHOCs). The department particularly focuses on all aspects of emerging and re-emerging infectious diseases: reservoirs and mechanisms of transmission and persistence of pathogens in their environment, virulence factors, host pathophysiological processes, the innate immune response and the role of vaccines. The department is led by Arnaud Fontanet.

IDENTIFICATION OF AN ATTENUATION MECHANISM IN FLAVIVIRUSES

West Nile virus (WNV), a member of the *Flavivirus* genus and currently one of the most common arboviruses worldwide, is associated with severe neurological disease in humans. Despite its global reemergence, there is currently neither treatment nor human vaccine available to cure or prevent the disease. The membrane glycoprotein (M) has been associated with virus-induced pathogenesis. Researchers identified a key amino acid residue at position 36 of the M protein whose mutation impacts WNV secretion and promotes viral attenuation. They also identified another amino acid at position M-43 whose mutation stabilizes M-36 substitution both *in vitro* and *in vivo*. Moreover, they found that introduction of the two mutations together conferred a full attenuation phenotype and protection against a lethal challenge with wild-type WNV, eliciting high neutralizing antibody production in mice. This study thus establishes the M protein as a new viral target for rational design of attenuated WNV strains. Applied to other flaviviruses, this approach should help in designing new vaccines against these viruses that are an increasing threat to global human health.

Source: J. Basset & al., J. Virol., April 8, 2020.

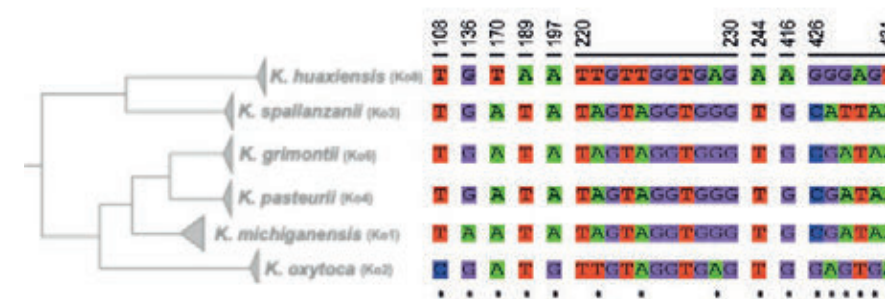


DESCRIPTION OF TWO NEW SPECIES OF BACTERIA RESPONSIBLE FOR ANTIBIOTIC-ASSOCIATED HEMORRHAGIC COLITIS

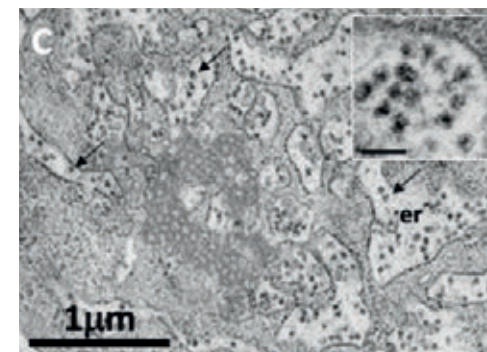
Bacteria of the group, *Klebsiella*, include emerging pathogens that cause multidrug resistant infections in humans and animals. Accurate classification and a diagnosis of the various members of this group is the first step towards defining their clinical importance and tracking their global epidemiological spread. Two novel species of *Klebsiella* were discovered in collaboration with the University

of Pavia, and were integrated in the microbial taxonomy as *Klebsiella pasteurii* and *Klebsiella spallanzanii* in recognition of the contribution of Louis Pasteur and Lazzaro Spallanzani to rejection of the spontaneous generation theory for microbes. Both species were isolated from environmental sources and humans. They are related to, but distinct, from *Klebsiella oxytoca*, which causes antibiotic-associated hemorrhagic colitis. Biomarkers for their rapid identification were discovered, which will allow microbiology laboratories to detect them in human infections.

Source: Merla C & al., Front Microbiol., October 25, 2019.



M-36 MUTANT WNV PARTICLES ARE RETAINED WITHIN THE ER LUMEN OF INFECTED MAMMALIAN CELLS.



A NEW ABRIDGED REGIMEN FOR RABIES POST EXPOSURE PROPHYLAXIS

When the rabies virus is transmitted after the bite of a rabid dog, death ensues in all cases. Timely access to adequate rabies post-exposure prophylaxis (PEP) prevents RABV transmission in ~100% of cases but remains a challenge in developing endemic countries, especially for rural and poor populations. A research program was rolled out at the Institut Pasteur du Cambodge (IPC) with the Institut Pasteur (Paris) to explore the abridgment of the established one-month/four intradermal (ID) session schedule.

The researchers undertook a thorough epidemiological review of clinical outcomes in PEP noncompleters after a bite by a confirmed rabid or sick-looking dog and a prospective self-controlled serological study among patients bitten by confirmed rabid dogs.

The robust findings led the World Health Organization to adopt the new, one-week/ three ID sessions "IPC protocol" in its updated guidelines. This reduces direct (health) and indirect (travel) costs and improves equity of access to PEP. This vaccination schedule is now used in nine countries.

Source: Cantaert T & al., Lancet Infect Dis., December 2019; 19(12):1355-1362.

DEPARTMENT OF TECHNOLOGY AND SCIENTIFIC PROGRAMS

The Department of Technology and Scientific Programs is committed to developing a very high-level technological environment to further enhance the outstanding research conducted at the Institut Pasteur.

17 C2RT
UNITS

3 C2RA
UNITS

1 SPIS
UNIT

The Department of Technology and Scientific Programs, which is structured around its three centers of expertise (C2RT, C2RA, and SPIS)*, helps scientific departments achieve their goals in terms of outstanding research. It aspires to meet their current and future technological and animal testing requirements, while also supporting research through the introduction of incentive measures in line with the Institut Pasteur's scientific strategy. Its new Vice-President, Michael Nilges, was appointed in 2020. Throughout 2019, the Department of Technology and Scientific Programs under Christophe d'Enfert provided research teams with access to infrastructure equipped with cutting-edge equipment and managed by high-level experts. In consultation with the scientific departments, the Department of Technology and Scientific Programs has adopted a policy of pooling and partnership with regard to strategic equipment requirements. Moreover, in close collaboration with the Information Systems Department, the Department of Technology and Scientific Programs helps develop and deploy digital technology for scientists on campus and enhance internal computation and storage resources (see inset 1 on right-hand page).

A dynamic continuum based on coordination of the Department of Technology and Scientific Programs' three centers of expertise and visibility of their activities

The scientific departments tap into technological expertise offered by **Center for Technological Resources and Research (C2RT)** units, notably:

- by accessing cutting-edge technologies and methodologies and their developments;
- and through training on the use of certain pieces

of equipment, giving them greater independence. The C2RT offers a diverse arsenal of technologies covering omics analyses now extended to single-cell studies, multi-scale imaging applied to host-pathogen interactions, nanoimaging with the expansion of our cryo-electron microscopy capabilities, biomolecule design, production and structural analysis, cell sorting and phenotyping, microfluidics, and 3D cell culture (with the introduction of organ-on-a-chip technology).



Moreover, the scientific departments can rely on the **Center for Animal Resources and Research (C2RA)** to meet their animal testing requirements, with its Central Animal Facility (AC), Mouse Genetics Engineering Center (CIGM), and Center for Production and Infection of Anopheles (CEPIA). The C2RA provides the infrastructure required for *in vivo* analysis of biological processes and validation of preventive and therapeutic approaches, particularly through animal testing performed under optimal ethical and regulatory conditions.

In consultation with the scientific departments, the Department of Technology and Scientific Programs has also drawn up a document setting out best practices to be implemented by research teams and technological platforms to save everyone time, providing as many people as possible with access to platforms (see inset 2 on page 48).

Finally, the Center for Scientific Incentive Programs (SPIS), which coordinates the introduction of scientific incentive measures, provides campus and International Network units with: (1) calls for proposals and (2) focused scientific events (see inset 3 on page 49).

* The Center for Technological Resources and Research (C2RT), the Center for Animal Resources and Research (C2RA), and the Center for Scientific Incentive Programs (SPIS).

1

SET-UP OF THE HIGH-PERFORMANCE COMPUTING (HPC) TECHNOLOGICAL PLATFORM

The purpose of this new technological platform led by Youssef Ghorbal is to design, set up, and maintain HPC infrastructure for Institut Pasteur scientists. In addition to installing and managing HPC clusters (administration, availability, upgrading), the technological platform provides support and advice on cluster onboarding and optimal use of resources. The technological platform also provides a wide range of bioinformatics software in the clusters and offers its expertise on optimizing this software and scientists' codes. Finally, the platform develops specific software, which is industrialized in collaboration with Institut Pasteur research units.



COMMUNICATION AND BEST PRACTICES

In collaboration with the scientific departments, the Department of Technology and Scientific Programs has drawn up a best practices guide aimed at maximizing access and optimizing collaboration between C2RT and C2RA teams throughout the lifespan of a project. **In addition, two separate brochures on the C2RT and C2RA have been prepared and disseminated.** These brochures give research teams an overview of:

- the expertise, know-how and services offered by the 20 platforms at the C2RT and C2RA to help them progress with their projects;
- the steps to follow if they want to ask for more information from a specific platform, submit a request, or start a collaborative project.

OVER 200 PEOPLE WORK AT THE DEPARTMENT OF TECHNOLOGY AND SCIENTIFIC PROGRAMS

87% ENGINEERS AND TECHNICIANS

13% ADMINISTRATIVE STAFF

QUALITY

6 UNITS ARE ISO9001 CERTIFIED

9 UNITS HAVE IBISA ACCREDITATION

New services, tools, and methods for 2019

Independent access to equipment

C2RT and C2RA units set up tailored training on the independent use of certain pieces of equipment. Some of the Biomix technological platform's state-of-the-art equipment can be used independently by accessing a special room for DNA microarray genotyping and a room for performing all stages of high-throughput sequencing. The Production and Purification of Recombinant Proteins Platform (PF3PR) set up tailored training on expression in prokaryotic systems and protein purification. This training enables scientists to use the platform's chromatography systems independently and provides them with autonomy in their experimental approach with regard to recombinant proteins.

New technological resources provided

C2RT and C2RA units also provided Institut Pasteur scientists with several new technological and experimental resources. Using joint funding from the Greater Paris Region, the Photonic Biolmaging (PBI) UTechS installed a high content screening (HCS) system to support research on complex disease models. In partnership with Institut Pasteur Korea, the PBI UTechS is developing the HCS system and introducing new paradigms using artificial neural networks. The Biological NMR Platform incorporated hydrogen/deuterium exchange mass spectrometry (HDX-MS) technology, a powerful structural biology tool that works in tandem with NMR, crystallography, and cryo-electron microscopy. Using the HDX-MS technology, it is possible to characterize protein interactions, changes in protein conformation and dynamics, and protein folding.

New tools and methods

In 2019, the CIGM optimized the zygote electroporation technique to enable the integration of all forms of CRISPR/Cas9 systems, with the aim of generating new lines of targeted transgenic mice. The Central Animal Facility provides mice with controlled microbiota for in-depth studies on how the microbiota and its constituents are related to the emergence of various diseases, including autoimmune disorders.

The Cytometry and Biomarkers UTechS introduced the Nano Sorting method, which optimizes the ability of high resolution flow cytometers to detect, analyze and sort subcellular vesicles. Applying this approach to virus sorting, the scientists attained a higher resolution than the theoretical sensitivity limits and were able to characterize HIV virions. Their findings open up new possibilities for research into the biodiversity and pathogenicity of nanoparticles.

The Ultrastructural Biolmaging UTechS developed cryo-CLEM techniques (combining fluorescence microscopy and cryogenic electron microscopy).



LAUNCH OF NEW INCENTIVE MEASURES

To promote the emergence of projects and talent within the Institut Pasteur and its International Network, the SPIS launched two new calls for Transversal Research Program (PTR) and Inter-Pasteurian Concerted Action (ACIP) proposals (in collaboration with the Department of International Affairs) in 2019, aimed at supporting collaborative research projects in line with the 2019-2023 Strategic Plan. The SPIS joined forces with the Center for Translational Science (CRT) to organize the "Antibio-Storm" scientific activity day on antibiotic resistance with a view to promoting collaboration between Institut Pasteur scientists and Paris Public Hospital Network (AP-HP) clinicians. In connection with the Brain Connectivity and Neurodegenerative Diseases priority scientific area, the SPIS and the Brain and Spine Institute (ICM) jointly organized a **symposium entitled "Neurosciences and Disease"**.



THE TECHNOLOGICAL OBJECTIVES OF THE DEPARTMENT OF TECHNOLOGY AND SCIENTIFIC PROGRAMS

- Step up our analysis and artificial intelligence capabilities through an appropriate strategy.
- Boost internal resources for computing, storage, and networking.
- Establish a new infrastructure for simultaneous analysis of the host, vector and pathogen under biosafety level 3 containment conditions (animal facility, insectarium, imaging capabilities).
- Offer a set of cryo-electron microscopes enabling ultrastructural analysis in the cellular environment.
- Offer shared metabolomics resources for sample preparation and analysis.
- Step up our capabilities for offering humanized animal models.
- Boost our ability to identify novel diagnostic and therapeutic solutions.
- Implement shared electronic data collection and analysis (ELN, LIMS).

DEPARTMENT OF INFORMATION SYSTEMS

In addition to its role ensuring that IT infrastructure and equipment is fully functional for all Institut Pasteur staff, the Information Systems Department also has an important part to play within a cutting-edge research institute. In accordance with the Institut Pasteur's 2019-2023 Strategic Plan, the Information Systems Department is tasked with *"boosting internal resources for computing, storage and networking, and developing partnerships with cloud solution providers"*.

The Institut Pasteur boasts a cutting-edge technological facility underpinned by innovative technologies thanks in part to three key projects that received special investment in 2019 and featured in the Strategic Plan. Their contribution was to support research requiring significant computing resources, and provide scientists with high-performance IT equipment, services, and autonomy.

Facilitating access to big data

10 Gbps high-speed Internet connections are available to all laboratories that request them. Their rollout began in 2019 and is being continued in 2020. This equipment allows real-time access to big data, an increasingly important scientific requirement. Every day, scientists transfer data from the centralized storage space to their workstations. Some of the disciplines involved include computational biology, which uses genomic data, and neuroscience (a key focus of the Strategic Plan) through artificial intelligence projects. In particular, cryo-electron microscopy has benefited, with images produced by one of the world's most powerful microscopes, the Titan Krios™ generating huge quantities of data that would have been impossible to manipulate several years ago. Moreover, the powerful Internet connection (several times 10 Gbps with several operators) facilitates interaction with partners in France and throughout the world.

Increasing data storage capacity

In 2019, the Institut Pasteur's internal storage capacity reached 25 petabytes (PB). This equates to 25 million billion characters (the size of a FASTQ file containing a human genome is 200 gigabytes) used to store and safeguard data generated

by scientists' work, which constitutes the Institut Pasteur's scientific heritage.

Boosting computing and analysis power

Big data analysis raises technological issues in terms of computing power. Reflecting scientists' faith in the Information Systems Department, a working group reporting both to the Information Systems Department and the Department of Technology and Scientific Programs installed a supercomputer with similar power to national computers in a "mesocenter" (a type of computing cluster similar to those shared by several universities) to analyze big data. This computing cluster has become more powerful year-on-year (7,000 processor cores in 2019 compared to approximately 10,000 in 2020). From 2020, a steering committee will periodically set priorities for this cluster and determine how it can best meet Institut Pasteur requirements.

In addition to these three major projects, a fourth project will see full WiFi coverage of the Paris campus.

Creating data management resources

The Information Systems Department set up a data management group tasked with structuring datasets to enable their reuse and long-term storage. This group has built a number of solutions for scientists.

→ **A solution based on the REDCap** software developed by Vanderbilt University in the US to manage online databases (especially for clinical trial follow-up). REDCap is now integrated in the Institut Pasteur information system. The institute is

a bridgehead for the promotion of this tool in France, coordinating the entire French user community. The Information Systems Department is rolling out REDCap on the Paris campus and within the International Network. It also delivered a course in Cambodia on how to use the tool.

The data management group works closely with the Scientific Secretariat General, which has drawn up a data management plan, now a prerequisite for increasing numbers of funding bodies. Due to the significant increase in demand for data management, a separate platform reporting to the Department of Technology and Scientific Programs has been set up. The Information Systems Department views this as a mark of success.

Considering new tools that are technologically useful to campus staff

→ **Supplying the "Owey" cloud platform** providing scientists with the following services: very high-capacity hosting, instant data sharing between remote sites, personalized and restricted access to certain data, securing particularly sensitive project data (using data silos), data structuring (organized by geographic site supplying the data, patient visit, etc.) essential to large-scale projects, standardization of data generated by different sources (various telemedicine platforms, hospital platforms for antibiotic resistance studies, data platforms for various research teams that annotate genes in different ways, etc.), and metadata management. Owey is a datalake (a database with powerful analytical tools) developed as part of the Inception* project, and is tailored both to pooling data from around the world and multi-disciplinary research. In particular, the Information Systems Department

collaborated with the team led by Thomas Bourgeron, Head of the Human Genetics and Cognitive Functions Unit, which works on autistic spectrum disorders. As a result, Owey now hosts European data from the AIMS-2-TRIALS project, one of the world's most valuable multidisciplinary databases for clinical research on autism. Finally, by interfacing REDCap with Owey, the Information Systems Department has created a unique system enabling automated sharing in line with participants' consent.

→ Enabling scientists to develop *ad hoc* tools.

The OWEY platform is based on Kubernetes infrastructure. This provides users (bioinformaticians, scientists) with maximum autonomy to create their own tools, deploy them, and potentially publish them online. Drawing on this expertise, the Information Systems Department now offers scientists agile solutions. The CRISPR Browser** developed by the Synthetic Biology Unit led by David Bikard is one illustration of this. This type of "scientist-led" development has proved more flexible, faster, and less expensive than previous approaches.

→ Promoting the use of artificial intelligence algorithms.

In recent years, the Information Systems Department has integrated cards (GPGPUs) in its computing systems enabling artificial intelligence (AI) algorithms to be run. In tandem with the Kubernetes infrastructure, these cards helped Christophe Zimmer's Imaging and Modeling Unit to devise several methods based on recent AI developments, which has led to scientific publications in the past two years. These include the ANNA-PALM*** method (for improving microscopy techniques) developed in 2018 and the ImJoy**** software (facilitating the adoption of AI in the biomedical community) produced in 2019. It is worth noting that the Institut Pasteur forged a partnership with NVIDIA, which invented the graphics processing units that are now also widely used in AI algorithms (NVIDIA's expertise proved useful for recent work carried out by the Decision and Bayesian Computation five-year group led by Jean-Baptiste Masson).

→ Deploying virtual desktop infrastructure (VDI) solutions.

Virtual desktops and workstations are useful for providing scientists with rapid access to software platforms without them physically needing to travel if these platforms have significant system requirements. This VDI solution optimizes scientists' time, enabling them to engage in distance learning, present tools at overseas conferences without having to travel with their workstations, and share large software tools among several users. This solution has notably been deployed for the Image Analysis Hub led by Jean-Yves Tinevez.

* Convergence Institute for the emergence of pathologies through individuals and populations

** <https://crispr-browser.pasteur.cloud>

*** <https://annapalm.pasteur.fr>

**** <https://imjoy.io>





ACADEMIC PARTNERSHIPS WITHIN FRANCE

The Institut Pasteur has a longstanding history of research and/or teaching partnerships with research institutions and universities in the Greater Paris region. One of the objectives of the 2019-2023 Strategic Plan is to consolidate and develop national partnerships to drive scientific excellence within the Institut Pasteur.

These partnerships with other institutions enable the Institut Pasteur to pursue four broad aims.

- To **formalize and consolidate** links with regional partners that facilitate the creation of joint units based at and/or outside the Institut Pasteur.
 - To **provide a framework** for researchers from these institutions to come and work on the Institut Pasteur's campus and Institut Pasteur researchers to spend time at external research organizations, schools and universities, accompanied by post-doctoral fellows and engineers where appropriate.
 - To **identify** potential scientific research organizations, teams and projects that could be associated with these partnerships and lead to opportunities for joint research units and researcher mobility.
 - To **promote** outstanding teaching and enhance the Institut Pasteur's appeal for future generations of scientists.
- Partnerships are governed by specific agreements, sometimes in connection with existing framework agreements that set the terms for cooperation (see inset).

An innovative partnership for the Hearing Institute

In 2019, the Institut Pasteur launched the Hearing Institute, demonstrating its commitment to pursuing innovative partnerships that advance science. This Institut Pasteur center carries out basic and medical research from an interdisciplinary perspective. It promotes an integrative approach to auditory neuroscience, with the aim of developing innovative diagnostic methods and preventive and curative treatments for hearing loss. The Hearing Institute is affiliated with Inserm through

a joint research unit. It also hosts CNRS teams. It was set up in partnership with the Fondation Pour l'Audition, which provides support and financial backing.

Partnerships with EPSTs

The Institut Pasteur's longest-standing partners among France's Public Scientific and Technical Research Establishments (EPSTs) are the CNRS and Inserm. A number of research structures are currently based at the Institut Pasteur campus, including accredited research teams (ERLs), joint research units (UMRs) and service and research units (USRs). These structures are jointly affiliated, either to the Institut Pasteur and the CNRS (one ERL, 10 UMRs and two USRs, including the Center for Bioinformatics, Biostatistics and Integrative Biology (set up in 2015)), or to the Institut Pasteur and Inserm (12 UMRs, one of which is based on the Necker campus (Institut Pasteur and Institute Imagine)). The Institut Pasteur also hosts a joint Institut Pasteur-INRAE (French National Research Institute for Agriculture, Food and Environment) unit. Finally, two joint units were set up on the Institut Pasteur campus to promote interdisciplinary research combining experimental approaches and methodological developments, one in partnership with the French National Research Institute for the Digital Sciences (Inria) and the other with the École Polytechnique and CNRS.

Partnerships with universities

These partnerships cover both research – five joint units are hosted on the Institut Pasteur campus, mainly jointly affiliated with Université de Paris – and teaching. Fourteen courses

can be included as part of a Master's program (first- or second-year Master's) at our partner universities (Université de Paris, Sorbonne Université, ENS/PSL, Paris-Saclay), 13 Institut Pasteur courses lead to the award of a university diploma (DU), and more than 20 courses count as doctoral school modules. Most of the courses are run jointly with Université de Paris, Sorbonne Université, Université Paris-Saclay and Paris Sciences et Lettres (Université PSL). Twelve Institut Pasteur courses are eligible for ECTS (European Credit Transfer System) credits from the Pasteur/CNAM School which awards the Advanced Master's in Public Health, accredited by the French Conférence des Grandes Ecoles. Finally, the "Médecine-Sciences" program is run in partnership with the École normale supérieure (ENS), Institut Curie and PSL.

Partnerships with the Paris Public Hospital Network

To support research projects that associate the basic research conducted by the Institut Pasteur's teams with translational and clinical research, the Institut Pasteur and the Paris Public Hospital Network (AP-HP) annually publish joint calls for proposals to host hospital-based physicians, either as guest researchers or via a partnership contract, or to set up joint units on the Institut Pasteur campus. Three joint units were set up for a five-year period in 2016, and a dual-site Institut Pasteur/AP-HP/Paris-Sud University joint research unit was set up in 2013.

Hosting scientists from external research organizations (OREX)

The joint units hosted at the Institut Pasteur are partly composed of OREX scientists and engineers from EPSTs, universities, and the AP-HP, etc. The Institut Pasteur currently hosts 142 scientists and 36 engineers employed by partner institutions, mainly from the CNRS (81 scientists and 17 engineers), Inserm (37 scientists and 16 engineers) and Université de Paris (13 scientists/lecturers and 5 university hospital scientists/lecturers).



BASIS FOR RESEARCH PARTNERSHIPS

- Research field, program and length of the partnership.
- Scientific leaders of the project and staff involved.
- Allocation of skills, staff, human and financial resources and equipment.
- Expenditure forecast and funding of the partnership.
- Commercialization of results (publications, intellectual property, etc.).

BASIS FOR TEACHING PARTNERSHIPS

- Course title, program and length, qualification(s).
- Course coordinators and composition of organizing committees.
- Student selection process and numbers.
- Allocation of skills, staff, human and financial resources and equipment among the parties.



HERVÉ BOURHY

HEAD OF THE FRENCH NATIONAL REFERENCE CENTER FOR RABIES, ALSO A WHO COLLABORATING CENTER, AND HEAD OF THE LYSSAVIRUS EPIDEMIOLOGY AND NEUROPATHOLOGY UNIT
SEE PAGES 45 AND 78 TO READ ABOUT A NEW RABIES TREATMENT PROPOSED BY HERVÉ BOURHY AND HIS COLLEAGUES. LEARN MORE ABOUT THE INSPIRATION BEHIND THE PICTURES ABOVE ON PAGE 96.

2. PUBLIC HEALTH MISSION

A key challenge facing the Institut Pasteur is how best to address today's public health issues and anticipate future health needs. It is committed to strengthening the link between scientists and patients through epidemiological surveillance and clinical research.

CENTER FOR TRANSLATIONAL SCIENCE (CRT)

The Center for Translational Science (CRT) promotes the transfer of knowledge from academic research to the clinical field, and vice versa. The center is a place where clinicians can develop new research ideas, improve our understanding of disease and enhance patient care.

Professor Bruno Hoen was appointed as Medical Research Director for the Institut Pasteur and the Center for Translational Science in October 2019. Professor Hoen specializes in infectious and tropical diseases, especially infective endocarditis, bacterial meningitis and HIV infection. He previously served as Head of Department at the university hospitals in Besançon, Guadeloupe and Nancy.



SUPPORT FROM THE CRT FOR THE 2019-2023 STRATEGIC PLAN

- A meeting was organized for scientists and physicians from the Institut Pasteur and the Brain and Spine Institute to strengthen the partnership between the two structures.
- Twelve events were held in 2019 to boost cooperation between scientists and medical professionals.
- Agreements were concluded with 11 hospital practitioners to develop translational projects in 2019.



Developing partnerships with medical facilities and attracting physicians to the campus

Since the CRT was set up in 2014, partnership agreements have been concluded with the AP-HP, Necker Hospital and Sainte-Anne Hospital. The CRT also provides funding so that junior and more experienced hospital professionals, both physicians and pharmacists, can be hosted in Institut Pasteur research units, where they develop translational research projects. Dr. Chantal Henry, a psychiatrist recruited under this scheme, published an article in 2019 that shed new light on the role of lithium in bipolar disorder.

Encouraging the emergence of new translational projects and boosting their visibility

The CRT runs a wide variety of scientific events to promote dialog and encourage collaboration between clinicians and scientists. At the monthly Pasteur Medicine Quarter-Hour sessions, doctors come to campus to speak about their work. Recordings of the sessions are then made available online.* This year, there was a particular focus on the strategic areas of antibiotic resistance and brain connectivity/neurodegenerative diseases, with the organization of two events for clinicians and scientists in cooperation with the Center for Scientific Incentive Programs.

* <https://www.youtube.com/channel/UCWuRt-UrE7bWnz820pcFEDQ/featured>

Advancing clinical research within the International Network

The aim of INCREASE (the International Network Clinical Research Sustainable Initiatives) is to develop clinical and translational research projects involving the International Network. In 2019, the ESAA clinical trial was launched in cooperation with Epicentre to assess the action of an antivenom treatment in real-life conditions in Cameroon.

Open Desk and supporting translational research

Since 2017, the CRT's Open Desk scheme has provided guidance for scientists embarking on research projects involving human subjects by supporting them through the ethical, regulatory and administrative procedures with the help of a committee of internal and external experts. In 2019, the CRT and its partners held discussions aimed at improving the service offered to scientists and issued ten recommendations that will be implemented in 2020-2021.



THE THREE CRT STRUCTURES

- **The CRT Clinical Core** conducts preparatory work and provides ongoing support for research projects in France and at international level after their initial presentation at Open Desk sessions. In 2019, the Clinical Core set up two working groups based on the recommendations made, with the aim of drawing up a risk assessment chart and a policy on institutional responsibility for research. These two documents will serve as the first stages in improving the services offered to the scientific community. The team also forged new key partnerships for the introduction of a national clinical trial, initiated by physicians in the Institut Pasteur Medical Center, to assess the efficacy of a combination antibiotic therapy for hidradenitis suppurativa.
- **The ICAREB platform** coordinates two prospective cohorts of volunteers and manages the related collections of biological resources, which are available to the scientific community. The ICAREB team is also involved in clinical investigation, such as for the ZIKASPELL project, for which around 60 control subjects not infected with the Zika virus were recruited so that they could be compared with infected individuals. And for the first time in 2019, a research project was devised in close collaboration with a patient association as part of a study on familial adenomatous polyposis.
- **The CRT Technical Core** is jointly affiliated with the Center for Technological Resources and Research. It offers a unique array of sophisticated technologies that can be used in translational research. In 2019, a new machine was installed for cell culture in physiological oxygen pressure conditions similar to those in tissues. A single web portal for all the Institut Pasteur's single-cell gene expression analysis technologies was also set up. Finally, a new screening method was introduced for the selection of subcellular particles such as HIV viral particles.



NATIONAL REFERENCE CENTERS (CNR)

The Institut Pasteur hosts 14 National Reference Centers (CNRs) in mainland France (12 in Paris and two in Lyon) and four associated CNR laboratories in French Guiana. The current five-year term for CNRs, assigned by the French National Public Health Agency (Santé publique France or SpF), began on April 1, 2017 and will run until 2022.

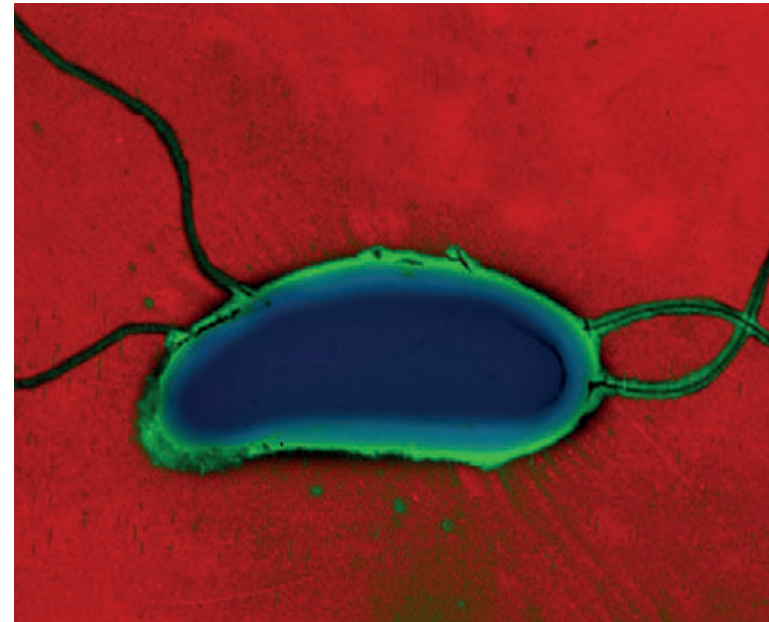
CNRs provide support for health authorities and work in association with their host research units to fulfill four key public health missions:

- diagnosis and microbiological expertise;
- advising healthcare professionals and authorities;
- contributing to epidemiological surveillance;
- contributing to the alert system.

The CNRs' activities – highly visible to the general public during major health crises – draw on the expertise of the Institut Pasteur's scientists and its ability to transfer innovative scientific and technological research to the field of public health.

Cholera outbreak in Yemen elucidated using genomics

Scientists at the Institut Pasteur (Vibrios and Cholera CNR and Enteric Bacterial Pathogens Unit) joined forces with the Wellcome Sanger Institute and several international organizations to study the biggest cholera outbreak in recent decades. This occurred in Yemen at the south-western tip of the Arabian Peninsula, a country that is currently in the grip of war. Since September 2016, more than 1 million people have been affected by the acute diarrheal infection, which has claimed 2,300 lives. An initial wave of the outbreak was seen in 2016 followed by a surge in 2017, suggesting that two separate bacterial strains were responsible. Using high-throughput sequencing of the genome of bacterial strains that emerged in Yemen and neighboring countries between 2014 and 2017,



scientists analyzed the accumulation of small point mutations in the bacteria's genome over the generations and trace the "family tree". The strains that caused both waves of the outbreak share the same lineage, which did not arrive directly from South Asia or the Middle East; it came from the Horn of Africa, from Tanzania and Kenya. The scientists also found that the Yemeni strains are sensitive to several antibiotics commonly prescribed to treat cholera, but also to polymyxins. An antibiotic-sensitive strain is therefore capable of causing 1 million cases of cholera and conversely, multidrug resistance to antibiotics is not necessarily associated with greater virulence. This study illustrates how important it is to combine epidemiological data with laboratory data to monitor the circulation of strains and improve efforts to control cholera. These findings have contributed to progress on the Global Task Force on Cholera Control international roadmap, which was set in motion by the WHO to achieve a 90% reduction in cholera deaths by 2030.

Source: François-Xavier Weill, Marie-Laure Quilici & al., Nature, January 2, 2019.

Microbiological surveillance of *Listeria* in France and international expertise

The *Listeria* CNR works alongside the French public health and food safety authorities to conduct microbiological surveillance of *Listeria* in France. In 2019, it sequenced over 2,000 strains of *Listeria monocytogenes* from clinical and food samples using the P2M sequencing platform. These strains were subsequently typed using the cgMLST method,

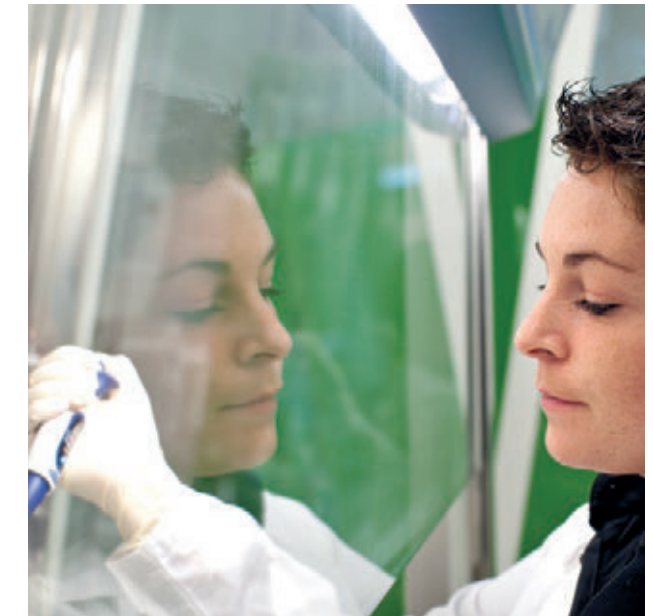
which has become the gold standard for analyzing genomes of this bacterium. Through these analyses, it is possible to identify clusters linked to a common source and identify this source to prevent an outbreak. The CNR team also runs the WHO Collaborating Center for *Listeria*. In this role, it collaborated with microbiologists and epidemiologists from the National Institute for Communicable Diseases in Johannesburg, South Africa to investigate the largest outbreak of listeriosis on record (937 cases). The WHOCC for *Listeria* was involved in field investigations and helped type strains from clinical, food and environmental samples. The outbreak was traced to consumption of mortadella produced in a factory whose production line was contaminated. The findings of these investigations were published in the *New England Journal of Medicine*.

Source: Thomas J & al., N Engl J Med., February 13, 2020.

Investigating foodborne outbreaks – an effective syndromic approach appreciated by health authorities

In 2019, the CNR for Anaerobic Bacteria and Botulism was commissioned 13 times (a fourfold increase compared to 2018) to assist with the microbiological and epidemiological investigation of *Clostridium perfringens* or *Bacillus cereus* foodborne outbreaks in military barracks, retirement homes, and company canteens. These bacteria often cause foodborne illnesses with virtually identical clinical signs, thus complicating food and veterinary investigations until the microbe is isolated and identified. The CNR developed a real-time PCR* assay focused on the genes of these bacteria's main virulence factors. This can be applied on receiving patients' stool samples or potentially contaminated food specimens, enabling the health authorities to focus their efforts and respond quickly within the space of a day. Strains from patients' stools and food specimens are subsequently isolated and their genomes sequenced at the Institut Pasteur's Mutualized Platform for Microbiology to complete toxin typing, check that they are identical, compare them with isolated strains from other foodborne outbreaks, and sound the alert if a single strain has caused several cases in the same specific location, time frame or in the same food type. Instant mashed potato flakes contaminated with *Bacillus cytotoxicus* spores are strongly suspected of causing a foodborne outbreak that claimed the lives of five individuals (investigation ongoing).

* Enzymatic amplification technique.



14 NATIONAL REFERENCE CENTERS

- ANAEROBIC BACTERIA AND BOTULISM
- WHOOPING COUGH AND OTHER *BORDETELLA* INFECTIONS
- CORYNEBACTERIA OF THE *DIPHTHERIAE* COMPLEX
- *ESCHERICHIA COLI*, *SHIGELLA*, *SALMONELLA*
- VIRAL HEMORRHAGIC FEVERS
- HANTAVIRUSES
- LEPTOSPIROSIS
- *LISTERIA*
- MENINGOCOCCI AND *HAEMOPHILUS INFLUENZAE*
- INVASIVE MYCOSES AND ANTIFUNGALS
- PLAGUE AND OTHER *YERSINIA* INFECTIONS
- RABIES
- VIBRIOS AND CHOLERA
- RESPIRATORY VIRUSES (INCLUDING INFLUENZA)

MEDICAL CENTER (CMIP)

The Institut Pasteur Medical Center (CMIP) is where the Institut Pasteur comes into direct contact with patients in Paris. It offers a range of services including a vaccination center; consultations for infectious and tropical diseases, travel medicine and allergies; and an Anti-Rabies Center. It has held ISO 9001 v2015 certification since 2018.



The Institut Pasteur International Vaccination Center (CVI) is a leading center for people traveling to countries with a different environment and health and hygiene conditions. It has an outstanding reputation and attracts high numbers of people seeking vaccinations and specific information for trips abroad.

Vaccinations and travel medicine

Two categories of travelers make use of the International Vaccination Center and the travel clinic: those who attend privately prior to holidays, family getaways or religious travel such as pilgrimages, and those from public institutions, companies and especially NGOs going on foreign business trips, who come on the basis of contracts concluded with the Institut Pasteur. These travelers are seen before their departure and sometimes also when they return to France. Travel medicine is often closely linked with recent outbreaks of emerging infectious diseases at the international level, an area in which the Medical Center's expertise is widely recognized. This was the case throughout 2019 with the Ebola virus outbreak that emerged in 2018 in the Democratic Republic of the Congo. Many of the humanitarian volunteers traveling to the country were treated at the CMIP before setting off.

Consultations

As well as providing vaccinations and advice for travelers, especially vulnerable patients (those with HIV, organ transplants

or other immune deficiencies) and humanitarian aid workers, much of the Medical Center's work involves treating diseases imported by returning travelers (malaria, dengue, rickettsial infections, leishmaniasis, amebiasis, etc.), HIV or hepatitis virus infection, and widespread infectious diseases such as Lyme disease.

Some of these conditions are monitored in collaboration with Necker-Enfants Malades Hospital, via the Necker-Pasteur Infectiology Center (CINP). Most of the physicians from the

Infectious and Tropical Diseases Department at Necker Hospital hold clinics at the CMIP, alongside physicians from the Institut Pasteur. Their work includes treating a high caseload of patients infected with HIV or viral hepatitis, which also serves as the basis for clinical research. One area in which the Medical Center specializes is dermatology, especially hidradenitis suppurativa. The CMIP monitors a large number of patients and is internationally recognized for its expertise in this condition. The Anti-Rabies Center treats patients that have been exposed to the rabies virus (through a bite, a scratch, the licking of a wound or a mucous membrane), usually during a trip abroad. The multidisciplinary allergy team has expertise in all types of allergies.

Clinical research

The Medical Center is involved in clinical research related to its areas of medical specialization: cohorts in the field of HIV infection, most often in conjunction with the French Agency for Research on AIDS and Viral Hepatitis (ANRS); the pathophysiology of hidradenitis suppurativa (genetics and immunology, in collaboration with the ICAReB platform, Institut Pasteur research units and Necker Hospital); and vaccinology (retrospective analysis of the immune response to post-exposure rabies vaccination in immunosuppressed individuals, based on data from the Anti-Rabies Center). A comparative therapeutic trial for hidradenitis suppurativa was accepted for funding by the French Hospital Clinical Research Program (PHRC) and is due to begin in late 2020. The aim is to endorse the treatment currently recommended by the CMIP's dermatologists. The new insights generated by these projects fully justify the CMIP's role within the Center for Translational Science and the future Vaccinology Center envisaged in the Strategic Plan.

71,117 VACCINES
ADMINISTERED

55,827 VISITS
TO THE INTERNATIONAL
VACCINATION CENTER

11,013 CONSULTATIONS FOR INFECTIOUS
AND TROPICAL DISEASES
AND TRAVEL MEDICINE

2,865 CONSULTATIONS
AT THE ANTI-RABIES CENTER

1,508 CONSULTATIONS
FOR ALLERGIES

WHAT THEY HAVE TO SAY ABOUT US

**"THANK YOU FOR THE FRIENDLY WELCOME
AND THE ADVICE, FROM BOTH NURSES
AND PHYSICIANS. WELL DONE TO THEM –
I AM MOST IMPRESSED! AND THANK YOU."**

**"EXCELLENT ADVICE, EXCELLENT SERVICE.
ESSENTIAL FOR FINDING OUT THE LATEST
UP-TO-DATE INFORMATION BEFORE SETTING OFF
ON A TRIP ABROAD. AN INVALUABLE SERVICE.
THANK YOU!"**

Word-for-word accounts (originally in French) from forms filled out by Medical Center users as part of ongoing efforts to improve the quality of service and treatment offered to patients.



**2019-2023
STRATEGIC
PLAN**

A KEY ROLE FOR THE CMIP

Draw on the expertise of the International Vaccination Center as part of efforts to pool strengths in the field of vaccinology, involving immunologists, microbiologists, epidemiologists and vaccine specialists, as well as the Cochin-Pasteur Vaccinology Clinical Investigation Center and the Institut Pasteur's Center for Translational Science.



3. DEVELOPMENT OF RESEARCH APPLICATIONS MISSION

The Institut Pasteur is at the forefront of innovation. It is constantly developing applications for its research and pursuing its mission of technology maturation and transfer through industrial partnerships, start-ups and invention disclosures.

CLAIRE HÉRITIER

GLOBAL PARTNERSHIP CONTRACT LEADER IN THE TECHNOLOGY TRANSFER
AND ENTREPRENEURSHIP OFFICE
LEARN MORE ABOUT THE INSTITUT PASTEUR'S PARTNERSHIPS ON PAGE 65,
AND ABOUT THE INSPIRATION BEHIND THE PICTURES ABOVE ON PAGE 96.

RESEARCH APPLICATIONS AND TECHNOLOGY TRANSFER

The Research Applications and Industrial Relations Department is responsible for the Institut Pasteur's fourth mission – innovation development and technology transfer. Its role is to support the entire innovation process: identification of potential applications, protection, innovation development, promotion, transfer, and post-contract management. The aim is to bring medical solutions and products for patients to market faster through industrial partnerships and licenses, or by forming start-ups.

With its multidisciplinary, cross-cutting approach to research, the Institut Pasteur is ideally positioned to convert its technologies and innovations into advances for patients in diagnostics, vaccines, therapies, and technology. In 2019, the Research Applications and Industrial Relations Department (DARRI) continued to implement its strategy by completing its internal restructuring, setting up an innovation accelerator, optimizing the positioning of patents in strategic fields, and promoting the Institut Pasteur's invention work more intensively.

Protecting inventions

In 2019, 50 invention disclosures were registered, resulting in 14 new priority patents being filed and 16 provisional applications (software, expertise, and biological material). In keeping with the maturation of inventions strategy and the policies adopted by the innovation accelerator, priority was specifically given to projects selected for their high transfer and development potential. A new US patent was granted in 2019, increasing and extending protection of the Lentivirus platform and in particular its vaccine applications within the fields of gene and cell therapy such as CAR-T cell therapies. A patent issued for Europe secured the development of a pneumocystis pneumonia diagnostic kit in collaboration with an industrial partner. Similarly, a wide-ranging patent covering the assessment of individuals' immune capacity led to a license agreement with one of the Institut Pasteur's historic partners.



50 INVENTION
DISCLOSURES

14 NEW PRIORITY
PATENTS AND
16 PROVISIONAL
APPLICATIONS

246 INDUSTRIAL
CONTRACTS
SIGNED IN 2019

285 INDUSTRIAL
CONTRACTS
IN PLACE

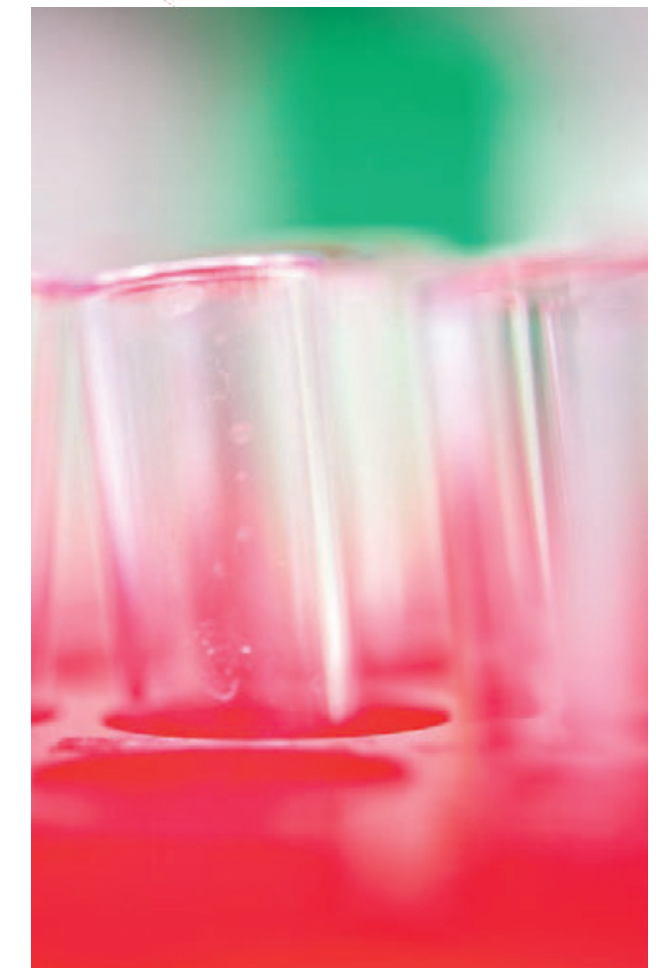
This kit will eventually benefit patients who are at risk due to immunodeficiency and patients undergoing treatments with immunosuppressive effects.

Detecting, funding, and developing innovation

In order for innovations to come to light, scientists need to be made aware of the industrial applications of their work. One-to-one meetings are the favored means of informing scientists of the societal and industrial implications of applications of their research. On-campus events ("Welcome day", seminars, departmental or themed day events, etc.) are also used for this purpose. In 2019, a set of tools to fund and support various innovation phases was also implemented to encourage creativity, innovation, and entrepreneurship among Institut Pasteur scientists. Consequently, DARRI backed 18 innovative new research programs, in their early or advanced stages, in partnership with the Pasteur Microbes and Health Carnot Institute, with funding provided over 12 or 24 months. A committee of Institut Pasteur and external experts was formed to certify several research programs offering high innovation potential. The innovation accelerator, which was also launched in 2019, should ensure optimal development of selected projects through financial backing and enhanced support for projects. The aim is to ultimately generate a pipeline of 7 to 10 projects. Currently, five laboratories focused on fundamental and translational research receive support from the innovation accelerator with a view to optimizing technology transfer to industry partners. Through close liaison with the Business Development team greater understanding of industrial partners' needs and expectations is gained and assistance is provided to scientists seeking to form start-ups.

Forging new partnerships

In addition to license agreements, over 40 R&D partnerships were forged in 2019, notably including:
→ **A partnership and license agreement with the Bill & Melinda Gates Medical Research Institute (GMRI)** with a view to developing a quadrivalent vaccine for infections caused by *Shigella* and granting GMRI an exclusive free license for developing countries.
→ **A partnership with Sensorion** and the Genetics & Physiology of Hearing Unit led by Professor Christine Petit in the field of gene therapy for restoring, treating and preventing hearing problems through a specific program aimed at correcting hereditary monogenic forms of hearing loss, including those caused by mutations of the gene coding for otoferlin.



BOOSTING COOPERATION WITH INDUSTRY THROUGH CIFRES

The CIFRE scheme (Industrial Agreements for Training Through Research) seeks to foster the development of public-private research partnerships by co-funding the training of PhD students recruited by companies. Students are assigned to a research project related to the industrial operator's R&D strategy. This is shared with an academic laboratory, governed by a partnership agreement, and provides the basis for the PhD student's thesis in accordance with the Order of August 7, 2006 on doctoral training. In 2019, the Institut Pasteur supported the training of seven PhD students through joint research projects.

→ An R&D partnership between the company **OM PHARMA** and the Mucosal Inflammation and Immunity Group led by Molly Ingersoll within the Immunobiology of Dendritic Cells Unit.

Consolidating key partnerships

→ In 2019, a project led by Lars Rogge in the Immunoregulation Unit was selected for funding under the **Sanofi Innovation Awards Program**. His project involves examining the immune response signature in relation to therapeutic responses to anti-TNF therapy.

→ Following the framework agreement signed in 2017 with the **Hoffman-Laroche Group** facilitating interaction with the group's businesses (Genentech, Roche Pharma, Institut Roche), two new R&D partnership agreements were signed – one with Uwe Maskos' Integrative Neurobiology of Cholinergic Systems Unit and the other with Marcel Hollenstein's five-year group (Bioorganic Chemistry of Nucleic Acids).

→ The company **Oncovita** develops new therapeutic solutions with a focus on treating various cancers. This Institut Pasteur spin-off signed an exclusive license agreement in 2019 to develop, manufacture, and market new oncolytic viruses based on the “measles” proprietary platform.

CARNOT ACCREDITATION RENEWED FOR THE INSTITUT PASTEUR

Following a call for renewal in June 2019, the Institut Pasteur was once again awarded this accreditation for its Pasteur Microbes and Health Carnot Institute (iC PMS). The Institut Pasteur has been part of the Carnot network since the accreditation was first introduced in 2007, in recognition of the scientific quality of its research and the professionalism of its technology transfer activities. A restructuring was carried out in 2019 aimed at improving coordination of DARRI and iC PMS activities. This led to such initiatives as a joint innovation funding program. The innovation accelerator established in 2019 to support Institut Pasteur research projects with high industrial potential is also jointly managed by the DARRI and iC PMS. *“I am delighted that this accreditation has been renewed as it validates our strategic decisions enabling us to adapt to biotechnological developments and profound changes that have occurred in the health industry in recent years. Combining funding strategies, technical support, and commercial expertise, the innovation accelerator is precisely the tool we needed to foster industrial partnerships and bring medical solutions and products developed in our laboratories to market faster.”* Jean-Christophe Olivo-Marin, Director of the Pasteur Microbes and Health Carnot Institute.

→ **Theravectys**, an Institut Pasteur spin-off, seeks to develop new vaccine and prophylactic solutions for treating and preventing infectious diseases. In 2019, the Institut Pasteur and Theravectys renewed their partnership to boost the development of a pipeline based on products in development through a two-year extension to their joint laboratory set up in 2017.



2019-2023
STRATEGIC
PLAN

Assessing the safety and efficacy of health products

2019 saw our licensed partners continue work on several clinical trials:

→ The project to develop a vaccine candidate for the Lassa virus conducted in partnership with **Themis Biosciences with support from the Coalition for Epidemic Preparedness Innovations (CEPI)**, working alongside Sylvain Baize's team, reached a critical stage with the start of Phase I clinical trials in October 2019.

→ Following the Food and Drug Administration (FDA) approval to start Phase I clinical trials on treating inflammatory bowel disorders with a phage cocktail developed with Laurent Debarbieux's teams, **Ferring Pharmaceuticals** initiated the clinical trials in the United States, with the first patient treated in May 2019.

→ Having published outstanding results for Phase II trials concerning the development of a chikungunya vaccine based on measles vector technology, **Themis Biosciences** was granted Fast Track designation by the FDA providing priority support with procedures for entering Phase III. Chikungunya is a mosquito-borne disease for which there is currently neither treatment nor prevention option.

INNOVATION CHALLENGES

1. Foster closer cross-disciplinary involvement in the development of research applications among scientists on campus and all relevant stakeholders.
2. Set up a Consultative Innovation Committee and appoint business development correspondents in the departments and centers.
3. Pursue a more proactive policy to detect and support innovative projects.
4. Identify innovative solutions to get external stakeholders (investment funds, industry partners, Bpifrance investment bank, etc.) involved in all stages of the innovation process, especially the upstream phase (proof of concept).
5. Support start-up projects before they get off the ground.
6. Develop partnerships with incubators so that they can take over as soon as start-ups reach the setup phase.
7. Create spin-offs.





LLUIS QUINTANA-MURCI

HEAD OF THE HUMAN EVOLUTIONARY GENETICS UNIT

SEE LLUIS QUINTANA-MURCI'S APPOINTMENT AS A PROFESSOR AT COLLÈGE DE FRANCE ON PAGE 18.
LEARN MORE ABOUT INSPIRATION FOR THE PICTURES ABOVE ON PAGE 96.

4. EDUCATION AND TRAINING MISSION

On the Institut Pasteur campus, a cosmopolitan community of Master's and PhD students, and healthcare professionals, receive state-of-the-art scientific and medical teaching. The aim is to train up a new generation of scientists who are actively engaged in global public health issues.

TRANSFERRING AND SHARING SCIENTIFIC KNOWLEDGE

Education and training are an essential part of the Institut Pasteur's activities, continuing the legacy of its founder, Louis Pasteur. For the past 130 years, ever since the first microbiology course taught by Émile Roux in 1889, the Institut Pasteur has played a key role in teaching life sciences at the international level.

Each year, over 1,200 students, PhD students and healthcare professionals from around 70 countries attend one of the 60 courses and workshops run at the Institut Pasteur in Paris or at one of the 32 institutes in the Institut Pasteur International Network. Over 600 young scientists are also hosted by laboratories on the Paris campus to train as scientists and complete their undergraduate, Master's and PhD research projects.

A unique setting for training in science and research

The Institut Pasteur's reputation for excellence in research provides a unique, hands-on environment for young scientists, who come to complete internships from undergraduate to PhD level in its laboratories. The Institut Pasteur also runs excellent courses for Master's and PhD students, as well as vocational science courses leading to recognized university diplomas. Courses in Paris are run by scientists on campus, with input from lecturers based at partner institutions in France (Université de Paris, Sorbonne Université, Université Paris-Saclay, Université PSL, the Institut Curie, the CNRS, Inserm and the CNAM) and abroad. The involvement of expert scientists in Institut Pasteur courses is pivotal to the success of our teaching, giving students access to the very latest developments in research, especially in life sciences and public health. Experimentation and practical work are a particular strong point of the Institut Pasteur's educational approach, setting it apart from other institutions. The development of the Institut Pasteur International Network has had a major impact on teaching,



in terms of both the scientific subjects taught and the international makeup of the students.

To maintain its leading position, the Institut Pasteur is extending its teaching activities by increasing the emphasis on online courses (MOOCs), opening up courses to younger students, encouraging multidisciplinary and links with medicine, and promoting entrepreneurship and business development.

900 STUDENTS
EACH YEAR

300 PHD STUDENTS
ON THE INSTITUT PASTEUR CAMPUS



The Institut Pasteur and online courses in life sciences and health

The Institut Pasteur develops online teaching activities as a way of extending the reach of the courses taught at its Education Center or at institutes in the International Network. In just three years, the Institut Pasteur has produced 18 MOOCs in life sciences and/or health which have proved hugely successful in terms of numbers (1,900 to 7,300 students enrolled per session) and international visibility (95 to 151 countries). To promote its MOOCs in China, the Institut Pasteur signed an agreement with a Chinese distribution platform, XuetangX, via the France Université Numérique (FUN) platform.

The Institut Pasteur ran seven MOOCs in 2019, four of them new courses: Viruses and Human Cancers, Advances in Stem Cell Biology, Epigenetics, and Human Population and Evolutionary Genetics. The other three MOOCs – HIV Science, Innate Immunity, and Medical Entomology – were run for a second time. Various records were broken in 2019 – the Tuberculosis MOOC attracted more than 12,000 learners and the Medical Entomology MOOC was followed in 166 countries. Another astonishing statistic is that every single country on the American continent had a learner registered at least once for a Pasteur MOOC; this was also the case for Africa, with the exception of two countries (Eritrea and Somaliland). In 2019, a second MOOC, Resistance

to Antibacterial Agents, was made available online on the XuetangX platform. With the help of the Institut Pasteur de Dakar, this MOOC was also hosted on the platform of the Virtual University of Senegal, where it attracted 200 learners, a record number for Senegal and its neighboring countries for a MOOC hosted on this regional platform. In December 2019, the Institut Pasteur launched the first global online diploma in the field of life sciences, the Institut Pasteur Online Diploma in Infectious Diseases (DNM2IP). The diploma is awarded to registered learners who pass the supervised online exam for five of the 15 MOOCs in the program.

The Institut Pasteur currently produces 23% of the life science MOOCs and 12% of the health MOOCs available on the FUN platform. In these two fields, the Institut Pasteur is the leading MOOC creator in France, ahead of Sorbonne Université and the CNAM.

Predocutorial programs

The Institut Pasteur is keen to offer more training for students at earlier stages in their academic career. It has developed several predoctoral programs for students at middle school, undergraduate and Master's level. The "Collège 3" program gives middle school students in their fourth year the chance to come and find out about different research professions in a secure, structured environment. Students are hosted in an Institut Pasteur research unit, where they are supervised by a tutor. A dedicated team also prepares a series of activities to help them find out more about the Institut Pasteur and its departments and resources. The Amgen Scholars Program gives around 20 students from European universities and higher education institutions the opportunity to work on a research topic for eight weeks in one of the Institut Pasteur's laboratories. This international program is run entirely in English and culminates in a conference in Cambridge, UK. The Institut Pasteur also has partnerships with several European universities and hosts interns via the EU's Erasmus+ program, as well as Master's students from Columbia, Stanford and South Florida universities in the United States and the University of Cambridge in the UK.

The Institut Pasteur set up its own International Genetically Engineered Machine (iGEM) team in 2015 as a way of varying its predoctoral courses and consolidating its position at the forefront of innovation in synthetic biology. In 2019, the Institut Pasteur team was composed of ten undergraduate and Master's students from a variety of disciplines (biology, physics, chemistry and law). The members worked on a rapid diagnostics project using electrodes in carbon nanotubes fitted with aptamers with an affinity for pathogenic bacteria (the project was named "Diagnosis is Now Easier," or DIANE). Alongside the existing partnerships with the universities PSL and Paris-Saclay, and SUPBiotech, new partnerships were





“BORDET” YEAR GROUP (PPU 2019)

The 2019 year group was composed of 14 students, 11 from Europe (Germany, Italy, Romania, Russia, Spain, Sweden and the United Kingdom), one from America (United States) and two from Asia (China and Vietnam). In 2019, the Institut Pasteur received 1,099 finalized applications from 756 applicants for the 44 proposed research projects, confirming the considerable interest in the program.

In 2019, a new PPU program was launched (PPU-Oxford), based on cooperation between the Institut Pasteur and the Department of Chemistry at the University of Oxford. The aim of this program is to promote synergistic projects to tackle antimicrobial resistance. With the PPU-Oxford program, PhD students work on collaborative research projects between the two institutions and spend several months of their PhD in the partner laboratory. The exchange provides the students with cross-disciplinary expertise. Two PhD students from the 2019 year group are taking part in this program. Once again in 2019, the PPU PhD students were given the opportunity to take part in joint activities (seminars, oral presentations and the annual retreat), under the guidance of a dedicated scientific committee. The PPU program is also a chance to experiment with new teaching concepts, such as the Robotics workshop, open to all PhD students on campus.

concluded with AgroParisTech for the iGEM program. The iGEM Pasteur students were supported by DeepTech Founders (partnership with BPIFrance) and French standards agency AFNOR for the regulatory aspects. The 2019 team received an award from Groupe Pasteur Mutualité and was awarded a silver medal, nominated for Best Supporting Entrepreneurship, and recognized for biosafety and biosecurity.

Training through research for PhD students

With 134 research units in Paris and a network of 32 institutes worldwide, the Institut Pasteur is a higher-education hotspot for many young scientists. Each year, around 80 PhD students complete their studies in laboratories on the Paris campus. The Institut Pasteur provides scientific supervision for PhD students through thesis committees, as well as personal support with a tutoring program, a dedicated office and a structure for post-doctoral career development.

The Institut Pasteur in Paris runs specialized PhD programs, like the Pasteur-Paris University (PPU) international doctoral program, open to students with a Master's degree (or equivalent) from a foreign university. This high-level program, launched in 2008, is run in close partnership with Université de Paris, Sorbonne Université and Université Paris-Saclay. It is a three-year program leading to a PhD from a French university.

Each year, the Institut Pasteur also awards grants for the completion of PhDs in the International Network, outside mainland France. Research topics can be related to any subject under study in the International Network, ranging from infectious diseases (infectious pathophysiology, immunology, microbiology, epidemiology, virology and parasitology) to public health activities (diagnosis, surveillance, resistance, etc.). Applicants must hold a Master's or equivalent degree and be enrolled in a doctoral school at a French or non-French university.

The Institut Pasteur, Institut Curie and École Normale Supérieure (ENS) are continuing their “Médecine-Sciences” program, which reflects the major changes in medical practice and biomedical research brought about by recent scientific and technological progress. The program, launched in 2015, includes an early introduction to research, with the aim of training up professionals with both scientific and medical expertise. Students are recruited through a competitive examination at the end of their second year of medical or pharmacy studies. The many advantages include guaranteed funding for the first three years, effective scientific and medical tutoring, a prestigious ENS qualification and a PhD in Science. Graduates of the Médecine-Sciences program enjoy excellent career prospects in academia or the healthcare industry, in France or at the international level.

Scientific entrepreneurship training

In keeping with its vocation, the Institut Pasteur has always been committed to finding applications for its research, and this is reflected in its teaching. To this end, several initiatives were developed during 2019, including the continuation of the “Startup Breakfast” series – informal monthly events for Institut Pasteur scientists interested in business development, with guest speakers including successful biotechnology entrepreneurs, representatives of funding bodies or heads of business incubators –, and a start-up workshop in July 2019 with practical sessions on specific projects led by junior Institut Pasteur scientists, an initiative that will be repeated in 2020.

Over the years, the Institut Pasteur has developed highly structured teaching activities at the local, national and international level, enhanced by the involvement of leading experts and professionals. The courses and undergraduate and continuing training on offer at the Institut Pasteur enjoy an outstanding international reputation, attracting promising young scientists from all over the world and helping to build an international network of researchers. The Institut Pasteur trains these young scientists in basic research, while also providing guidance in business development and company creation.

Further information: <https://www.pasteur.fr/en/education>



INSTITUT PASTEUR 2019 PHD GRADUATION CEREMONY

The graduation ceremony for PhD students on campus who defended their thesis in 2019 was held on December 13, 2019. Four PhD students from the Institut Pasteur in Belgium, Greece, Lille and Bulgaria were also honored at the ceremony. At the event, Stefan W. Hell, 2014 laureate of the Nobel Prize in Chemistry, gave an address in which he shared his personal views on the research profession.

The ceremony was attended by Institut Pasteur staff, representatives from partner organizations, and figures from political, diplomatic and business circles with links to the Institut Pasteur. Launched in 2013, the annual graduation ceremony has become a major event in the campus calendar, serving as a showcase for the professional excellence produced by the Institut Pasteur's research and training. The next ceremony will take place on December 4, 2020, with guest speaker Emmanuelle Charpentier, a Member of the French Academy of Sciences and Academy of Technologies for her development of the CRISPR-Cas9 gene editing technology.



5. INTERNATIONAL

The Institut Pasteur International Network is composed of 32 institutes united by Pasteurian values and missions in the service of public health. This unique network is an outstanding base for the development of international scientific cooperation.

ANNA-BELLA FAILLOUX

HEAD OF THE ARBOVIRUSES AND INSECT VECTORS UNIT

READ ABOUT ANNA-BELLA FAILLOUX'S STUDY ON THE MOSQUITO THAT TRANSMITS THE ZIKA VIRUS IN THE SOUTH OF FRANCE ON PAGE 13. LEARN MORE ABOUT THE PHOTOGRAPHS ABOVE ON PAGE 97.

INTERNATIONAL HIGHLIGHTS OF 2019

FEBRUARY

DR. AMY KRISTINE BEI HEADS A NEW FOUR-YEAR RESEARCH GROUP (G4) ON MALARIA IN DAKAR ❷

A new four-year research group (G4) was set up at the Institut Pasteur de Dakar. It began its work in February following the signing of an agreement between the Institut Pasteur and the Francophone University Agency (AUF), in collaboration with the Yale School of Public Health. The Malaria Experimental Genetic Approaches and Vaccines group is led by Dr. Amy Kristine Bei, Assistant Professor at the Yale School of Public Health. The aim is to shed light on the interaction between parasite diversity and immune selection and to use this knowledge to guide the selection of vaccine candidates.



EFFECTIVE ALGORITHM FOR EARLY DETECTION OF SIGNIFICANT DENGUE CLUSTERS IN CAMBODIA ❶

Scientists from the Institut Pasteur du Cambodge and the Institut Pasteur in Paris confirmed the usefulness of an algorithm applied to national surveillance data for detecting dengue outbreaks as far in advance as possible. The results were published in *PLoS One* as part of the ECOMORE project, which is aiming to improve the national surveillance system for dengue in Cambodia, particularly by consolidating the existing network of sentinel hospitals to obtain the most reliable data.

JANUARY

ANTIBIOTIC RESISTANCE WORSENER BY CONTAMINATION OF FOOD PRODUCTS IN CAMBODIA ❶

Antibiotic resistance is particularly problematic in low- and middle-income countries (LMICs). New research by the Institut Pasteur in Paris and the Institut Pasteur de Cambodge, published in the journal *Emerging Infectious Diseases*, suggests that the spread of antibiotic-resistant bacteria in low- and middle-income countries may be exacerbated by foodborne bacteria. The scientists' findings were based on research into the eating habits and environmental exposure of women on the BIRDY program. Tackling antimicrobial resistance is one of the priority areas in the Institut Pasteur's Strategic Plan.



MARCH

2017 PNEUMONIC PLAGUE OUTBREAK IN MADAGASCAR CHARACTERIZED BY SCIENTISTS ❸

Scientists from the Institut Pasteur de Madagascar and the Institut Pasteur in Paris, in collaboration with the Malagasy Ministry of Public Health, the World Health Organization and international experts, published an article in the journal *The Lancet Infectious Diseases* describing the scale and transmission dynamics of the 2017 pneumonic plague outbreak in Madagascar. The research was supported by the Institut Pasteur via the ASIDE project and its cooperation with the U.S. Department of Health and Human Services.

APRIL

NEUROLOGICAL IMPACT OF THE ZIKA VIRUS FINALLY EXPOSED ❹

Although the Zika virus is well known to scientists and physicians, the incidence of neurological complications and their clinical profiles and prognoses remain shrouded in mystery. In a study published in *Neurology*, teams of scientists from various institutions including the Institut Pasteur in Paris and the Institut Pasteur de la Guadeloupe revealed the long-term effects of the virus.



2019 PRINCE ALBERT II OF MONACO—INSTITUT PASTEUR PRIZE AWARDED TO JOACIM ROCKLÖV ❺

At a ceremony attended by Professor Stewart Cole, President of the Institut Pasteur, His Serene Highness Albert II, Sovereign Prince of Monaco, awarded the Prince Albert II of Monaco–Institut Pasteur Prize to Professor Joacim Rocklöv for his research on climate-related arboviral disease outbreaks.

MARCH

REVIEW DAY FOR THE AFRIBIOTA RESEARCH PROGRAM ON CHILD MALNUTRITION IN THE CENTRAL AFRICAN REPUBLIC AND MADAGASCAR ❸

The Afribiota project, a multidisciplinary research program led by Philippe Sansonetti and Pascale Vonaesh that was launched in 2015 with the aim of improving our understanding of chronic child malnutrition, has come to an end after four years of collaborative work between the Institut Pasteur, the Institut Pasteur de Bangui and the Institut Pasteur de Madagascar. A discussion meeting, attended by French and international scientists, clinicians and representatives from public health and nutrition organizations, was held to mark the end of Afribiota and to prepare for a follow-up program, which will involve more intervention research.



MAY

PIERRE-MARIE GIRARD APPOINTED AS THE INSTITUT PASTEUR'S VICE-PRESIDENT INTERNATIONAL AFFAIRS ❻

On a proposal from Professor Stewart Cole, President of the Institut Pasteur, Professor Pierre-Marie Girard was appointed as the Institut Pasteur's Vice-President International Affairs. The decision was approved by the Institut Pasteur Board of Governors on April 19, 2019. Pierre-Marie Girard is Head of the Infectious Diseases and Tropical Medicine Department at Saint-Antoine Hospital (part of the Paris Public Hospital Network or AP-HP) and a Professor in Infectious Diseases and Tropical Medicine in the Faculty of Medicine at Sorbonne Université. He took up the post on May 2, 2019.

JUNE

SNAKE BITES: STUDY LAUNCHED IN CAMEROON TO EVALUATE ANTIVENOM SERUMS ❶

A study entitled "Snake bites in Cameroon: evaluating antivenom serums in Africa based on data in real-life conditions" was launched on June 26 and 27, 2019 at a kick-off meeting in Yaoundé. It will take place over a two-year period at 14 health centers in Cameroon. The study, coordinated by the Institut Pasteur and

known by its French acronym ESAA, will evaluate the clinical tolerance and efficacy of an antivenom serum registered in Cameroon.



JULY

INSTITUT PASTEUR INAUGURATES A SCIENTIFIC PLATFORM AT THE UNIVERSITY OF SÃO PAULO INNOVATION CENTER 2

On July 4, 2019, the Institut Pasteur inaugurated the Pasteur-USP scientific platform at the University of São Paulo Innovation Center (Inova USP), which hosts 17 innovation laboratories. The platform became an associate member of the Institut Pasteur International Network in November 2019 at the 51st Council of Directors meeting in Yaoundé.

WOLBACHIA, BACTERIA TO COMBAT DENGUE 3

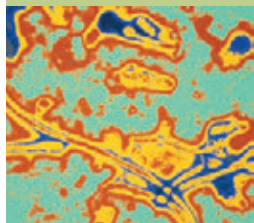
The first mosquitoes carrying *Wolbachia*, bacteria that prevent them from transmitting arboviruses (including dengue, Zika and chikungunya), were released on Wednesday July 10, 2019 in Nouméa, New Caledonia, as part of the World Mosquito Program, which involves teams from the Institut Pasteur de Nouvelle-Calédonie.



AUGUST

SCIENTIFIC TEAMS FROM THE INSTITUT PASTEUR INTERNATIONAL NETWORK INVOLVED IN EFFORTS TO TACKLE EBOLA IN THE DEMOCRATIC REPUBLIC OF THE CONGO 1

The Institut Pasteur International Network is playing an active part in efforts to combat the Ebola outbreak raging in the North Kivu and Ituri Provinces of the Democratic Republic of the Congo (DRC), as it did for the duration of the Ebola outbreak in Guinea, by drawing on the expertise of the Institut Pasteur de Dakar and several of its scientists currently deployed in the DRC. The current outbreak is the tenth to have been declared in the DRC since the disease emerged in the country in 1976.



SEPTEMBER

RABIES: SHORTER, CHEAPER VACCINATION SCHEDULE FOLLOWING A SUSPECTED RABID DOG BITE 4

A study by teams from the Institut Pasteur du Cambodge and the Institut Pasteur in Paris, published in *The Lancet Infectious Diseases* on September 26, 2019, confirmed the efficacy of the new post-exposure rabies vaccination schedule developed in the Institut Pasteur International Network and adopted by the World Health Organization (WHO). Post-exposure vaccination by intradermal injection of reduced doses following injuries caused by animals now takes place in three sessions (days 0, 3 and 7) over a week, instead of four sessions over a month.

LAUNCH OF THE NATIONAL HEALTH LABORATORY PROJECT IN MYANMAR 5

The French Development Agency (AFD), the European Union and the Myanmar Ministry of Health and Sports are working together to improve the country's capabilities for diagnosing and controlling infectious diseases. The National Health Laboratory (NHL) project was launched in Yangon on September 27, 2019. The aim is to strengthen the country's ability to investigate all types of disease and control emerging public health threats. The Institut Pasteur, which is providing support for the NHL for the detection, diagnosis and treatment of diseases such as leptospirosis, will lead the training part of the project.



OCTOBER

EMERGENCE OF YELLOW FEVER VIRUS IN LATIN AMERICA: RESULTS OF A MAJOR STUDY AMONG THE GENERAL POPULATION 6

In light of the emerging threat of yellow fever in Latin America, scientists from the Institut Pasteur de la Guyane carried out a large-scale epidemiological study, published in *PLoS Neglected Tropical Diseases*, to estimate the vaccine coverage of the population and identify factors associated with vaccination. Although yellow fever vaccine coverage was estimated to be 95.0% over the entire country, some western areas in French Guiana, connected by inland waterways to countries where vaccination is not compulsory, have low levels of vaccine coverage, especially in children under 16 not attending school, adults who have recently immigrated to the territory and disadvantaged populations with low socio-economic status.

NOVEMBER

ANTICIPATING AND REACTING RAPIDLY TO OUTBREAKS: CONSORTIUM WINS THE PRIX GALIEN MEDSTARTUP AWARD 7

A consortium between the Praesens Foundation, the Institut Pasteur, the Institut Pasteur de Dakar, the University of Nebraska Medical Center and Twist Bioscience Corporation (Nasdaq: TWST) won the Prix Galien MedStartUp award in the category "Best Collaboration Dedicated to the Developing or Underserved Populations Worldwide." The consortium works together to develop, evaluate and scale up a range of innovative solutions on the African continent to ensure better preparedness and response to infectious disease outbreaks in at-risk areas.



51ST COUNCIL OF DIRECTORS AT THE PASTEUR CENTER IN CAMEROON, YAOUNDÉ 8

The 51st Institut Pasteur International Network Council of Directors meeting was held in Yaoundé from November 12 to 15, 2019, on the 60th anniversary of the Pasteur Center in Cameroon, under the high patronage of the President of the Republic of Cameroon, His Excellency Paul Biya. During the meeting, the 2019 Pasteur International Talent award was presented to Dr. Oumar Faye from the Institut Pasteur de Dakar and Dr. Paulo Carvalho from the Carlos Chagas Institute/Fiocruz by Professor Stewart Cole, President of the Institut Pasteur, and Professor Pierre-Marie Girard, Vice-President International Affairs.



MOBILITY AND EXCHANGE PROGRAMS BETWEEN SCIENTISTS IN THE NETWORK

56 SCIENTISTS IN THE INTERNATIONAL NETWORK

received training through the Calmette & Yersin program, including three post-doctoral fellows and 14 PhD students

12 INTERNSHIPS FOR YOUNG FRENCH RESEARCHERS

in the International Network funded by the Pierre Ledoux-Jeunesse Internationale Foundation

8 THREE-MONTH MISSIONS

in the International Network for newly recruited Institut Pasteur scientists

3 ONGOING FOUR-YEAR RESEARCH GROUPS (G4)

10 INTERNATIONAL COURSES

funded by the Pasteur International Network Association



ADRIEN NOUGARET

ALIAS ZERATOR, STREAMERS AND THEIR COMMUNITIES MOBILIZED FOR MORE THAN 54 HOURS TO SUPPORT THE INSTITUT PASTEUR DURING THE Z EVENT. THIS VIDEO GAME MARATHON WAS ORGANIZED IN SEPTEMBER 2019. LEARN MORE ON PAGE 97.

6. OUR RESOURCES

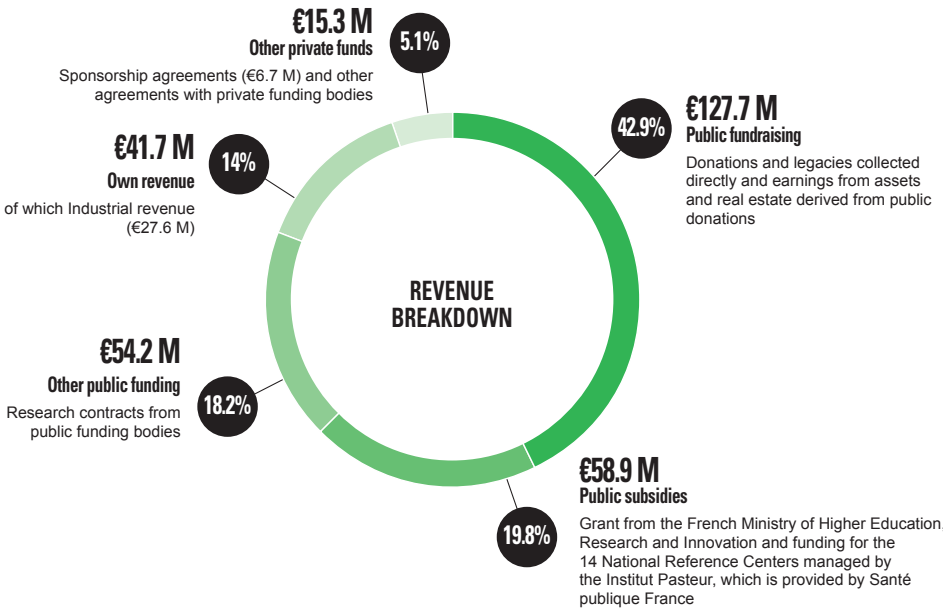
Public generosity has always been crucial to the Institut Pasteur's success. And the Institut Pasteur is committed to optimizing its resources to support scientists and pursue a stable, human-centered economic model that will underpin its long-term development.

FINANCIAL REVIEW OF 2019

The Institut Pasteur’s economic model is characterized by its multi-sourced funding, from public and private realms, which supports its resolutely long-term aim – to prevent and treat diseases, particularly infectious ones, through research, education, public health initiatives and knowledge transfer activities with a view to finding applications that benefit human health.

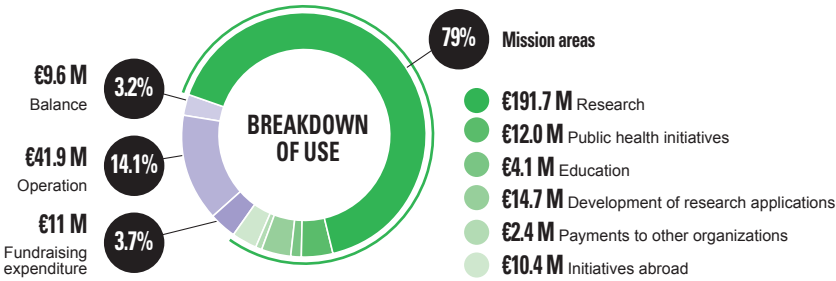
RESOURCES

As indicated in the Institut Pasteur 2019 *Use of resources statement*, the revenues reported in the profit-and-loss account amounted to €297.8 million, with the following breakdown.



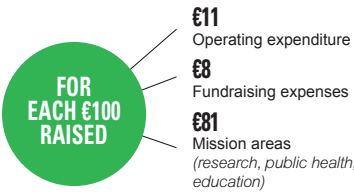
USE

The revenues reported in the profit-and-loss account are earmarked as follows: Institut Pasteur mission areas €235.2 M, operation €41.9 M, and fundraising expenses €11.0 M. The remainder is used to fund initiatives and long-term investments.



PUBLIC GIFTS AND DONATIONS

Within the range of different funding sources relied upon by the Institut Pasteur, the proportion of gifts and donations is on the rise; €127.7 M was raised in 2019*. In addition to its mission areas, the public gifts and donations received in 2019 covered the Institut Pasteur’s fundraising expenses and operating expenditure.



* See chart above and Institut Pasteur 2019 *Use of resources statement* in the financial report.

THE INSTITUT PASTEUR’S ASSETS

Having been a foundation officially recognized for its charitable status since its inception in 1887, the Institut Pasteur must also hold assets, built up over time, and make them grow. The aim of these assets is to sustain the work of the foundation by annually generating income so that it can continue its missions of public interest; efficient asset management guarantees its ability to fulfill these missions over the long term. The Institut Pasteur has four main types of productive asset – property to let, long-term financial investments, cash and equity securities.

In 2019	€M	%
Total	917	100
Property	205	22
Securities	660	72
Private equity/strategic partnerships	12	1
Cash	40	5

Productive assets account for the equivalent of three times the Institut Pasteur’s annual operating costs (ratio set out in late 2019). These assets generated €19.1 M during the 2019 fiscal year, reported in the profit-and-loss account, representing a reduction of €15.8 M in relation to 2018.

EARNINGS FROM ASSETS

In 2019	€M
Total	19.1
Property	6
Securities	10
Cash	3.1

As well as the income generated, the Institut Pasteur has statutory provisions and a reserve policy to ensure that its assets are regularly built up when the fiscal year ends with a surplus. In addition to its productive assets, the Institut Pasteur owns all its buildings in rue du Docteur Roux in Paris and its scientific equipment, reported on its balance sheet as tangible capital assets. It also owns its brand name and a portfolio of patents, which are not reported on the balance sheet but in the profit-and-loss account for their revenue from license agreements.

INCOME STATEMENT

The financial statements presented in the financial report concern the Institut Pasteur foundation in Paris, the Institut Pasteur de la Guadeloupe and the Institut Pasteur de la Guyane.

In 2019	€M
Institut Pasteur operating revenue	268.7
Institut Pasteur operating expenses	293.7
Contribution from IP Guadeloupe and IP Guyane	0.1
Operating income	- 24.9
Institut Pasteur financial result	13.8
Contribution from IP Guadeloupe and IP Guyane	- 0.0
Financial income	13.8
Recurring operating income	- 11.1
Institut Pasteur non-recurring income	50.1
Contribution from IP Guadeloupe and IP Guyane	- 0.9
Non-recurring income	49.2
NET INCOME	38.1

Recurring operating income showed a deficit of €11.1 M, as against €10.3 M for 2018. In 2019, this deficit was comprised of an operating deficit of €24.9 M, which was partially offset by surplus financial income of €13.8 M. Non-recurring income posted a profit of €49.2 M, primarily due to the reversal, in 2019, of the provision recorded against stable stock investments in 2018, which amounted to €44.9 M. Due to this surplus, in 2019 the Institut Pasteur recorded net income of €38.1 M, as against €-30.6 M in 2018.



AN EFFECTIVE SUSTAINABLE DEVELOPMENT STRATEGY

One year into its 2019-2023 Strategic Plan, the Institut Pasteur’s commitment to sustainable development is clearly visible.

Green Campus/Responsible Campus

In 2019, through its Green Campus/Responsible Campus project, the Institut Pasteur continued with the positive momentum started nearly a decade ago. Green Campus/Responsible Campus is based around three main objectives: preserving resources, preventing pollution, and sharing ideas and best practices. Contributions and ideas from Institut Pasteur employees are regularly incorporated into the initiative. The introduction of a Reuse room, recognition of the Institut Pasteur at the Green Gown Awards, and the development of a mobility plan all attest to the Institut Pasteur’s proactive commitment to environmental protection.

Participation in the Green Gown Awards

The Institut Pasteur took part in the fifth edition of the Green Gown Awards, organized by the French Environment Ministry. The awards strive to recognize higher education institutions that have implemented innovative sustainable development projects on their campus that generate real benefits for society. The Institut Pasteur entered its Green Campus/Responsible Campus project in the “Responsible institution of the year” category, for institutions committed to promoting a more sustainable society. The Institut Pasteur came second in this category.

Reuse room at the Institut Pasteur

The Institut Pasteur took part in the fifth edition of the Green Gown Awards, organized by the French Ministry of Ecological and Solidarity Transition. The aim of the awards is to recognize higher education institutions that have implemented innovative sustainable development projects on their campus that achieve real benefits for society. The Institut Pasteur entered its Green Campus/Responsible Campus project in the “Responsible institution of the year” category, for institutions committed to promoting a more sustainable society. The Institut Pasteur came second in this category.

Mobility plan

The mobility plan is a series of measures to optimize and improve the efficiency of staff movements with the aim of reducing emissions and lessening road traffic. A survey was carried out from June 21 to July 13, 2019 to assess the mobility of Institut Pasteur staff. The results of the survey were taken into account when drawing up the Institut Pasteur mobility plan. The plan incorporates the following measures:

- exploring the option of adding a roof to campus bicycle parks;
- new bicycle parks;
- traffic calming in rue du Docteur Roux;
- use of clean vehicles.

The mobility plan enables the Institut Pasteur to step up its action in the area of sustainable development.

RECYCLING



67.60 t

of materials handled in 2019



0.25 t

of aluminum cans



3.77 t

of glass



7.72 t

of plastic and polystyrene



0.21 t

of batteries



25.88 t

of paper and cardboard



1.66 t

of polypropylene tip boxes



28.11 t

of WEEE

OTHER RECOVERY



5.85 t

of dried organic waste

REUSE



15.22 t

of pallets reused

HUMAN RESOURCES: MEETING THE NEEDS OF INSTITUT PASTEUR STAFF

“Work more effectively together and empower each individual so as to create an attractive, collaborative working environment” – this cross-cutting, strategic priority provided an ambitious agenda for the HR measures implemented in 2019.

A healthy working environment

“Working more effectively together” means making ongoing improvements to the quality of working life for the Institut Pasteur community.

→ The introduction of working from home in 2019 was a clear demonstration of the Institut Pasteur’s commitment in this area. A huge number of staff made use of the scheme this year to achieve a better balance between their professional and personal lives.

→ The paid leave donation scheme was also welcomed by staff as a way of encouraging kindness and generosity among

teams. The aim is to help employees with severely ill children or caring for a family member or close acquaintance with a disability or loss of independence.

→ The HR teams also worked to improve the prevention and management of sensitive situations. A more effective procedure and a series of sessions to raise awareness among managerial staff helped facilitate dialog and ensure that every voice can be heard.

→ Finally, also this year, various joint preventive measures helped safeguard health in the workplace, such as the continued partnership between the Institut Pasteur and the AP-HP Massage and Physiotherapy Training Institute to prevent musculoskeletal disorders (MSDs), and the provision of tailored hearing protectors and safety glasses with prescription lenses.

Encouraging, guiding and advising the Institut Pasteur community

→ In 2019, the HR Department **pursued its efforts over recent years to digitize and modernize** its processes, with the introduction of paperless payslips, the launch of an online internal job exchange and the digitization of home working requests. All these measures help simplify the daily lives of the Institut Pasteur’s staff.

→ Employees have continued to enjoy **valuable career guidance and management** – the MAASCC welcome, support and career development structure for scientists provided personalized support, round tables, after work careers events and skills workshops throughout 2019 for Master’s and PhD students, scientists and engineers.

→ In the area of labor relations, an electronic voting system was used to elect new staff representatives, with members being elected to the new **Social and Economic Committee**, now the sole staff representative body. The HR teams were also closely involved in the launch of the Hearing Institute after holding a number of constructive information and consultation sessions.

→ The HR Department has pledged to **recognize and value the work of Institut Pasteur staff** more effectively, for example with the salary increase in January 2019 for PhD students, who have always made a major contribution to research activities.

STRATEGIC
PLAN
2019-2023

AMBITIOUS HR TARGETS

- Introduce a strategy for forward-looking management of jobs and skills (starting with discussions on the development of scientific professions)
- Secure the EU’s “HR Excellence in Research” award
- Continue to recruit wisely and support organizational structures
- Pursue measures to improve the quality of working life
- Promote gender equality: in 2019, the work of the “Women and Science” project team resulted in the development of an action plan containing specific measures that will be implemented in 2020 to improve the representation of women in senior scientific positions.

ON CAMPUS

2,780
staff members
on campus
(as at 12/31/2019)



2,217
IP employees
(71.9% with permanent contracts)

510
employees from external
research organizations
(OREX)

53
interns

Of the **2,727** IP & OREX employees (excluding interns)

12.7% administrative and
technical managers
27.5% non-managerial staff
59.8% senior scientists, engineers
and health officers

DIVERSITY ON CAMPUS

42.7
average age
of IP employees

59%
of IP staff
are women

74
nationalities
on campus

FOCUS ON RECRUITMENT

408
people hired in 2019
(excluding fixed-term to permanent contracts)



59.8%
women hired

43.6%
scientists
(excluding engineers)

26.5%
under the age
of 25

PROFESSIONAL CATEGORIES AT THE INSTITUT PASTEUR

Of the 2,217 Institut Pasteur employees,
percentage per category
(as set out in the Jobs and Skills Guide)

65.3% Research

32.4% Administrative
and Technical

2.3% Health

SKILLS DEVELOPMENT (training)



4,460 staff registered on training courses,
including **890** OREX employees and interns

€3,400k invested
in professional training

(costs including time spent on training
and compulsory contributions)

40,020 training
hours including **6,800** for members of
external organizations (OREX) and interns

CAREER SUPPORT FOR SCIENTISTS



89 state-employed researchers
and engineers
met with the Careers Committee

154 PhD students and post-doctoral
fellows followed the career guidance
program at the MAASCC welcome,
support and career development structure
for scientists

46 career events
(round tables, sessions, etc.) held including
28 skills and CV workshops

DONATIONS, SPONSORSHIP AND LEGACIES EVER COMMITTED TO DEFENDING RESEARCH

In 2019, nearly a third of the Institut Pasteur's resources came directly from individual and corporate donations and legacies. This vital support has a direct impact on our work.

In 2019, the Institut Pasteur received financial support from almost 311,000 individual donors, a remarkable figure due in large part to the charity "Z Event" held from September 20 to 22, 2019. Created in 2016 by Adrien Nougaret and Alexandre Dachary, the annual Z Event assembles video game live streamers for a marathon session lasting more than 50 hours in which content is streamed live and viewers are encouraged to donate money to a charity. In 2019, the organizers chose the Institut Pasteur as the cause they would be supporting. The funds raised through the generosity of these individuals, as well as our loyal donors, partner companies and foundations, will enable the Institut Pasteur's scientists to continue their vital work, optimize its impact and explore new avenues for research.

Nearly 27,000 of our donors have chosen to set up a direct debit, which enables them to spread their donations over the entire year.

For the 13th year in a row, our donors showed extraordinary generosity in supporting the Institut Pasteur's research during Pasteurdon, which ran from October 9 to 13, 2019. Pasteurdon 2019 owes its success to actor Alexandra Lamy, patron of the campaign since 2011, and to more than 40 media partners – TV channels and radio stations – that broadcast the campaign film free of charge and rallied their presenters and journalists to the cause. The 2019 edition of Pasteurdon was based on that ubiquitous symbol of scientific research, the white lab coat. Alexandra Lamy and all the celebrities supporting the Institut Pasteur were encouraged to don the "uniform" of our scientists, bearing the Institut Pasteur logo, in response to the slogan "Defending research together."



ON DECEMBER 19, 2019, ADRIEN NOUGARET, ALIAS ZERATOR, CAME TO MEET THE RESEARCHERS AT THE INSTITUT PASTEUR, THREE MONTHS AFTER THE Z EVENT VIDEO GAME MARATHON WHICH SET A FUND-RAISING RECORD.



SOME OF THE LAB COATS CUSTOMIZED BY CONTEMPORARY GRAFFITI ARTISTS DURING PASTEURDON 2019.

A dozen graffiti artists also got involved in the "Put on your lab coat" campaign (#MetsTaBlouse), customizing the lab coats of the Institut Pasteur's scientists and transforming them into unique works of art.

Donations from companies and foundations

2019 saw the eighth edition of the Sanofi-Institut Pasteur Awards, presented to scientists in recognition of their innovative work in life science and biomedical research. Once again in 2019, the Institut Pasteur's sponsors and partners got behind the 13th edition of Pasteurdon. The Le Roch-Les Mousquetaires Foundation, which provides direct funding for two research programs on food safety, elicited the support of the Les Mousquetaires group via the sale of charity-linked products in the Intermarché and Bricomarché store chains. ASSU 2000, a Pasteurdon partner for the sixth year running with its ongoing support for research on cardiovascular diseases, continued its charity-linked product campaign for Pasteurdon, with a donation made for every new insurance policy taken out.

WHAT THEY HAVE TO SAY ABOUT US

"GOOD LUCK WITH YOUR RESEARCH
AND WELL DONE TO ALL THE SCIENTISTS."

"I HAVE EVERY FAITH IN YOU. THANK YOU
FOR ALL THAT YOU ARE DOING."

"TO HELP SCIENTISTS FIND A TREATMENT
AND THEN A VACCINE FOR THE CORONAVIRUS
AND ALL VIRUSES IN GENERAL. THANK YOU."

The social welfare company, AG2R LA MONDIALE, a loyal and generous Pasteurdon partner with its sport-based fundraising campaign “Vivons Vélo,” once again set the bar high, raising a total of nearly €100,000 for the Institut Pasteur.

Another highlight of 2019 was the opportunity to welcome new sponsors on board: the Fondation IPSEN, La Mutuelle du Médecin and the Fondation Tourré.

In total, donations from companies and foundations in France raised over €7 million.

Legacies increasingly shared

In 2019, 120 new legacies were submitted to the Board of Governors, representing a total of €93 million. The Institut Pasteur shares most of the legacies bequeathed to it with several other institutions.

Life insurance policies continued to represent a leading source of recurring income and remained stable in 2019, raising €15.3 million. As with legacies and gifts, these policies offer favorable tax arrangements in that they are exempt from transfer duties.

Quality strategy: pioneering certification renewed

The Institut Pasteur's Legacies and Real Estate Assets Management Office is still the only department of its kind in France to have applied quality procedures to all its activities. Following the annual audit, AFNOR Certification renewed the Institut Pasteur's ISO 9001:2015 certification for 2019.

Communications activities

In 2019, for the fifth year in a row, a major annual promotional campaign for legacies and gifts was launched on radio stations and TV channels, on the web and in the mainstream and legal press to raise awareness of these important long-standing funding sources for the Institut Pasteur. The number of people seeking information about legacies, life insurance and donations, as well as gift notifications, continued to rise. Questions concerning more innovative schemes, such as the temporary transfer of usufruct rights and posthumous gifts, have also become more frequent. To manage all these new contacts, the Legacies and Real Estate Assets Management Office employs two dedicated staff members in charge of legator relations. Benefactors can contact them for advice and guidance or speak to one of the office's three legal experts. The six-monthly “Legacies and Gifts” newsletter is the main means of communication with legators. The tenth edition was sent out at the end of 2019. The newsletter focuses on a specific aspect of gifts, legacies or life insurance policies in each issue, generating substantial feedback and many personal testimonials.

The Think Tank on Philanthropic Trusts, which was set up by the Institut Pasteur following the success of its first Conference on Philanthropic Trusts in 2009, continued its work and issued opinions. The experts in this think tank include notaries, lawyers and bankers. It is currently the only platform where experts from a variety of disciplines can come together to discuss questions relating to generosity and philanthropy.

PASTURIANS WHO COMMITTED TO VIVONS VÉLO, THE SPORTS AND SOLIDARITY OPERATION FOR THE INSTITUT PASTEUR.



MAJOR SPONSORS



SPONSORS

AG2R LA MONDIALE
ASSU 2000
AUCTORIANA ANSTALT
CERCLE FSER
CRPCEN
DENNIS AND MIREILLE GILLINGS FOUNDATION
FLORENCE GOULD FOUNDATION
FONDATION AIR LIQUIDE
FONDATION BEYTOUT
FONDATION BTP PLUS
FONDATION COGNACQ-JAY
FONDATION DANIEL ET NINA CARASSO
FONDATION EDF
FONDATION IPSEN
FONDATION LE ROCH-LES MOUSQUETAIRES
FONDATION POUR L'AUDITION
GROUPE PASTEUR MUTUALITE
JANSSEN HORIZON
LHW STIFTUNG
MSD AVENIR
MUTUELLE DU MÉDECIN
MUTUELLE DU PERSONNEL AIR FRANCE
NOUVELLE CASSIUS FONDATION
ODYSSEY REINSURANCE COMPANY
PFIZER
SACEM
VOLKSWAGEN STIFTUNG

PARTNERS

BNP PARIBAS
BPE
SOCIÉTÉ GÉNÉRALE

BOARD OF GOVERNORS

(APRIL 2020)

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

BOARD OF GOVERNORS BUREAU	OTHER MEMBERS
Christian Vigouroux CHAIRMAN French Council of State Department Head	Geneviève Almouzni CNRS Director of Research, team leader at the Institut Curie, Paris
Hubert du Mesnil VICE-CHAIRMAN Ponts et Chaussées engineer and Chairman of Tunnel Euralpin Lyon-Turin	Gilles Bloch Chairman and Chief Executive Officer of Inserm (French National Institute for Health and Medical Research)
Artur Scherf VICE-CHAIRMAN Head of the Biology of Host–Parasite Interactions Unit, Institut Pasteur	André Choulika CEO and Co-Founder of the Collectis Group
Sandrine Etienne-Manneville SECRETARY Head of the Cell Polarity, Migration and Cancer Unit, Institut Pasteur	Stéphanie Fougou Ingenico Group General Counsel
Alban Hautier TREASURER Assistant Director of the Budget Division within the French Ministry of Public Action and Accounts	Muriel Hilaire-Soule Head of the Pasteur Museum, Institut Pasteur
Antoine Triller PERMANENT GUEST OF THE BUREAU Head of Research at Inserm and Director of the École Normale Supérieure Institute of Biology	Susan Liautaud Independent Director (Susan Liautaud & Associates Limited)
	Jean-Claude Manuguerra Head of the Environment and Infectious Risks Research and Expertise Unit, Institut Pasteur
	Inès-Claire Mercereau Chief Advisor to the French Government's Accounting Office
	Anne Paoletti Scientific Director for Biology and Health at the Directorate-General of Research and Innovation, French Ministry of Higher Education, Research and Innovation
	Claudia Pena-Rossi Medical Director, DNDi (Drugs for Neglected Diseases initiative)
	Antoine Petit President of the CNRS (French National Center for Scientific Research)
	Félix Rey Head of the Structural Virology Unit, Institut Pasteur
	Jérôme Salomon Director-General for Health, French Ministry of Solidarity and Health
	Marie-Noëlle Ungeheuer Head of the Clinical Investigation and Access to BioResources Platform (ICAReB), Institut Pasteur
	Marie-Hélène Verlhac Director of the CIRB (Center for Interdisciplinary Research in Biology), Collège de France

SCIENTIFIC COUNCIL

(APRIL 2020)

The Scientific Council advises 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.

ELECTED PASTEURIAN MEMBERS

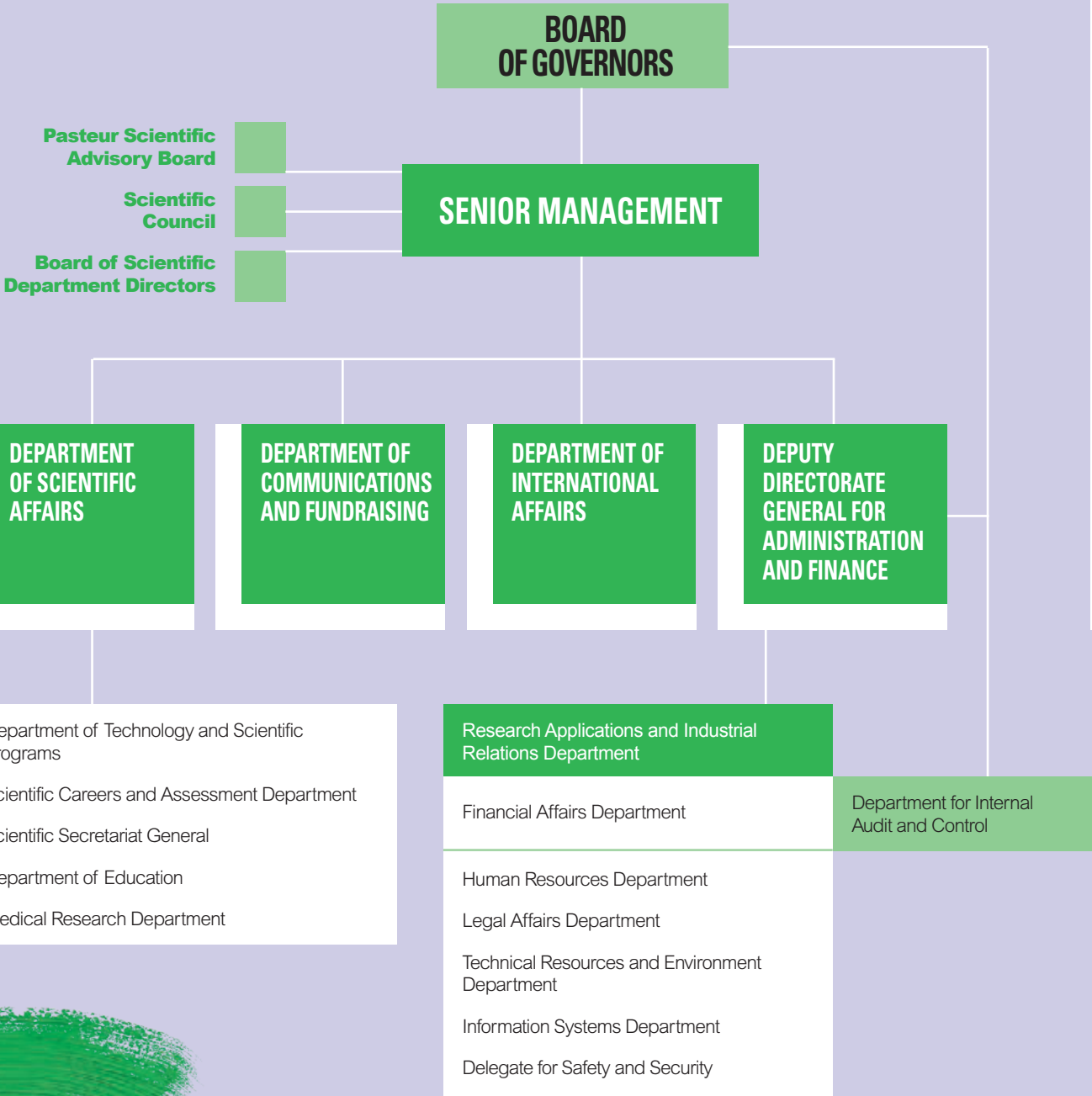
- Arnaud Échard**
Head of the Membrane Traffic and Cell Division Unit
- Jean-Marc Ghigo**
SECRETARY
Head of the Genetics of Biofilms Unit
- Aziz El Amraoui**
Head of the Progressive Sensory Disorders, Pathophysiology and Therapy Unit
- Michaela Müller-Trutwin**
VICE-CHAIR
Head of the HIV, Inflammation and Persistence Unit

EXTERNAL MEMBERS

- Amos Bairoch**
Prof. Department of Human Protein Science, Computer and Laboratory Investigation of Proteins of Human Origin (CALIPHO), University of Geneva Medical School, Switzerland
- Arturo Casadevall**
Prof. Microbiology and Immunology Department, Albert Einstein College of Medicine, New York, USA
- Angela Gronenborn**
Prof. Department of Structural Biology, University of Pittsburgh School of Medicine, Pittsburgh, USA
- François Guillemot**
Senior Group Leader, Neural Stem Cell Biology Laboratory, the Francis Crick Institute, London, UK
- James Di Santo**
CHAIR
Head of the Innate Immunity Unit
- Philippe Bastin**
Head of the Trypanosome Cell Biology Unit
- Carmen Buchrieser**
Head of the Biology of Intracellular Bacteria Unit
- Carla Saleh**
Head of the Viruses and RNA Interference Unit
- Eva Harris**
Prof. Division of Infectious Diseases and Vaccinology Director, Center for Global Public Health, UC Berkeley School of Public Health, USA
- Nicholas Hastie**
Prof. MRC Human Genetics Unit, MRC Institute of Genetics and Molecular Medicine at the University of Edinburgh, Edinburgh, UK
- Anne O'Garra**
Senior Group Leader, Laboratory of Immunoregulation and Infection, the Francis Crick Institute, London, UK
- Julian Parkhill**
Prof. Genomics of Bacterial Pathogens, Sanger Institute, Cambridge, UK

GOVERNING BODIES

(APRIL 2020)



MANAGEMENT OF THE INSTITUT PASTEUR

(APRIL 2020)



Stewart Cole
President



François Romaneix
Senior Executive Vice-President Administration and Finance



Christophe d'Enfert
Scientific Director

The President, a figure from the world of science, prepares and implements strategic planning. He is supported by a management team comprising an Executive Board and a Senior Management Board.



Isabelle Buckle
Vice-President Research Applications and Industrial Relations



Jean-François Chambon
Vice-President Communications and Fundraising



Pierre-Marie Girard
Vice-President International Affairs and International Network



Pascal Masse-Navette
Director for Internal Audit and Control



Nathalie Denoyés
Vice-President Technical Resources and Environment



Michael Nilges
Vice-President Technology and Scientific Programs



Stéphane Fournier
Vice-President Information Systems



Odile Hermabessière
Vice-President Human Resources



Bruno Hoen
Medical Research Director



Nathalie de Parseval
Scientific Secretary General



Françoise Perriolat
Vice-President Financial Affairs



Monica Sala
Director of the Education Department



Patrick Trieu-Cuot
Vice-President Scientific Careers and Assessment



Samuel Valcke
Vice-President Legal Affairs

PORTRAITS OF PASTEURIANS



1. RESEARCH MISSION P.20

The damage that the bacterium *Helicobacter pylori* (seen in the large background image) does to the DNA in our gastric cells plays an important role in the development of cancerous lesions. Eliette Touati and her team are studying this in order to shed light on the mechanisms responsible for the development of cancer caused by bacterial infection. On the clinical side, by testing blood samples taken from patients, they are searching for biomarkers that can be used for diagnosis of gastric cancer at a very early stage.



2. PUBLIC HEALTH MISSION P.54

Rabies continues to burden many poor rural communities worldwide. Hervé Bourhy's lab, which is also a French National Reference Center and a WHO Collaborating Center, performs diagnostic tests for rabies incidences in France and collaborates with health authorities for surveillance efforts and international rabies-control education. Their research focuses on rabies lyssaviruses (infected murine brain cell in large background photo), and their patterns of evolution and replication, particularly while adapting to the specific environments of their host whether bat, dog, or human. His lab is also involved in drug development.



3. DEVELOPMENT OF RESEARCH APPLICATIONS MISSONS P.62

These images evoke some key aspects of research application development. On the top left, is the Institut Pasteur Inventor's Prize that some Pasteurian researchers receive in recognition of their specific innovation. The background photo of silkworm eggs and the drawing of a silkworm on a branch refer to one of the first industrial partnerships: Louis Pasteur's cure for the silkworm disease in 1865 which rescued the imperiled silk industry. On the top right, an "organ on chip" developed by Emulate®, a biotech company with which an organ on chip center was established at the Institut Pasteur through a strategic collaboration. Claire Héritier, interfacing between law, business and science, guides Institut Pasteur research units in their collaborations with industry partners.



4. EDUCATION AND TRAINING MISSION P.68

Appointed professor at Collège de France and member of the Academy of Sciences in 2019, Lluís Quintana-Murci specializes in human genetics, with a particular focus on populations, human evolution and diversity. How the admixture of our ancestors with Neanderthals affected our immune responses to viruses, the migratory routes of the Bantu peoples through Africa, and genes that both enable us to survive infections and affect our different ways to respond to therapeutic treatments are key topics of interest of his lab. His work is highly multidisciplinary, touching on a wide variety of scientific disciplines ranging from anthropology, history and linguistics to genetics, immunology and even virology.

5. INTERNATIONAL P.74

These images portray some of the concerns of an international medical entomologist: mosquito migration from forests into urban areas, shown via a photograph a Rio de Janeiro; a mosquito larva seen under a microscope; a female *Aedes aegypti* mosquito, and field work being performed in Brazil. In her laboratory, which has links with the Institut Pasteur International Network, Anna-Bella Failloux receives samples of insects that are prevalent throughout the world and sometimes cause dangerous epidemics. Anna-Bella works hand-in-hand with her team to study virus transmission mechanisms and how viruses develop and multiply in their hosts. Her photo was taken in the new insectarium.



6. OUR RESOURCES P.80

During the 2019 Z Event, 54 streamers mobilized their communities for more than 54 hours in aid of the Institut Pasteur. €3.5 million was raised during the video game marathon, which saw the participation of France's top e-sport players. This extraordinary sum was directly allocated to scientific research. The Institut Pasteur is very proud to have been involved in such a large-scale event, which attracted interest and support from well beyond the traditional video game streaming community. The event was a first for the Institut Pasteur, and represented an opportunity to rally an entirely new audience to its cause in 2019.



Institut Pasteur / Department of Communications and Fundraising – 25-28, rue du Docteur-Roux – 75724 Paris Cedex 15, France. **Photo credits:** Photothèque Institut Pasteur; William Beaucardet; AdobeStock/13smile; AdobeStock/deConcio; AdobeStock/f11photo; AdobeStock/Ingo Menhard; AdobeStock/Jiri Prochazka; AdobeStock/katiekk2; AdobeStock/pixelaway; AdobeStock/Syda Productions; AdobeStock/Tartila; AdobeStock/whitehouse; AdobeStock/ZhouEka; Anastassia Mikhailova/Institut Pasteur; Christine Schmitt; David Arraez; Didier Goupy; Eduardo Rocha; Emulate®; François Gardy; François Schweisguth; Institut Pasteur de la Guyane/Pascal Gaborit; Institut Pasteur de Nouvelle-Calédonie/Arnaud Tarantola; Institut Pasteur/A-M. Pais-Correia, M-I. Thoulouze et A. Alcover, Lymphocyte Cell Biology Unit – S. Guadagnini, *Plateforme de microscopie ultrastructurale* – A. Gessain, Oncogenic Virus Epidemiology and Pathophysiology Unit; Institut Pasteur/Arnaud Tarantola; Institut Pasteur/Artur Scherf; Institut Pasteur/Charles Dauge; Institut Pasteur/Charles Dauge – Colorization Jean-Marc Panaud; Institut Pasteur/Christine Schmitt; Institut Pasteur/Claude Hannoun and Charles Dauge; Institut Pasteur/Lionel Costa; Institut Pasteur/Marie-Christine Prévost, *Plateforme de microscopie électronique*; Carmen Buchrieser, Genomics of Microbial Pathogens Unit; Institut Pasteur/Musée Pasteur; Institut Pasteur/Nathalie Sol-Foulon and Olivier Schwartz, Virus and Immunity Unit – Marie-Christine Prevost, *Plateforme microscopie ultrastructurale* – Colorisation Jean-Marc Panaud; Institut Pasteur/Olivier Schwartz, Virus and Immunity Unit with Stéphanie Guadagnini and Marie-Christine Prévost, PFMU Imagopole; Institut Pasteur/Perrine Bomme; Institut Pasteur/Sylvain Brisse; Institut Pasteur/Valérie Choumet; Institut Pasteur/Valérie Zeitoun; Jean-François Charles/Institut Pasteur; Julien Burlaud-Gaillard and Philippe Roingeard, Inserm and université de Tours; Konstantin Postumitenko; Laurent Audry; Magali Herrant; Maxime Rotival; McElreavey; Nader Yatim; Olivier Panier des Touches/DolceVita; Picasa; Pierre Gounon; RYSK / Mika Cotellon-Chapter2; Timo Verdeli; Thomas LANG; Valérie Zeitoun; Vibol HUL/Institut Pasteur Cambodia; All rights reserved. **Design and production:** **WAT** - wearetogether.fr - 1911_00720. ISSN: 1632-0115.

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