international network
Institut Pasteur

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international network
Institut Pasteur

RIIP Institut Pasteur International Network

2012 REPORT

32
Institutes
worldwide

Contents

A community committed to serving the most vulnerable

ALICE DAUTRY PRESIDENT OF INSTITUT PASTEUR

The Institut Pasteur International Network comprises 32 institutes worldwide, a vast community of committed scientists working together on international public health research projects. The Institut Pasteur leads numerous scientific work programmes between the institutes in the Institut Pasteur International network, and is responsible for the scientific and administrative management of fourteen of them. It is therefore well-positioned to orchestrate the scientific programme of the international network, which also involves numerous external partners.

Leading and strengthening the Institut Pasteur International Network involves three key activities: recruiting and training researchers, strengthening technical resources and equipment for major projects, and developing international cooperation. The Institut Pasteur International Network has chosen to build strong links with major international partners. Research to combat disease requires joining forces with a wide range of regional and international players. It is only by combining diverse skills as well as human and financial resources, that we will be able to meet the human health challenges of the futures. The Pasteur International Network is now actively facilitating the development of projects involving several members of the international network and other partners. In addition, international cooperation has been initiated with numerous organisations, including the WHO in 2012, to help countries to improve their surveillance, detection and response systems in accordance with International Health Regulations.

The Institut Pasteur network focuses primarily on scientific and technical training to ensure that scientific progress benefits most people. Some institutes have started using e-learning platforms to train personnel. A new programme was developed in 2012 to provide researchers from developing countries with the conditions they require to conduct research in their home country; it entails providing support over a four year period to independent research groups set up and directed by researchers returning to their home country. Two researchers were selected in 2012 to manage groups in Africa.

Support is also given through the Dedonder-Clayton prize, which rewards outstanding scientific research on HIV/AIDS and infectious diseases by talented young researchers from developing countries. It was awarded for the first time in 2012 to two researchers from the Pasteur Centre in Cameroon and the Institut Pasteur in Cambodia. The members of the Institut Pasteur International Network have been enhancing and upgrading resources for several years. They are now equipped with state-of-the-art technology and technical resources. High level biosafety (P3) laboratories have been set up in Cambodia, in the Central African Republic and in the Ivory Coast.

Only by combining skills, as well as diverse human and financial resources, will we be able to meet the human health challenges of the future.

The Institut Pasteur International Network is involved, through numerous partnerships and programmes, in research and surveillance of diseases, particularly infectious diseases, disease prevention, combatting epidemics and pandemics, and training technicians, engineers and PhD researchers in all of the regions in which is located. The global network of Institut Pasteur is unique and, more generally a widely beneficial vector of progress.

Scientists at the forefront

FRANÇOISE BARRÉ-SINOUSSI HONORARY PRESIDENT OF THE INSTITUT PASTEUR INTERNATIONAL NETWORK AND NOBEL PRIZE IN MEDICINE IN 2008

Just last May, we celebrated the thirtieth anniversary of the discovery of the AIDS virus. It has proven to be one of the deadliest pandemics in modern history. One of the lessons it has taught us is how vulnerable we are to emerging and re-emerging infectious diseases. Today, as the last few years have clearly shown, we are aware that pathogens can hit anywhere and at any time. Due to their poor health systems, disadvantaged countries bear the brunt of infectious diseases. The major diseases of poverty, namely malaria, tuberculosis and HIV and even viral hepatitis, claim millions of lives every year. A key purpose of the global Institut Pasteur International Network is to help these countries find solutions to the health problems they face and to prepare them to deal urgently with new threats.

Institut Pasteur professionals worldwide are at the forefront, detecting epidemics, alerting the health authorities and providing tailored solutions to halt their development. Through public health work and the research programmes set up in partnership with national authorities and local healthcare facilities, the network institutes participate in enhancing capacity and in technology transfer to young scientists, biologists, doctors and healthcare professionals. Regional training and cooperation with other network institutes enable such benefits to be extended well beyond the Institutes' country of location. By its very nature and by upholding solidarity-based values, the global Institut Pasteur International Network is a powerful driver of South-South cooperation.

The importance of research is paramount, particularly as experience has repeatedly shown the beneficial structuring effect it has on health services. By participating in clinical research, which is highly demanding in terms of quality and standards, health services gain expertise and set up the systems and working methods required to meet international standards. Ultimately, research programmes enable direct improvement in all phases of testing, treatment and overall patient care.

By its very nature and by upholding solidarity-based values, the global Institut Pasteur International Network is a powerful driver of South-South cooperation.

We should also keep in mind the integral role that civil society can play in public health. For example it played a key part in the early years of the AIDS epidemic. Extending far beyond their primary social or political function, the non-profit organisations set up to combat HIV have become true protagonists of public health and research. In many countries with limited resources, representatives of civil society provide support to public services. They participate in education, prevention, testing and care for communities affected by HIV and other diseases, and assist in patient treatment. Strengthening the bonds between the network institutes and local communities and not-profit organisations, for all diseases, with surely to benefit everyone and especially patients.

Pasteurians in the world: the new faces of the international network

MARC JOUAN SECRETARY-GENERAL OF THE INSTITUT PASTEUR INTERNATIONAL NETWORK

Since 2010, a whole host of developments have taken place in the international network. For example new institutes were opened in Laos and Shanghai, a framework agreement was set up with the World Health Organization (WHO), we have adopted a stronger position on international health issues, and we get up new international research programmes on infectious diseases.

All of these developments focus on one priority: finding solutions to combat infectious diseases. This means working in vastly changing environments, impacted by population growth, increasing urbanisation, economic changes and ecological and political upheavals. In line with international health regulations, we have expanded local diagnosis capacity and have set up or extented support to surveillance programmes.

The essential role that our laboratories play in both medical care and in optimising surveillance networks is often not fully appreciated. The strength of the network resides in its enduring structure and in our commitment of our researchers. The international network's teams were actively involved in dealing with the avian influenza epidemic in Cambodia, enteroviruses in Vietnam and Cambodia and the plague epidemic in South America. Such mobilisation is only possible with the involvement of international partners. The French Development Agency has provided support for a new project to assess the health risks arising from upheavals in secondary ecosystems and economic developments in South-East Asia. The French Ministries of Foreign Affairs and of Higher Education and Research, and the United States Health Department draw on the international network for support in dealing with the challenging globalisation of infectious diseases.

The Institut Pasteur International Network has made research one of its priorities to combat infectious diseases. Research is closely linked to each country's health requirements and concerns international poverty-related health issues (such as AIDS, tuberculosis and malaria) and the major causes of child morbidity and mortality. Numerous teams in Africa and Asia also work on identifying emerging pathogens, anthropozoonoses and vector-borne diseases, and on understanding the risk factors of these emerging diseases. Finally, research on antimicrobial drug resistance and combatting somewhat ignored infectious diseases in Southern countries (rabies, arboviruses, viral hepatitis, leishmaniasis, Buruli ulcer...) are other areas currently being developed.

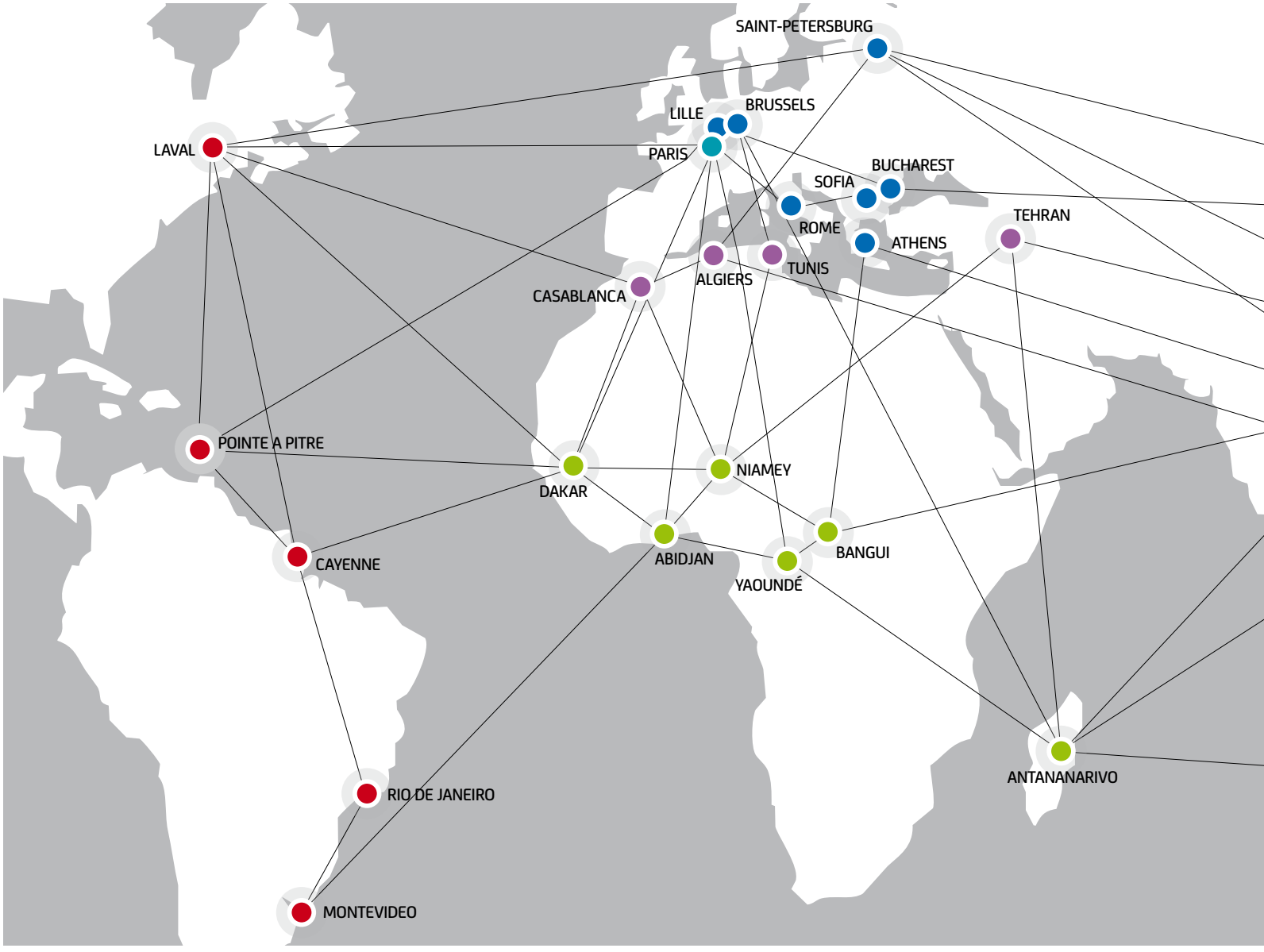
The strength of the network resides in our enduring structure and in our commitment of our researchers.

Strengthening human resources is one of the network's priorities. This means attracting young scientists who wish to conduct research in endemic areas, as well as those wishing to share the knowledge they gained through international experience with those back in their home country.

In this report we pay tribute to the men and women who make up the international network. The portraits of these researchers illustrate the wide range of environments in which research is developing, all with a common goal. It shows how human endeavor extends beyond the individual to the community and is the very essence of the international network.

A global network

The Institut Pasteur International Network is a partnership of 32 public health and research institutes spread over the five continents. It emerged from Louis Pasteur's desire to actively combat infectious diseases, through high-quality research.



Europe

- **FRANCE - PARIS**
  INSTITUT PASTEUR
- **BELGIUM**
  SCIENTIFIC INSTITUTE OF PUBLIC HEALTH[1]
- **BULGARIA**
  STEPHAN ANGELOFF INSTITUTE
- **FRANCE**
  INSTITUT PASTEUR IN LILLE
- **GREECE**
  HELLENIC INSTITUT PASTEUR
- **ITALY**
  INSTITUT PASTEUR - CENCI BOLOGNETTI FOUNDATION
- **ROMANIA**
  CANTACUZINO INSTITUTE
- **RUSSIA**
  INSTITUT PASTEUR IN SAINT PETERSBURG

Americas

- **BRAZIL**
  FIOCRUZ
- **CANADA**
  INRS-INSTITUT ARMAND FRAPPIER
- **GUADELOUPE**
  INSTITUT PASTEUR IN GUADELOUPE
- **GUYANE**
  INSTITUT PASTEUR IN FRENCH GUIANA
- **URUGUAY**
  INSTITUT PASTEUR IN MONTEVIDEO

Africa

- **CAMEROON**
  PASTEUR CENTRE IN CAMEROON
- **COTE D'IVOIRE**
  INSTITUT PASTEUR IN COTE D'IVOIRE
- **MADAGASCAR**
  INSTITUT PASTEUR IN MADAGASCAR
- **NIGER**
  CERMES
- **CENTRAL AFRICAN REPUBLIC**
  INSTITUT PASTEUR IN BANGUI
- **SENEGAL**
  INSTITUT PASTEUR IN DAKAR

MATI[2]

- **MOROCCO**
  INSTITUT PASTEUR IN MOROCCO
- **ALGERIA**
  INSTITUT PASTEUR IN ALGERIA
- **TUNISIA**
  INSTITUT PASTEUR IN TUNIS
- **IRAN**
  INSTITUT PASTEUR IN IRAN

Asia

- **CAMBODIA**
  INSTITUT PASTEUR IN CAMBODIA
- **CHINA**
  INSTITUT PASTEUR OF SHANGHAI - CHINESE ACADEMY OF SCIENCES
  HONG KONG UNIVERSITY-PASTEUR RESEARCH CENTRE
- **KOREA**
  INSTITUT PASTEUR KOREA
- **LAOS**
  INSTITUT PASTEUR IN LAOS
- **NEW CALEDONIA**
  INSTITUT PASTEUR IN NEW CALEDONIA
- **VIETNAM**
  NATIONAL INSTITUTE OF HYGIENE AND EPIDEMIOLOGY
  INSTITUT PASTEUR IN HO CHI MINH CITY
  INSTITUT PASTEUR IN NHA TRANG

1. Associated institute.
2. Morocco, Algeria, Tunisia, Iran.

32 Institutes worldwide

Significant events

The Institut Pasteur International Network comprises 32 institutes, a vast community of committed scientists actively working on international public health research projects. On all five continents, 2011 and 2012 were marked by abundant scientific developments, events and partnerships.

INAUGURATIONS

Laos: 32nd institute in the Institut Pasteur International Network 1

The Institut Pasteur of Laos was inaugurated in January 2012 in Vientiane. Directed by Dr Paul Brey, the centre's main purpose is to prevent the risk of pandemics in Laos and South-East Asia, a region which is hard hit by diseases such as chikungunya, Japanese encephalitis and even dengue fever and malaria. With its 1,600 sq. m (17,222 sq. ft) of laboratory space and 60 employees, it considerably enhances the country's research capacity and autonomy in terms of diagnosis and prevention. In November 2012, the institute welcomed the French President, François Hollande, on an official visit to Laos.

Bangui: two high-security laboratories

On 1 July 2011, two high biosafety level laboratories (BSL 2 and BSL3) funded by the French Ministry of Employment, Labour and Health were inaugurated at the Institut Pasteur of Bangui in the presence of Alice Dautry, President of Institut Pasteur, and the ambassadors and representatives of national and international institutions. Mirdad Kazanji, Director of the Institut Pasteur of Bangui, stated: *"The biosafety level 2 and 3 laboratories strengthen our diagnostic capabilities enabling in-depth research into emerging viral and bacterial diseases and HIV/Aids."*

Institut Pasteur of Shanghai: creation of an incubator 3

In March 2011, the Institut Pasteur of Shanghai created a biotechnology business incubator: Advance BioChina. It will host and support 25 companies from all over the world over the next five years. The Institut Pasteur of Shanghai was set up as a non-profit research organisation in 2004 by the Chinese Academy of Sciences, the Institut Pasteur and the Shanghai Municipal Government. Its Director General, Ralf Altmeyer, specified that companies *"will benefit from [the incubator's] knowledge and expertise in China, and from its technology platforms".* The Institut Pasteur of Shanghai - Chinese Academy of Sciences inaugurated its new premises in Shanghai's city centre, in the presence of French president, François Hollande, on 26 April 2013.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New Caledonia: first high level biosafety laboratory

The Biosafety level 2 (BSL2) laboratory of the Institut Pasteur of New Caledonia was inaugurated on 22 February 2012. The laboratory enables the diagnosis of respiratory viruses, research on arboviruses (dengue and chikungunya) and the study of TB drug resistance. It supports regional cooperation between the Institut Pasteur of New Caledonia and the Pacific Community, which runs the Pacific Public Health Surveillance Network (PPHSN) and LabNet.

Pasteur Centre of Cameroon: renovation of virology laboratories 6

The Pasteur Centre was inaugurated on 26 January 2012 by the public health minister, André Mama Fouda, and by Françoise Barré-Sinoussi, following the renovation of the virology laboratories. The work was funded by the Total Foundation as part of the sponsorship agreement between Total Cameroon and the Pasteur Centre of Cameroon.

ANNIVERSARIES

Institut Pasteur of Bangui celebrates its 50th anniversary 2

On 25 February 2011, the Institut Pasteur of Bangui celebrated fifty years of presence in the Central African Republic. The anniversary gave it national and international scientific media attention, highlighting its research, training and public health work for the Central African population.

The Institut Pasteur of the Ivory Coast is 40 4

Created in 1972, the Institut Pasteur of the Ivory Coast celebrated its 40th anniversary with the inauguration of a new biosafety level 3 (BSL-3) laboratory for multidrug-resistant tuberculosis. The disease is a major problem in the country, particularly due to co-infection with the AIDS virus. For Mireille Dosso, Director of the institute, *"the facility will improve diagnosis of tuberculosis, particularly in children".* Despite the political, economic and social crisis that has severely affected the country, the Institut Pasteur of the Ivory Coast remains unfailingly dynamic.

Institut Pasteur of Hô Chi Minh-City: Already 120 years old! 5

On 18 November 2011, the Institut Pasteur of Hô Chi Minh-City, created by Albert Calmette in 1891, celebrated its 120th anniversary in the presence of the Minister of Health, Nguyen Thi Kim Tien, and representatives of numerous French and international scientific institutions. The scientific symposium associated with the ceremony dedicated to emerging pathologies confirmed the active role of the Institut Pasteur of Hô Chi Minh-City in infectious disease surveillance and research in Vietnam and South-East Asia.

Montevideo: 5 years on

Created in 2006, the Institut Pasteur of Montevideo celebrated its 5th anniversary on Tuesday 6 December 2011. Its director, Luis Barbeito, highlighted the institute's scientific and technological advances since its creation and presented future groundbreaking projects. The Institut Pasteur of Montevideo has nine technology platforms, two laboratories and five groups of young scientists. It is the first institute of the Institut Pasteur International Network in a Spanish-speaking country.


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AGREEMENTS SIGNED

Risks of epidemics: cooperation agreement with the WHO

In September 2012, the Institut Pasteur and the World Health Organization (WHO) signed a cooperation agreement to help countries manage the risks of epidemic outbreaks. The programme should strengthen their surveillance, alert and detection capabilities, by applying the principles set out in the WHO's International Health Regulations. The agreement also provides for field epidemiology and laboratory training programmes (FELTP), as well as the surveillance and control of vectors and reservoirs. The Institut Pasteur and the international network will contribute their technical expertise in these fields.

Agreement with the Cirad 7

On 10 October 2012, the Institut Pasteur and the Centre for International Cooperation in Agronomic Research for Development (Cirad) signed a framework agreement to improve international scientific cooperation.

HEALTH INTERVENTIONS

Chikungunya in New Caledonia

In February 2011, the New Caledonian health authorities announced the first case of chikungunya. The Institut Pasteur of New Caledonia biologically confirmed around thirty cases. The institute, in association with the National Reference Center (NRC) for Arboviruses and the platform for genotyping pathogens (PF8) of the Institut Pasteur of Paris, conducted a molecular analysis on the first indigenous case of the virus. The results showed that the strain of chikungunya virus came from Asia, unlike the strain that had spread in the Indian Ocean, which originated in East, Central and South Africa. The results confirm the Asian origin of the virus currently active in New Caledonia.

Bacterial meningitis in Sub-Saharan Africa

Between 1 January and 11 March 2012, Benin, Burkina Faso, Chad, Ivory Coast and Ghana were affected by a bacterial meningitis epidemic (6,685 cases of meningitis, of which 639 deaths).
The Institut Pasteur of Ivory Coast actively participated in confirming the cases. With the support of the Preventive Medicine Agency (AMP) and the LaboMobil, personnel were assigned to perform bacteriological diagnosis in epidemic areas, assist the Paris research centre in conducting molecular diagnostics and extend local technicial diagnostic capacity. The etiology of *N. meningitidis* W135 was confirmed, leading to orders for tetravalent vaccines and a vaccination campaign in the central-north risk area.

TRAINING

Focus on training in Niger 10

In 2012, the Medical and Health Research Centre (Cermes) in Niamey, Niger, inaugurated the Pierre and Anne-Marie Moussa centre, providing accommodation and training for interns. The centre will support research and education development in Africa. A course on "environmental education" was held. Training health care students and professionals is key to improving health care and the response to epidemics in Niger and other countries in the region. The Areva Foundation has also provided support for education on combatting malaria.

Dengue and West Nile under surveillance in the Mediterranean region

Since 2006, the EpiSouth Network has coordinated health surveillance in the Mediterranean region. The Institut Pasteur and the Turkish Public Health Institution have been actively involved, since 2010, in setting up a network of Mediterranean laboratories to detect risks of infection, particularly relating to the West Nile virus, dengue virus and related biosafety risks. In July 2012, the first "Dengue and Biosafety" training session was held in Paris. Seventeen Mediterranean countries participated.

Strong ocupation by countries from the "South" in the GFN course

The Institut Pasteur of Madagascar held the third course for the Indian Ocean region on the surveillance of food-borne infections "Global Food-borne Infections Network (GFN)", under the auspices of the WHO and the International Division of the Institut Pasteur of Paris. There were 24 participants from the Comoros, Mauritius and Seychelles, but and also from Madagascar and the Central African Republic.

Epidemiology in Dakar

From 7 to 11 May 2012, the Institut Pasteur of Dakar held a training workshop on R software. It was organised and hosted by Vincent Richard from the Epidemiology of Infectious Disease Unit and financed by the Institut Pasteur International Network. Eleven scientists participated from the Institut Pasteur of Madagascar, Algeria, the Ivory Coast, Dakar and Cermes, as well as Senegalese scientists from Cheikh Anta Diop university, CHU de Fann, the national programme against nosocomial infections and from the health and development institute. The workshop allowed the various participants to become autonomous in programming R software. The workshop training will be extended through video conferencing to scientists from the participating institutes of the Institut Pasteur International Network, with the help of trained staff.

Hô Chi Minh-City hosts an international workshop on clinical research

From 17 to 21 September 2012, an international workshop on "Epidemiological Health Research Methods" was held at the training centre of the Institut Pasteur of Hô Chi Minh City (Vietnam). The objective was to provide basic practical knowledge on designing and implementing study plans for clinical research on infectious diseases. Thirty-four students from international NGOs, health ministries, universities and the Institut Pasteur of Hô Chi Minh-City attended the workshop, from across the Asia-Pacific region including Cambodia, China, New Caledonia, Indonesia, Laos, Myanmar, the Philippines, Thailand and Vietnam.


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PROJECTS

Hand, foot and mouth disease in Cambodia: winning regional cooperation!

In 2012, Asian countries recorded a steady increase in enterovirus 71 (EV71) infections, the main causal agent of hand, foot and mouth disease, particularly in China and Vietnam. The first cases appeared in Cambodia in April 2012. The close scientific links between the Institut Pasteur of Cambodia and Shanghai enabled a rapid and efficient response to the new threat. Full genome sequencing was performed rapidly thanks to international cooperation (Institut Pasteur of Cambodia, Shanghai and Paris and Hong Kong university) and showed genomes almost identical to the C4 genotype of viruses isolated in China and Vietnam. Institut Pasteur International Network researchers are now taking action to identify the risk factors arising from the severity of this epidemic. In a competitive international environment, such collective success again illustrates the strength of the Institut Pasteur International Network and the extent of its integration with regional medical and scientific facilities and services.

French Guiana plans to eradicate malaria

Encouraged by a decline in malaria incidence in the country over the last decade, the teams from the Institut Pasteur of French Guiana have been highly involved in both surveillance and research on parasitology (study of resistance to antimalarial drugs and parasitic population dynamics) and medical entomology (study of vector mosquitoes and their resistance to insecticides). In 2012, an agreement was signed between the Institut Pasteur and the Military Health Service to undertake an ambitious research programme on the Plasmodium vivax parasite.

Malaria: combatting on all fronts in Africa

Since 2002, the Global Fund to Fight AIDS, Tuberculosis and Malaria has financed numerous programmes in the countries most affected. In 2012, several projects submitted by the Institut Pasteur International Network to combat malaria were selected to be financed by the 5% initiative, entailing an indirect contribution from France to the global fund, set up by the French Ministry of Foreign Affairs. The Institut Pasteur of Madagascar will thus be able to coordinate a vast multidisciplinary study in Africa, in cooperation with the Pasteur Centre in Cameroon, Cermes (Niger) and the Institut Pasteur of the Ivory Coast. The projects undertaken by Cermes (surveillance of resistance to antimalarial drugs in Africa), the Institut Pasteur of Laos (medical entomology) and the Institut Pasteur of Cambodia (parasite reservoir study) were also selected.

MEETINGS

The 45th meeting of the Board of Directors of the Institut Pasteur International Network (Korea): focus on biotechnology 9 11

The 45th meeting of the Board of Directors of the Institut Pasteur International Network took place from 24 to 26 September 2012 at the Institut Pasteur of Korea. A full day was dedicated to an international scientific symposium on “Unsatisfied Medical Needs and Technological Innovation”.

Institut Pasteur of Montevideo: act II 13

The Institut Pasteur of Montevideo held the second regional meeting of the Americas “Alliance for molecular research on infectious diseases” from 28 to 31 October 2012.
http://pasteur-network-meeting.org/Montevideo2012/

STRonGer, a programme to strengthen French Guiana! 12

STRonGer is short for Strengthening Transdisciplinary Research on Infectious and Emerging Diseases in French Guiana. The scientific programme is aimed at significantly strengthening medical research capacity in the French Guiana in the short term, in order to better respond to the population's health risks from infectious diseases. StronGer is the first Research Potential programme of the European Union's 7th Framework Programme for Research and Development to be coordinated by the Institut Pasteur of French Guiana. All European and Guyanese partners attended the kick-off meetings on 13 and 14 December 2011 in French Guiana.

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

Surveillance of emerging respiratory diseases in Phnom Penh

The Asia-Pacific regional meeting of the Institut Pasteur International Network took place in Phnom Penh (Cambodia) at the end of May 2011. For the occasion, an international symposium on "surveillance and research on respiratory diseases and other emerging infectious diseases" was held from 29 to 31 May 2011. The symposium was the focal point of various regional projects, with input on the outcome of the Surveillance and Investigation of Epidemics in Southeast Asia (Sisea) project, supported by the French Development Agency.

http://pasteur-network-meeting.org/KH2011/

The 44th meeting of the Board of Directors of the Institut Pasteur International Network targets young researchers 8 14

The 44th meeting of the Board of Directors of the Institut Pasteur International Network convened in Paris from 8 to 10 November 2011. For the occasion, a full day was dedicated to an international scientific symposium for young researchers from the Institut Pasteur International Network, entitled "Global Health Challenges: Opportunities for the Institut Pasteur International Network". Over 270 scientists attended the symposium, which allowed many fruitful exchanges. Several prizes were awarded for outstanding oral presentations, one to Camilo Arias-Goeta (Institut Pasteur) on chikungunya transmission, another to Christine Matte (INRS-Institut Armand Frappier) on infection mechanisms of macrophages by *Leishmania major* and Serge SADEUH-MBA (Pasteur Centre of Cameroon) on enterovirus transmission. A prize was awarded for the best poster to Sima Drini (IP Tunis) on immune responses to *Leishmania* proteins.

http://pasteur-network-meeting.org/Paris2011

The Pasteur International Network Association

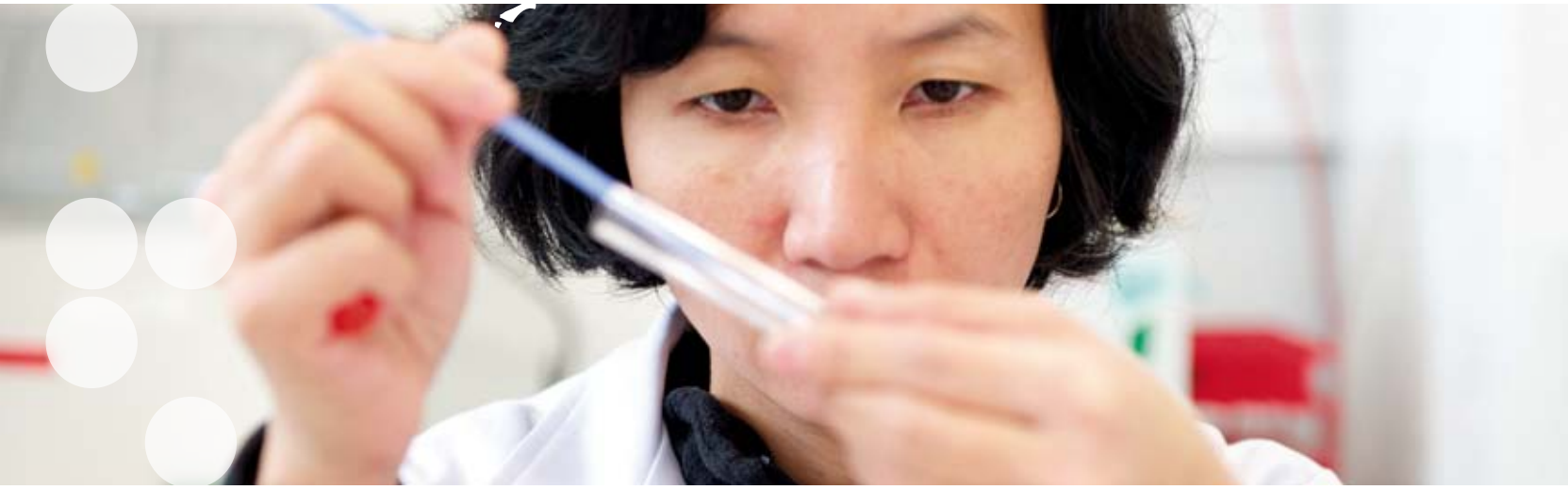
The Pasteur International Network association, was created in 2011, to strengthen scientific partnership opportunities. Founded under French association law of 1901 and housed on the Institut Pasteur campus in Paris, it is designed to facilitate the implementation of scientific projects. Its first initiative was to set up a new partnership with the government of Gabon to combat tuberculosis in Africa and Asia.

HAL-Institut Pasteur International Network (RIIP)

HAL (Hyper Articles online) is an online, open, multidisciplinary bibliographical archive. The Institut Pasteur International Network has its own portal called HAL-RIIP: http://hal-riip.archives-ouvertes.fr/. All publications in which Institut Pasteur International Network researchers have participated are available online, classified by author, institute or topic, along with an overview of progress on ongoing research.

Network researchers'

portraits



Researchers worldwide are actively involved in finding solutions to combat infectious diseases. From individual diagnosis to optimising surveillance, Institut Pasteur International Network professionals are key drivers of improvements in public health.

RESEARCH TRAINING PUBLIC HEALTH

"Working with a multidisciplinary approach"

SARA EYANGOH MANAGES THE MYCOBACTERILOGY UNIT

Research, training and public health initiatives have been undertaken to gain an understanding of how the Buruli ulcer, a debilitating skin disease found in rural areas, is transmitted.

RESEARCH TRAINING PUBLIC HEALTH

How significant is the Buruli ulcer in terms of public health in Cameroon?

We have identified an average 350 active cases every year, since 2002. So the infection is relatively serious. Epidemiological simulations conducted by the national programme against the Buruli ulcer have found that 3.5 million people are at risk. The annual incidence is around 3,500 cases per year. The Nyong river basin in the centre of Cameroon has been described for several decades as an endemic area of M. ulcerans, but we recently identified another area, the Bankim district[1]. This shows the geographic expansion of Mycobacterium ulcerans. Since 2005, antibiotics have been available to treat the disease, which can cure 80% of cases if detected in the early stages. Unfortunately, there is not yet a field test for diagnosing the infection, and as it is indolent for patients in the early stages it can easily be mistaken for other less serious diseases. In addition, in Cameroon, the Buruli ulcer is prevalent in rural areas where many associate it with witchcraft; frequently patients arrive at health care facilities with advanced stages of the infection.

Frequently patients arrive at health care facilities with advanced stages of the infection.

How is the mycobacterium transmitted?

The mode of transmission is still not fully known and is precisely what we are currently trying to establish. Transmission occurs either by direct contact with the mycobacterium through a skin wound, or by an insect bite. We also suspect that water bugs may be both hosts and vectors. We recently found the bacilli in the saliva of water bugs and discovered that the colonisation rate of M. ulcerans in salivary glands varies depending on the species, and is closely related to seasonal variations[2]. We conducted work on the Buruli ulcer in the Nyong region to identify the risk factors associated with the disease and compare the habits of people infected with those not infected by the disease. The outcome confirmed that wearing long clothes for work in the fields, correctly treating wounds and, surprisingly, using mosquito nets at night, were disease protection measures.[3][4]
We have now adopted a multidisciplinary approach and are continuing the work with epidemiologists in Paris, with the IRD for the study of trophic chains and with Angers university for environmental microbiology. Our aim is to identify all animals living in these aquatic environments and the way in which they interact in order to understand how the bacilli are transmitted and identify the associated reservoirs.

Do you combine research work with training?

Yes, but also public health initiatives. For protective purposes we have held awareness days in endemic areas on the theme "Hygiene

As a national reference laboratory, over the past two years we have significantly improved the technical platform.

education, new arms against the Buruli ulcer", with the support of the Health Minister, the French embassy's cultural activities department and the national programme against malaria.
In addition, we draw on our experience of M. ulcerans microbiology to train qualified technical staff by holding clinical diagnosis training sessions every two years with the financial support of Institut Pasteur International Network and the World Health Organization. Over 30 technicians, scientists and biologists from 13 Buruli Ulcer endemic African countries attended the last course in 2011.

You also work on tuberculosis?

Yes, more than 24,000 cases are declared each year, particularly combined with HIV infection. As the national reference laboratory, we have significantly improved the technical platform over the last two years. Today we apply all the diagnosis techniques recommended by the WHO.
In terms of research, we are focusing on the evolution of the genetic diversity of *Mycobacterium tuberculosis* strains. We have just published a study illustrating the gradual disappearance of *M. africanum*[5], responsible for the majority of tuberculosis cases in sub-Saharan Africa, and the spread of the "Cameroon" family strain that we previously described[6]. Are these strains more resistant to vaccination? Does HIV infection contribute to the emergence of this family? It would be useful to know why and how the Cameroon family is advantaged for developing new vaccines.

Buruli ulcer

It is a neglected tropical disease resulting from infection by *Mycobacterium ulcerans*, an organism which belongs to the family of bacteria that cause tuberculosis and leprosy. Infection leads to destruction of skin and soft tissue resulting in large ulcers usually on the legs or arms. Patients who are not treated early suffer long-term functional disabilities such as restricted joint movement and highly noticeable cosmetic problems. Early diagnosis and treatment are vital in preventing such disabilities. Buruli ulcer has been reported in many tropical and subtropical regions, although most cases occur in rural communities in sub-Saharan Africa. Nearly half of those affected are children under 15.
(Source WHO)

(1) Marion E et al, Geographic expansion of Buruli ulcer disease, Cameroon. Emerg Infect Dis. 2011 Mar;17(3):551-3.
(2) Marion E et al, Seasonal and regional dynamics of M. ulcerans transmission in environmental context: deciphering the role of water bugs as hosts and vectors. PLoS Negl Trop Dis. 2010 Jul 6;4(7):e731.
(3) Landier J et al, Adequate wound care and use of bed nets as protective factors against Buruli Ulcer: results from a case control study in Cameroon. PLoS Negl Trop Dis.2011 Nov;5(11):e1392.
(4) R. Pouillot, G. Matias, C. Mbondji, F. Portaels, N. Valin, F. Ngos, A. Ndjikap, L. Marsollier, A. Fontanet and S. Eyangoh. 2007. Risk factors for Buruli ulcer:a case control study inCameroon. PloS Neglected Disease. 1(3):e101.
(5) koro koro F, kamdem Simo Y, Fotso Piam F, Noeske Jurgen, Gutierrez Cristina, Christopher kuabane, Eyangoh S. Population dynamics of tuberculosis bacilli in Cameroon as assessed by spoligotyping. Journal of clinical Microbiology. 2013. 51(1).299-304.
(6) S. Ngo Niobe-Eyangoh, C. kuaban, P. Sorlin, P. Cunin, J. Thonnon, C.Sola, N. Rastogi, V. Vincent and M. C. Gutiérrez. Genetic Biodiversity of *Mycobacterium tuberculosis* complex strains from patients with pulmonary tuberculosis in Cameroon. 2003. J. Clin. Microbiol. 41(6): 2547-2553. 1094-1103.

ChARLI : Children's Antibiotic Resistant infections in Low-Income countries: an international cohort study

Low-income countries account for more than 90% of the annual 8 million deaths worldwide of children under five.
Death is mainly due to infectious diseases. The neonatal period (0-28 days) is highly risky and concerns 40% of deaths. The environment in low-income countries is highly favourable to the emergence and dissemination of antibiotic-resistant bacteria (antibiotics of uncertain quality freely available, precarious living conditions etc.). Resistance to antibiotics could therefore significantly increase mortality from bacterial infections. Recent instances of emerging and rapid spreading bacteria strains that are resistant to nearly all currently available antibiotics have exacerbated the threat.

While institutions have documented the problem of antibiotic resistant infections in low-income countries, the data available do not enable a precise evaluation of the impact on public health, particularly as other infectious diseases are priority issues in these countries.

The aim of the ChARLI programme is to evaluate the extent and consequences of severe infections from the neonatal period through childhood due to resistant bacteria in low-income countries. The information gathered will contribute to setting public health priorities and to establishing and implementing the measures required to control resistance to antibiotics in these countries.

An international cohort study on infection in children has been set up by the Institut Pasteur International Network, involving health professionals from hospitals, health centres and community centres in both rural and urban environments. In each demographically-defined geographical area, pregnant women are informed and invited to participate in the programme. The cohort includes the new-borns of participating mothers. The children are monitored actively until their second birthday and any infections contracted during the period are systematically treated.

The pilot phase of the ChARLI programme was launched in Madagascar in September 2012 with the support of the Monegasque International Cooperation. The pilot phase, which entails monitoring 1,000 children during the first six months of their lives, is necessary to enable the health professionals involved to appropriate the project, to improve the care to new-borns and to provide a preliminary estimate of the incidence of antibiotic drug resistance.

The project may then be extended to other countries.

“Constantly on alert to respond rapidly”

AMADOU ALPHA SALL SCIENTIFIC DIRECTOR AND HEAD OF LABORATORY, ARBOVIRUS AND VIRAL HAEMORRHAGIC FEVER UNIT

The unit is the regional reference laboratory dealing with the risk of emergence of yellow fever. It provides essential expertise for informed public health decision-making.

RESEARCH TRAINING PUBLIC HEALTH

How are you dealing with the yellow fever threat to public health?

Haemorrhagic fever and arboviruses are a major public health problem in Africa. We need to be constantly on the alert to monitor the emergence of these diseases and to find solutions fast. Since 2003, the regional office of the WHO has set up a network of twenty laboratories to strengthen surveillance of yellow fever. Our unit plays the role of reference laboratory in the network. Each time that an active case is detected, we receive samples and perform additional analyses to verify whether it is an epidemic, enabling the WHO to take appropriate measures. We are the only laboratory that plays this role on the entire African continent. Our activity is all the more important as anti-amaril (yellow fever) vaccines are extremely limited in quantity worldwide, and their use is stringently controlled.

How do you manage the risk of emergence?

When a case of yellow fever is reported in a border region, we have to decide whether or not to launch a vaccination campaign in the neighbouring country. For two years we have been working with several specialists to develop a protocol encompassing a number of parameters, such as the level of immunity of the population and entomological indicators, to estimate the risk of emergence and to propose various scenarios to control the outbreak.

Can it also be applied to other viruses?

Of course! In 2009, we initiated a research project to model and assess the risk of emergence of selvatic dengue and chikungunya in

What I enjoy most about my work is having the opportunity to work in an international, multicultural environment.

the Kédougou region in Senegal, in order to understand better the factors leading to emergence of the viruses through systemised risk analysis. The objective of the multi-disciplinary project (entomology, virology, climatology, primatology) is to understand how the virus, which spreads naturally between wild animals and mosquitos, is introduced and disseminated and how it creates epidemics in the domestic environment in human populations. For this, we use health data (analysing all cases of fever excluding malaria reported in a network of hospitals and healthcare facilities), entomological data (through the analysis of vectors and their bioecology), and data on the spread of arboviruses among primates in the region. Understanding these mechanisms is essential, as zoonoses, like avian influenza or SRAS, will be increasingly prevalent in the future.

What other areas of research are you working on?

Another part of our research is aimed at developing, evaluating and optimising diagnostic tools. There are few commercial kits for diagnosing arboviruses. So, we are trying to develop tests that can be used at the bed-side of patients or that are more effective than current versions. As part of the European VHF-diagnostics project[1] we have worked with Jean-Claude Manuguerra's team at the Institut Pasteur in Paris, to develop diagnostic test strips that can be used to diagnose the seven main haemorrhagic fevers. These tests should be used as first line tools for epidemic alerts. A mobile platform has also been developed as part of the project to perform more in-depth diagnoses and to provide treatment to break the transmission chain. The platform is now operational and has been used during major epidemics in several African countries. The diagnostic strips are currently being analysed in several field centres in five African countries.

Is the objective is also to understand how viruses emerge and survive in nature?

Absolutely, and for that we also need to know how they evolve in space and time. By analysing the molecular and phylogenetic evolution of viruses in various epidemiological environments, we can reconstruct their "history" and understand how they have spread. Have they re-emerged from a local environment? Were they introduced into a particular country once or on several occasions?
Recently, we showed that six different types of yellow fever had occurred in Senegal and that some of them were more quickly transmitted than others from one year to the next[2]. Our data also showed that Rift Valley Fever (RVF) was introduced five times into Senegal and Mauritania during the last century, all from East Africa[3], and that the dengue epidemics in Senegal and Cap Verde in 2009 were due to strains originating in Asia.

Our expertise is essential for informed decision-making on public health issues.

Do you also study the parameters that affect transmission?

It is also essential to understand how the virus and vector interact. In host vertebrates, the life span of arboviruses and haemorrhagic fever virus is only a few days. They spend the majority of their cycle in their vector in nature. It is not because a mosquito is associated with a virus that it is capable of effectively transmitting it as a vector. We are looking at the various parametres that can impact transmission. We have just published the results of this research for the Usutu virus. It was isolated in Swaziland at the end of the 1950s and appeared in Europe (Austria) in 2001. We know the virus well, although we still have little information on how it develops or which species it infects. The work conducted by an Austrian student, who did his thesis in my laboratory, shows for the first time that the mosquito Culex neavei is the natural vector of the Usutu virus, and could play a role in the cycle of transmission between animals and people and initiate emergence in human populations[4].

Training is key to your mission...

In addition to giving excellent results, the project has shown that our laboratory is capable of providing high quality training. We have many students from Dakar university, but also from the University of

Columbia (New York) and Galveston (Texas), where I taught. What I enjoy the most about my work is having the opportunity to work in an international, multicultural environment and to conduct fundamental research in a laboratory environment, while being involved in applied research on public health issues entailing significant field work. Today, I participate in high level meetings on public health policy, while going into fundamental research laboratories to discuss projects that could impact public health in the long term. This is only possible in structures such as the Institut Pasteur International Network.

(1) http://ec.europa.eu/research/health/infectious-diseases/emerging-epidemics/projects/151_en.html
(2) Stock NK, Laraway H, Faye O, Diallo M, Niedrig M, Sall AA. Biological and phylogenetic characteristics of yellow fever virus lineages from West Africa. J Virol. 2012 Dec 26. [Epub ahead of print]
(3) Soumaré PO, Freire CC, Faye O, Diallo M, de Oliveira JV, Zanotto PM, Sall AA. Phylogeography of Rift valley fever virus in Africa reveals multiple introductions in Senegal and Mauritania. PLoS One. 2012;7(4):e35216. doi: 10.1371/journal.pone.0035216.
(4) Nikolay B, Diallo M, Faye O, Boye CS, Sall AA. Vector competence of Culex neavei (Diptera: Culicidae) for Usutu virus. Am J Trop Med Hyg. 2012 Jun;86(6):993-6.

We have developed test strips that can be used to diagnose the seven main types of haemorrhagic fever.

Flu and respiratory viruses: continuous surveillance

The disease burden for Acute Respiratory Infections (ARI) is estimated at 3.9 million deaths (WHO, 2002). ARI are among the leading causes of death in children under 5 years, but diagnosis and attribution are difficult and uncertain. The need for an efficient surveillance network for respiratory infections focused on influenza and respiratory viruses became clear in 2009 with the emergence and worldwide spread of a new pandemic strain of Influenza A(H1N1) virus.
Continuous global surveillance is the cornerstone of preparedness and response. By this project, the Institut Pasteur and the international network will support the following overall goal: assist public health infrastructures of host countries (Senegal, Cameroon, Central African Republic and Cambodia) to build and strengthen core activities for influenza preparedness and response in support of the International Health Regulations (2005) (IHR) implementation.
In selected countries, the main objectives are:

1) Reinforce the pandemic influenza preparedness and response capacities
2) Strengthen communication capacities of Ministries of Health for outbreak alert
3) Strengthen existing surveillance networks for seasonal influenza and other respiratory viruses

Results and Actions in 2013
Set up of an influenza and respiratory virus surveillance system in Cameroun, Central Africa and Senegal with the aim to link these systems to integrated syndromic real-time surveillance. This would imply that all surveillance activities in a country are using similar structures, processes and personnel. The surveillance activities that are well developed in one area may act as driving forces for strengthening other surveillance activities, offering possible synergies and common resources.
In Cambodia 7 fatal human A/H5N1 cases have been confirmed since the beginning of the year. Evidence has been shown that all cases have been in contact with poultry prior to becoming sick, this stresses the importance of human/animal transmission studies on for example animal markets in endemic countries as Cambodia.
In the fall of 2013 a series of French speaking Central African twin courses on influenza and respiratory disease surveillance systems and IHR implementation as part of an Integrated Disease Surveillance will be organized for health care professionals from: Chad, Sao Tome and Principe, Gabon, Equatorial Guinea, CAR, Congo Brazzaville, Burundi, Cameroun and Senegal.
An international (CDC, IP, DHHS/ASPR, WHO) and multidisciplinary (laboratory and epidemiology) teaching team will be composed to support the course.

Website: www.InPRIS-ihrproject.com
This project was funded by the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services (DHHS)
(WHO, 2002: http://www.who.int/whr/2002/whr2002_annex2.pdf)

"Sharing the same vision of research"

HORTENSE FAYE-KETTÉ HEAD OF SCIENTIFIC RESEARCH

With 20 reference centres and a strong foothold in the Ivory Coast's health system, the Institut Pasteur drives Ivorian public health.

RESEARCH TRAINING PUBLIC HEALTH

What brought you to the Institut Pasteur?

I arrived at the Institut Pasteur of the Ivory Coast by luck. In 1984, I was a young medical student and was looking for a position in genetic histology. My choice in terms of priority led me to the Bacteriology-Virology Department of the Institut Pasteur of the Ivory Coast. It has proved to be exceptional opportunity. I worked my way up and am now university professor and head of scientific research at the Ivory Coast Institut Pasteur.

Training enabled you to strengthen your skills...

Thanks to the support of the International Division of the Institut Pasteur, I participated in training at the Paris Institut Pasteur on tropical microbiology in 1990 and on medical virology in 1992. These courses enabled me to develop my skills. They also benefitted my team, as I transferred my knowledge of new technologies learned in Paris, particularly in the field molecular biology, and setting up and maintaining data banks of biological samples.

What is the purpose of your research work?

Our research on the vaginal microbiome is aimed at studying the ecology and composition of the genital microbial system in women in the Ivory Coast. The objective is to determine the effects of the fragility of the vaginal mucus and susceptibility to sexually transmitted diseases. It is a significant public health issue. Indeed, women are particularly vulnerable to sexually transmitted diseases, due to both societal and biological factors. Work undertaken worldwide has shown the fragility of women's genital mucus. This is particularly important in environments where HIV prevalence is estimated at 3.4% of the population. The Ivory Coast is still one of the countries the most hard hit by this epidemic in sub-Saharan Africa.

I worked my way up and am now university professor and head of scientific research at the Ivory Coast Institut Pasteur.

More than ever, the Institut Pasteur of the Ivory Coast is playing an essential role in public health...

In terms of research, most of the work undertaken by the Ivory Coast Institut Pasteur is directly related to public health, due to the Institute's strong foothold in the country. However, efforts are being undertaken to increase the proportion of fundamental research. To support research, three major infrastructure projects are being deployed: a biobank and biological resource centre, the high biosafety P3 laboratory at the Adiopodoumé site and the live science engineering training centre. The Ivory Coast Institut Pasteur plays a major role in public health through its twenty national research centres (NRC) focusing on priority diseases.

The majority of disease outbreaks are confirmed within the NRCs, where microbiological surveillance and monitoring is conducted. Our institute also trains all microbiologists in the Ivory Coast. We also hold training sessions for French-speaking countries in the sub-region (Togo, Bénin, Burkina Faso) on resistance to antibiotics and molecular biology techniques.

How do you work together with other members of the network?

Of course we work together best with other institutes from the Institut Pasteur International Network on the African continent, as they are closest to us. We have joint research projects funded by the Pasteur concerted action initiative and network-wide research projects funded by the Institut Pasteur in Paris, but the high turnover of participants and lack of certain types of human resource makes it difficult to keep the projects going. The Institut Pasteur in Paris is a benchmark and leader on basic training, professional training, the acquisition of new technologies and internships to acquire skills.

What is your vision of the Institut Pasteur International Network?

It is a network of researchers that qualify as world-class researchers. It means: (i) training researchers with the Pasteur label that can work in any research institution, especially in institutes from the network; (ii) developing relations between institutes to share knowledge and experience; (iii) improving the visibility of the Institut Pasteur as an international research network. It also means sharing Pasteur values. At present, relations are vertical between the Institut Pasteur in Paris and the network. Relations need to become more transversal and horizontal between the institutes themselves, with North researchers coming more often to the South (the Institut Pasteur created the first visiting professor status in 2012 in a South institute). For me, being part of the Institut Pasteur International Network means sharing a common vision of research and sharing knowledge. Twenty-eight years on, I don't regret my destiny, which brought me to the Ivory Coast Institut Pasteur!

With HIV prevalence estimated at 3.4% of the population, the Ivory Coast is still one of the countries the most hard hit by the epidemic in sub-Saharan Africa.

Improved diagnosis of **bacterial meningitis**

Bacterial meningitis is a major public health issue for countries in the Sahel region, known as the meningitis belt. In this region, which stretches from Senegal to Ethiopia, more than 800,000 cases have been notified over the last fifteen years with an average mortality rate of 10%. The majority of victims are children under five (two thirds of cases observed). The youngest, aged between four and eighteen months, are the most vulnerable.

The meningococcus, pneumococcus and haemophilus are the three main bacterial agents responsible for meningitis in children. However, meningococcus is the only etiological agent capable of generating the epidemics observed periodically in Africa. It comprises a range of sub-types, including serogroups A, B, C, x, Y and W, which account for more than 99% of meningococcal meningitis cases. Meningococcus serogroup A (NmA) is responsible for between 80 to 85% of all reported cases. Consequently, the introduction of the new MenAfriVac® vaccine that targets NmA should significantly decrease the number of cases reported in meningitis belt countries.

However, following mass vaccination campaigns in local populations with MenAfriVac®, it is feared that bacterial strains present in those areas could change rapidly into serogroups that were in minority, so far.

In order to confirm the impact of the vaccine and the first encouraging results recorded, longer term surveillance is vital. It is essential for the countries concerned to have strong diagnostic capacity of bacterial meningitis. However, diagnosis is costly requiring equipment and techniques that are only possible for reference laboratories, which are often far from patients and the epidemic area. This hinders real time epidemiological surveillance of meningococcus meningitis.

The use of rapid diagnostic tests in the form of test stripes, simple to use and to analyse at the bedside of patient, and inexpensive, apperas to be a highly promising alternative to strengthen surveillance, particularly in remote areas. Currently, a first rapid diagnostic test developed jointly by the Institut Pasteur and Cermes exists to detect four out of the main serogroups of meningococcus, but two are still missing.

At the beginning of 2012, with the support of the Total Foundation, the Institut Pasteur launched a project to develop a kit of rapid diagnostic tests capable of identifying all the main serogroups of meningococcus. The core work of the project was offered as part of high-level doctoral training to a student from the Ivory Coast. Validating the rapid diagnostic tests in real life situations will rely on the expertise of institutes from the Institut Pasteur International Network present in the region and their involvement in the national surveillance system.

“Working closely with the health authorities”

VOAHANGY RASOLOFO HEAD OF THE MYCOBACTERIA UNIT

The incidence of tuberculosis is high in Madagascar. The unit works together with the national anti-TB programme for the diagnosis and surveillance of resistance to anti-tuberculosis drugs.

RESEARCH PUBLIC HEALTH

What role does the Institut Pasteur play in combatting tuberculosis in Madagascar?

The Institut Pasteur in Madagascar plays a leading role in Malagasy public health. Nationwide, the institute provides public health services, research and training. The institute is under the authority of the Health Ministry, which calls on our professionals regularly to deal with epidemics or investigate health issues. The Mycobacteria Unit has been the national reference centre since 1995. We work closely with the national programme combatting tuberculosis on the diagnosis and surveillance of anti-tuberculosis drug resistance. Our unit conducts research on the bacilli by smear microscopy of biological samples from patients with tuberculosis symptoms. We are the only laboratory in the country capable of cultivating and performing sensitivity testing to the treatment with Koch’s bacillus. In Madagascar, tuberculosis prevalence is quite high. The national programme detects more than 25,000 cases each year, approximately 15,000 of which are new cases of smear-positive pulmonary tuberculosis. All patients receive free treatment through by the national programme.

What type of research does your unit perform?

We carry out operational research projects in conjunction with the Malagasy health authorities. We have completed the molecular diagnosis of resistance to tuberculosis using smear microscopy. For patients that respond badly to antibiotic treatments for tuberculosis, diagnosing resistance is complicated. We have to transport

The national programme detects more than 25,000 cases each year, approximately 15,000 of which are new cases of smear-positive pulmonary tuberculosis.

sputum to Tananarive, where it is cultivated and tested for resistance. Through this new technique, we have shown that it is possible to detect resistance to the two main antibiotics used to treat tuberculosis by using sputum smear microscopy for patients' initial diagnosis[1].

We are also involved in applied research projects. We are currently jointly supervising a doctoral student who is working in the laboratory of Professor Solat at Paris-Sud university on the genetic diversity of strains of *Mycobacterium tuberculosis*.

In 2013, another student will be working for several months on the virulence of *M. tuberculosis* strains at the Institut Pasteur in Paris in the Mycobacterial genetics unit. Pulmonary tuberculosis is the most widespread form of the infection, but there are also cases where the bacillus finds its way into other organs leading to pleural, peritoneal and genital tuberculosis. The question is whether specific strains could lead to such extra-pulmonary tuberculosis (EPT).

In partnership with the same unit, we are participating in a new multi-centre project in conjunction with the Institut Pasteur in Bangui and the Pasteur Centre in Cameroon, aimed at assessing new methods of diagnosing tuberculosis in children [see below]. Finally, we recently published the results of several years' research showing that modern so-called "Beijing" strains gave inferior gamma interferon responses than other older strains[2]. Our clinical research was conducted on a cohort of patients and confirmed studies already published on cell culture. We are currently continuing this work in order to interpret the results by analysing other cytokines known to be involved in the immune response to tuberculosis.

You worked as a researcher in the pharmaceutical industry, what have you gained from the transition to public health?

They are such different worlds, it is very difficult to compare them. In industry, I worked purely for commercial purposes. When I joined the Institut Pasteur in Madagascar in 1992, I had no idea about public health. With hindsight, I have to say that on a personal level I am particularly content to have made the change, which triggered a feeling of being useful through my work. Here, we are much closer to patients' reality. It teaches us to be humble in terms of our knowledge, which is often focused on technology. In 1995, I took a course on medical mycobacteriology at the Institut Pasteur in Paris.

Here, we are much closer to patients' reality. It teaches us to be humble in terms of our knowledge, which is often highly focused on technology.

Better diagnosis of child tuberculosis

According to the WHO, 200 children die every day from this infection. While infants and young children are exposed to increased risk of serious types, child tuberculosis is a hidden epidemic in most countries. One of the reasons is the difficulty of diagnosis in children. Most developing countries still use a method based on detecting the presence of bacilli under the microscope. However, young children are generally not capable of providing sputum, and when they do, the sputum is often negative when examined.

Today, in developed countries, new methods based on molecular biology are used. The Mycobacterial genetics unit at the Institut Pasteur in Paris has just launched a multi-centre project in partnership with the teams of the Institut Pasteur in Bangui, Madagascar and the Pasteur Centre in Cameroon. The objective is to evaluate the effectiveness of these new diagnostic techniques on basic tests on children in developing countries. The results of the three year study should enable earlier diagnosis of child tuberculosis so that it can be treated as quickly as possible.

The emergence of **multidrug-resistant tuberculosis**

The emergence of multidrug-resistant tuberculosis (TB-MDR) and extensively drug-resistant tuberculosis (XDR) is a worrying phenomenon. The number of TB-MDR cases in the world was estimated at 500,000 in 2008, of which 10 % are XDR cases. Rapid diagnosis with study on resistance to antibiotics is necessary to deal adequately with TB-MDR. The objective of the project entitled "A laboratory network for tuberculosis diagnosis and drug susceptibility testing (DST) in Africa with the aim of avoiding multidrug-resistance emergence and transmission" financed by the OPEC Fund for International Development (Ofid) is to set up a network of eight reference laboratories in sub-Saharan Africa* to diagnose TB-MDR strains in conjunction with European laboratories**. The project, which began in late 2011, has enabled laboratories to be equipped with the material and reagents required for Hain™ testing (line probe assays) and with GeneXpert™ apparatus enabling a rapid diagnosis (two hours) of *Mycobacterium tuberculosis* resistant to rifampicine.
A training workshop was held in Cameroon at the beginning of 2012 on molecular diagnosis technologies for TB-MDR: the Hain™ technique, the GeneXpert™ technique and the sequencing analysis method. The first year results were disseminated on posters and via communication during the workshop, which was held in Cotonou in January 2013. During the workshop a diagnostic algorithm was proposed for the initial molecular testing to detect TB-MDR. The programme should be extended to regional reference laboratories in other countries, including the Gabon, the Democratic Republic of the Congo, Rwanda, Burundi, Mali, Senegal and Guinea Conakry. Some of these countries participated actively in the workshops by providing their own funding (Mali and Gabon), confirming that the network initiated by Ofid funding is operational and aiming for sustainability.

* Participants from South: Benin, Burkina Faso, Cameroon, Ivory Coast, Guinea-Bissau, Niger, Central African Republic, Togo.
External participants in the project: Mali, Gabon.
** Participants from the North: International Union against Tuberculosis (France), Institut Pasteur (Pr B. Gicquel, Molecular genetics unit), Royal Institute of Tropical Medicine (Belgium), San Raffaele Institute, Milan (Italy), Aarhus University Hospital (Denmark).

After my course, one of the participants asked the others what we did for the national programme against tuberculosis in our respective countries. I explained that I worked on research on genotyping and on the resistance of *M. tuberculosis* strains. The participant replied "There is no use in that. If someone told you to walk on your head, you would walk on your head?" I felt humiliated and his words stayed in my mind for years. It is true that in those days we had no treatment for resistant strains, he was trying to make me understand that the only way to break the transmission chain was by diagnosing and treating contagious people with pulmonary tuberculosis.
The stinging remark made me think a lot. So I decided to devote part of my working life to public health and teaching to be useful for my country. But it also strengthened my conviction to continue research. There is no reason for research on infectious diseases to be conducted solely in North countries, while the combat is in the South countries, which are primarily affected. That is my vision and my approach to my work today.

(1) N. Dubois Cauwelaert, H. Ramarokoto, P. Ravololonandriana, V. Richard, V. Rasolofo. DNA extracted from stained sputum smears can be used in the MTBDRplus assay. J Clin Microbiol (2011) 49 (10): 3600-3603.
(2) Niaina Rakotosamimanana, Vaomalala Raharimanga, Soa Fy Andriamandimby, Jean-Louis Soares, T. Mark Doherty, Maherisoa Ratsitorahina, Herimanana Ramarokoto, Alimuddin zumla, Jim Huggett, Graham Rook, Vincent Richard, Brigitte Gicquel, Voahangy Rasolofo-Razanamparany and the VACSEL/VACSIS Study Group. Variation in gamma interferon responses to different infecting strains of *Mycobacterium tuberculosis* in acid-fast bacillus smear-positive patients and household contacts in Antananarivo, Madagascar. Clin Vaccine Immunol (2010) 17 (7): 1904-1103

I decided to devote part of my working life to public health and teaching to be useful for my country.

"A wonderful opportunity for sharing knowledge"

POLIDY PEAN DOCTOR, HEAD OF THE HUMAN IMMUNOLOGY PLATFORM – ASSOCIATE PROFESSOR AT THE UNIVERSITY OF HEALTH SCIENCES AT PHNOM PENH

Our teams study immune response to HIV infection. They are involved in major international research projects through the PIIN.

RESEARCH

What is your role at the Institute?

I have been working for nine years at the Institut Pasteur in Cambodia, focusing particularly on immune response to HIV infection, but also working with Dr Daniel Scott-Algara's teams at the Paris Institute since 2003 and with Professor Patrice Debré's teams at Pitié-Salpêtrière hospital. I first investigated natural resistance to HIV infection in the Cambodian population. More recently, I have been studying the problems of inflammatory reactions occurring in HIV-seropositive patients co-infected with other diseases such as tuberculosis, as part of the Capri-NK project financed by the French National Agency for Research on AIDS and viral hepatitis (ANRS). Indeed, the reconstitution of the immune system in co-infected people treated for both diseases can generate paradoxical reactions exacerbating the patient's general state, which can be fatal. Such a paradoxical reaction is know as the Immune Reconstitution Inflammatory Syndrome (IRIS)[1].

I have always been very curious, and, naturally, very early aimed to do research.

Is a predictive test being developed?

There are not yet any predictive markers or diagnostic tests for IRIS. The work conducted jointly with Doctors Scott-Algara and Nerrienet from the Retroviral Infection Regulation unit (Institut Pasteur in Paris) showed that in the absence of antiretroviral treatment, there is a correlation between the activity of natural killer cells (NK) and the risk of triggering a paradoxical reaction[2]. This research was the subject of my thesis, which I defended successfully in December 2011. The work is important in terms of public health as it opens the way to developing a predictive test on triggering Iris, which should enable us to better apprehend diagnosis, improve patient care and manage medical complications better. We are continuing this research to improve the characterisation of the response of NK cells in co-infected patients. At the same time, we have also begun working with the Oswaldo Cruz Institute in Brazil, to confirm our results on a genetically different population from the population in Cambodia. We also plan to conduct a similar study on the African population in conjunction with an institute from the Institut Pasteur International Network on the continent.

Are you also involved in other research projects?

I am currently also involved in two new projects financed by the ANRS. The first is a multi-centre PAANTHER-01 trial in conjunction with the Pasteur Centre in Cameroon, aimed at improving the diagnosis of tuberculosis in children infected by HIV. The second project, again in collaboration with the team at the Retroviral Infection Regulation unit of the Institut Pasteur in Paris, will enable us to evaluate the impact in Cambodia of exposure to HIV and maternal antiretroviral treatment during pregnancy, after delivery and during breastfeeding on the innate immunity of uninfected newborns.

Thanks to the Institut Pasteur International Network, I have been involved in major international research projects. From a Cambodian perspective, the network is immense, and I am extremely lucky to be part of it. By joining the Institut Pasteur in Cambodia and the Institut Pasteur International Network, I have had the wonderful opportunity to share knowledge and discover new concepts that are highly useful to improving patient care.

What have you gained from working with the Institut Pasteur in Paris?

Enormous input in terms of expertise in my research field, and close ties forged over the years, which have really helped me to develop professionally. Sometimes, when I am confronted with an issue that I can't resolve or a technique that I don't master, exchanging with the teams in Paris enables me to overcome the difficulties. It also provides precious support for developing new research projects. It is beneficial on a personal level, but I can also use the new knowledge I learn to prepare courses, as I teach at the university of health sciences in Phnom Penh. More generally, the training I received on HIV immunology in Paris has enabled me to transfer certain techniques

From a Cambodian perspective the Institut Pasteur International network is immense, and I am extremely lucky to be part of it.

Polidy Pean - award-winning!

Last September, at the 45th Board Meeting of PIIN directors in Korea, Mathurin Tejiokem (Pasteur Centre in Cameroon) and Polidy Pean (Institut Pasteur in Cambodia) were awarded the 2011 and 2012 Dedonder Clayton prizes, for the high quality of their scientific work. The prize, which was created by the Institut Pasteur, is aimed at providing recognition and support for talented young scientists conducting research work on HIV/AIDS in countries with limited resources.

locally, at national level. For instance, techniques for numbering CD4 cells and implementing the immunology platform at the Institut Pasteur in Cambodia.
My research work was recently awarded the Dedonder-Clayton prize [see figure on previous page]. It was both a great surprise and great source of joy for me. The prize has boosted my motivation to continue working in research, which I would particularly like to dedicate to those who have assisted and supported my work.

(1) Immune Reconstitution Inflammatory Syndrome.
(2) Natural killer cell degranulation capacity predicts early onset of the immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients with tuberculosis – Blood 2012 Apr 5;119(14):3315-20.

The close ties forged with teams in Paris often enable me to overcome difficulties.

The South-East Asia encephalitis research programme (SEAe), improving diagnosis to improve treatment and the prevention of infectious encephalitis in South-East Asia

Encephalitis is a serious inflammation of the central nervous system associated with signs of neurological disorder. Because of high mortality and neurological sequelae, encephalitis is a public health concern worldwide. Encephalitis is frequently caused by infections predominantly from virus and bacteria. In Asia, where the most frequent etiologies are major public health problems (dengue, Japanese encephalitis, West Nile virus, enterovirus Nipah virus), encephalitis is one of the most frequent and serious reasons for child hospitalisation. Despite in-depth microbiological analysis and the use of advanced molecular biology techniques, the precise infectious origin of encephalitis remains unknown in over 60% of cases. In order to fill this knowledge gap, South-East Asia, a region of significant biodiversity and area of high risk of infectious disease emergence, is the most appropriate area to discover the mechanisms leading to encephalitis. The surveillance, detection and study of infectious encephalitis in South-East Asia is a major public health challenge, at both local and international level.

In 2012, an inter-institutional and multidisciplinary initiative was launched involving five countries in South-East Asia (Cambodia, Laos, Vietnam, Thailand and Indonesia) and France. With the support of the French Alliance for life sciences and health (Aviesan) and the World Organisation for Animal Health (OIE), the consortium forms the largest community of professionals involved in research on encephalitis. National health authorities in partner countries, major university hospital sites, and public and private health institutions have decided to participate in this major project in South-East Asia. The Institut Pasteur, Institut Pasteur International Network, the Inserm, the Cirad, Aix-Marseilles University, the Mérieux foundation, Oxford university, and the Wellcome Trust decided to join forces with local facilities to try to find solutions to the challenge of infectious encephalitis in South-East Asia.
The main objectives of the SEAe programme are to: (i) develop physio-pathological and etiological knowledge on infectious encephalitis; (ii) enhance diagnostic capacity and care of infectious encephalitis in partner hospital sites; (iii) identify and characterise the known and unknown pathogens responsible for cases of encephalitis; (iv) identify the transmission factors by an interdisciplinary "one health" approach associating human health, animal health and the environment; (v) obtain reliable data on existing infectious neurotrope agents to enable national and regional health authorities to better define their prevention policies and vaccine strategies. The implementation of the SEAe research programme began in Cambodia, Laos and Vietnam and will be extended subsequently to other partner sites.

“Developing the best tools against parasites”

DIDIER MÉNARD HEAD OF THE MALARIA MOLECULAR EPIDEMIOLOGY UNIT

In a region with the most resistant parasites to treatment, the purpose of the unit is to develop strategies to stop them spreading.

RESEARCH PUBLIC HEALTH

Are multidrug-resistant malaria parasites a major concern in Asia?

One of the main areas of research conducted by the malaria molecular epidemiology unit at the Institut Pasteur in Cambodia concerns the resistance of malaria parasites to anti-malarial treatments. While it is true that this infection is less of a burden in Asia than in sub-Saharan Africa [see figure on following page], the emergence of strains of Plasmodium falciparum that are resistant to the latest generation of drugs containing derivatives of artemisine is a major concern. We have known for a long time that the most resistant parasites are found in Asia. We noticed it in the 1960s when the first drug-resistant parasites appeared and spread several decades later to Africa, leading to unprecedented levels of mortality due to malaria. The area that is the epicentre for the emergence of these multidrug–resistant parasites is located along the border between Cambodia and Thailand, in the province of Pailin. The current situation urgently requires us to develop effective tools to detect and monitor the areas infected by these parasites and establish strategies to stop them spreading, to prevent a new health catastrophe.

How do you detect parasites that are resistant to artemisine derivatives?

Today, we detect parasites resistant to artemisine derivatives by conducting clinical tests, which means regularly taking blood from patients treated to calculate parasite clearance time. Generally, we study the chemosensitivity of parasites through in vitro assays, which enable us to determine the concentration of drug required to inhibit growth in 50% of parasites. However, this technique does not enable us to evaluate the sensitivity of parasites to artemisine derivatives. That is due to the fact that the method does not explore resistance in ring stage parasites. It is in this context that I worked with my colleague Dr Benoît Witkowski to develop a new in vitro ring stage survival assay (RSA), which measures the survival of parasites after exposure to a dose miming physiological conditions[1]. The test enables us to predict the level of sensitivity of parasites in the same way as clinical tests. The work is currently continuing through a project financed by the International Division of the Institut Pasteur, in order to validate the performance of RSA in various regions worldwide (French Guiana, Laos and Thailand), where distinct resistance profiles are found[2].

Interaction with local professionals and permanent contact with patients are essential when working on an infectious pathology like malaria.

Malaria

Malaria is a life-threatening disease caused by Plasmodium parasites, which are spread to people through infected mosquitoes bites. There are five types of parasites that cause malaria in humans, but Plasmodium falciparum and Plasmodium vivax are the most common. Plasmodium falciparum is the most deadly. In 2010, malaria caused an estimated 660,000 deaths, mostly among children in Africa, where a child dies of malaria every minute. Country-level burden estimates available for 2010 show that an estimated 80% of cases occur in 17 countries.

(Source WHO)

What is your strategy in Cambodia?

At the same time, we are working on evaluating the epidemiological situation of malaria and measuring the impact of anti-malarial strategies currently implemented in Cambodia. The usual tools we use to fight malaria are mainly diagnosis and rapid treatment of infected people and the distribution of impregnated mosquito nets to limit transmission. However, it is clear that these tools, while precious, will not enable us to reach the goal of eliminating malaria. For that, it is essential to act on the host, which means detecting and treating individuals that are infected but not sick (asymptomatic) as they are responsible for spreading the disease. Today, with new molecular biology tools, which are much more sensitive than microscopy, we are gaining a better understanding of malaria epidemiology and are discovering the hidden part of the iceberg. For instance, we estimated that only 1% of the population living in the province of Pailin in western Cambodia carried P. falciparum, but recent data show that prevalence is between 40 and 50 times higher.

Other areas of research?

The study of P. vivax, and understanding its biology, is also a major area of research in the unit. Wrongly considered a benign illness, P. vivax can result in serious forms, which appear to be on the increase. In some areas, the mortality rates for individuals with severe P. vivax malaria are comparable to those with P. falciparum, particularly due to the emergence of resistant strains. The study of parasites leads on from my previous studies in Madagascar, where we showed – in conjunction with the Madagascar's national programme against malaria, the molecular immunology unit of the Institut Pasteur (Odile Mercereau-Puijalon) and Case Western Reserve University in Cleveland (Peter Zimmerman) – that P. vivax was capable of infecting the red blood cells of people without Duffy antibodies (Duffy-negative subjects). Until then we had considered those subjects to be naturally protected against P. vivax malaria[3].

We are gaining a better understanding of malaria epidemiology and are discovering the hidden part of the iceberg.

This unexpected discovery has called into question certain vaccination strategies. In addition, it alerted us as to the possible spread of P. vivax in regions where it is currently absent, such as sub-Saharan Africa.

What are the advantages of the international network?

I have worked in the Institut Pasteur International Network since 1998 and I still appreciate working in the field. Interacting with local professionals and being in permanent contact with patients is essential when working on an infectious pathology such as malaria. At the same time, close ties with the Institut Pasteur units in Paris are essential.

In my mind, the permanent link between fieldwork and the Institut Pasteur is an essential component of my work. I facilitate the transfer of scientific and technological advances to endemic countries and escalate to researchers in the North countries priorities from a field perspective. Facilitating the exchange of information is one of the major advantages of the network.

(1) Witkowski B, khim N, Chim P, kim S, ke S, kloeung N, Chy S, Duong S, Leang R, Ringwald P, Dondorp AM, Tripura R, Benoit-Vical F, Berry A, Gorgette O, Ariey F, Barale JC, Mercereau-Puijalon O, Menard D. Reduced artemisinin susceptibility of Plasmodium falciparum ring stages in western Cambodia. Antimicrob Agents Chemother. 2012 Dec 3. [Epub ahead of print]
http://www.wwarn.org/about-us/news/new-vitro-assay-assess-artemisinin-resistance
(2) "Multi-site assessment of the reduced susceptibility to artemisinin of Plasmodium falciparum ring stage parasites using a new in vitro assay" Project Acip du RIIP.
(3) Ménard D et al, Plasmodium vivax clinical malaria is commonly observed in Duffynegative Malagasy people. Proc Natl Acad Sci U S A. 2010 Mar 30;107(13):5967-71.

A **mobile laboratory** in Cambodia: technology on the move on site

The malaria molecular epidemiology unit at the Institut Pasteur in Cambodia has developed a mobile laboratory enabling the detection and treatment of subjects infected by malaria parasites in less than twenty-four hours. It is a new arm to strengthen and improve the combat against malaria in Cambodia.

The mobile laboratory, which has been operational since October 2012, is fully autonomous, requiring no outside electricity, water or access to sewage facilities. It enables the detection of subjects infected by malaria parasites, using blood samples collected from the finger on blotting paper. The real time PCR tests are performed directly on site amid the Cambodian population. If the infection is detected, the subject is treated and cured. Up to 400 tests can be performed daily and the biological results issued, in compliance with all required quality standards.

At the same time, the mobile laboratory enables in vitro cultivation and testing of parasite sensitivity to anti-malarial treatments, which is extremely useful for studying resistance to P. vivax. Until now it had been impossible to routinely cultivate the parasite as it was too fragile to be transported from the collection point to the Institut Pasteur in Cambodia for cultivation.

The project “Repellents - an added control measure to long lasting insecticidal nets to target the residual transmission in South-East Asia: a step forward to malaria elimination” currently conducted in the province of Ratanakiri in the North East of Cambodia, by several research teams – the tropical medicine institute of Anvers, the national malariology centre and the Institut Pasteur in Cambodia, is aimed at measuring the effectiveness of using repellents in addition to long lasting insecticidal mosquito nets as additional measures to prevent the “residual” transmission of malaria.

ASIA – **INSTITUT PASTEUR OF SHANGHAI - CHINESE ACADEMY OF SCIENCES**

"Proud to belong to the network"

KE LAN DEPUTY DIRECTOR AND HEAD OF THE TUMOR VIROLOGY UNIT

The aim of this unit is to decode the molecular mechanisms by which human herpesvirus causes in the host latent infection for life.

RESEARCH PUBLIC HEALTH

Can you explain what is the main focus of your research ?

The research unit I lead is working on Kaposi's sarcoma associated Herpesvirus (KSHV). This is a gamma herpes virus whose main cellular target in-vivo are endothelial cells and B cells. The infection of B cells can cause diseases like primary effusion lymphoma and multicentric Castleman disease. Kaposi sarcoma develops as the result of the infection of endothelial cells. All the herpes viruses can establish life-long latent infection in the host. My work aims to decipher the molecular mechanisms by which KSHV establishes and maintains long-term persistent infection in the host as well as the oncogenesis mediated by this virus. We examine in particular the virus-host interactions and how they can drive life cycle control, immune evasion and pathogenesis of the virus[1]. Today, there is no specific treatment for Kaposi sarcoma beside surgery or radiation. We already know that activating the latent virus destroys the tumor cells. Our research can help develop specific approaches to treat Kaposi-sarcoma induced by KSHV.

Infection with KSHV is it a common infection?

In most of the world, the infection rate is about 5 to 10 % in the population. But we observe very high infection rate in around the Mediterranean sea like 20% in Greece and even between 30 to 50% in Central Africa. In 2010, we published a paper were we showed that in the Xinjiang Uygar Autonomous Region, in the Northwestern China, KSHV infection is endemic with 30% of the people being infected[2]. In the 80's-90's Kaposi Sarcoma was one of the most common opportunistic infection occuring in HIV infected patient developing AIDS.

Today, we are well recognized in the field of infectious diseases, and I am convinced that we will have a major impact on Chinese research.

Indeed, KSHV was identified in 1994 by US researchers from 8 HIV patients. Today population most-at-risk of developing Kaposi sarcoma are those immunosuppressed like the elderly, patients receiving chemotherapy for cancer or those under immunosuppressive treatment after an organ transplant. So it is a very newly discovered human herpesvirus and so far not much is known about it and it is thus interesting to be studied. For example, we still lack solid evidences concerning the routes of transmissions of this virus even though we know it might be transmitted by sexual intercourse or during pregnacy from an infected mother to her child.

How did you enter the Institut Pasteur of Shanghai?

After I spent almost 5 years in the USA, I really felt like going back to China and I started to look for a job at the end of 2005. I wanted to join an academic institution with a very high-level of research. I knew the strong reputation of the Institut Pasteur in Paris in the field of Infectious diseases. When I learnt about the existence of the Institut Pasteur of Shanghai, I strongly felt that it must be a top level institute. I applied for a position there and I was very excited to have the chance to be hired.

What is the particularity of the IP Shanghai in the chinese research landscape?

The IP Shanghai is a very young research institution co-founded in 2004 by the Chinese Academy of Science, the Shanghai municipal government and the Institut Pasteur in Paris. Following the SRAS pandemic, the Chinese and French governments signed a strategic agreement to fight emerging infectious diseases. The creation of the IP Shanghai results from this shared objective. I think that before the research capability of China in the field of infectious diseases was relatively weak. Our institution is gradually building up its reputation and reinforcing its capacities. So far we have now recruited 22 principal investigators working on many subjects like influenzae, HIV, enteroviruses, hepatitis viruses, other herpesviruses like HCMV. We also have groups working on innate and adaptive immunity. We already have a number of papers published each year in leading journal in the field of virology. We are also actively involved in national projects. I can say that we are already quite respected in the infectious disease field in China and I am confident that we will have a major impact on Chinese research.

What is your opinion about the Institut Pasteur International Network?

It is only when I started working in the Institut Pasteur of Shanghai that I realized that the Institut Pasteur had spread all over the world. Of course, I feel very proud of belonging to this vast network. I have a joint research program on HBV related carcinoma with Dr Yu Wei at

I knew the strong reputation of the Institut Pasteur in Paris in the field of infectious diseases.

the Institut Pasteur in Paris. We together cosupervised a PhD student who will graduate this year. At regional level, we were part of the very good SISEA[3] program in south east Asia in collaboration with the institutes in Cambodia, Lao and Vietnam. This programme aimed to develop surveillance and responses capabilities in the face of emerging pathogenic agents with epidemic potential in South-East Asia. Though this program is now finished, we continue to have tight contacts with the other institutes in particular thanks to our Director General, Dr Ralf Altmeyer who is very actively involved in the network as the regional representative for Asia. For example, in last summer there was an outbreak of hand foot mouth disease in Cambodia. With the support of the management team of the institute, Dr altmeyer coordinated the task force of experts from our institute that was sent in Cambodia to work with the Institut Pasteur there. Together they identified and sequenced the etiological agent responsible for this epidemic. It turned out to be an enterovirus whose genome is close to the strain circulating in China. This is a perfect example of how efficient the network can be in responding to emerging infectious diseases. This work was highly appreciated by Ministry of Health in China.

I truly think that the network is a richness and that we could even benefit more from it. I had recently been evaluated by the scientific

advisory board and it was suggested by Prof. Felix Rey that I identify some potential collaborators within Institutes of the Network in Africa as Kaposi sarcoma is mostly related to the AIDS epidemic there. I was attracted by the altruistic spirit in the long history of the RIIP, always ready to help solve unmet medical problems due to infectious diseases wherever they occur.

(1) Liang D, Lin X, Lan K. Front Microbiol. 2011;2:271.
(2) Wang X et al, Virol J. 2010 Mar 17;7:62.
(3) SISEA : Surveillance and Investigation of Epidemic Situation in South-East Asia.

We still do not have solid evidences about routes of transmission of the human herpesviruses, even though we know it can be transmitted sexually or during pregnancy from infected mother to child.

Hand, foot and mouth disease, investigating a deadly epidemic in Cambodia

Hand, foot and mouth disease (HFMD) is an infectious viral disease that mostly affects infants and children. The disease is characterised by fever, vesicular lesions on the mouth and rashes on the palms of the hands and soles of the feet. Often considered benign, it can sometimes lead to life-threatening neurological, cardiovascular and respiratory complications, particularly if the infection is caused by EV71. To date, there is no specific antiviral treatment or vaccine available.
In Asia, different EV71 virus strains responsible for major HFMD epidemics are spreading. In Vietnam, where the disease is endemic, EV71 is responsible for almost half of infections in people who tested positive for HMFD. In China, the health authorities have made this disease a priority, with more than 30,000 severe cases identified since 2008. The risk of spreading of highly pathogenic strains at regional and global level is high. Between April and July 2012, 66 very young children were admitted to Kantha Bopha Children's Hospital in Phnom Penh.
Almost all of them died from encephalitis associated with a severe pulmonary oedema within twenty-four to forty-eight hours following their admission. Faced with the tragedy, the Institut Pasteur in Cambodia analysed the first biological samples from patients admitted in a critical state. After several days of investigation, the test results showed that the vast majority of samples were EV71 positive. In Cambodia, HFMD had never been identified until then. The Cambodian health authorities fear a new epidemic in 2013.
After identifying EV71 as the main causative agent of the deadly HFMD epidemic in Cambodia, a collaborative project was rapidly set up between Institut Pasteur in Cambodia, Shanghai and Paris. Supported by the local health authorities, the project aims to address underlying public health and scientific issues, in particular by studying the clinical and biological factors affecting the severity of the EV71 infection.

“Inciting vocations”

SÉVERINE MATHEUS DEPUTY DIRECTOR AND HEAD OF THE TUMOUR VIROLOGY UNIT

Séverine Matheus has initiated a new approach to diagnosing dengue virus infection using blood samples collected on filter paper. A technique that has since been extended to other network institutes!

RESEARCH TRAINING PUBLIC HEALTH

What are your activities within the laboratory?

As a research engineer, I have worked for the virology laboratory at the Institut Pasteur in Guiana since 2003. The laboratory houses three national reference centres and the associated laboratories for arbovirus, influenza virus and hantavirus research in the Caribbean-Guiana region. Since my appointment in 2009 as deputy head of these research laboratories my work has been two-fold: public health expertise in association with laboratory missions and research on the dengue virus and hantaviruses.

Filter paper is now used in dengue surveillance?

Work initiated in 2007 in connection with my doctoral studies enabled me to validate a new approach for diagnosing dengue by collecting blood samples on filter paper. The approach is simple and cheap. A drop of blood absorbed on filter paper and kept at an ambient temperature enables all kinds of molecular and serological diagnostic tests to be performed, without the constraint of transporting blood samples to a specialised laboratory[1].

Today, this approach is used routinely by the national research centre as an epidemiological surveillance tool for dengue in the enclave areas of French Guiana, and also in the French islands of Saint Martin and Saint Barthelemy, which do not have local specialised laboratories[2]. The approach should be extended to other network institutes, particularly the Institut Pasteur in Bangui, with which we recently initiated skill transfers to enable the tool to be used for arbovirus surveillance.

My work is two-fold: public health expertise in association with laboratory missions and research on the dengue virus and hantaviruses.

You also conduct research on hantaviruses?

Alongside that work, I have initiated a study aimed at providing objective evidence of the spread of hantaviruses in French Guiana, which are responsible for a severe respiratory syndrome in humans. This work, which entails observing hospitalised patients with clinical signs but with no clear etiology, and environmental factors favouring the emergence of pathogens - enabled the identification in 2008 of the first native case of human hantavirus infection in Guiana[3]. The identification of this first case, followed by the diagnosis of two other

mortal cases in 2009 and 2010, lead me to conduct full sequencing of the virus, which has since been baptized the Maripa virus, in conjunction with the laboratory specialised in virus-host interactions at the Institut Pasteur in Guiana[4]. Due to the expertise developed on the issue, since 2012 the virology laboratory has housed the national research centre on hantavirus, an associated laboratory for the Caribbean-Guiana region.

In addition to research, do you believe that training is important?

Alongside our research activities, I supervise masters students. It is essential, as it enables me to share my experience on public health issues and research in the Guiana plateau region. I also hope to incite vocations. I also give virology courses as part of a university diploma on tropical medicine at Antilles-Guyane university.

We have recently set up skill transfers with the Pasteur Institute of Bangui in the Central African Republic.

(1) Matheus S, Meynard JB, Lacoste V, Morvan J, Deparis x. Use of capillary blood samples as a new approach for diagnosis of Dengue virus infection. J Clin Microbiol. 2007 Mar;45(3):887-90.
(2) Matheus S, Chappert JL, Cassadou S, Berger F, Labeau B, Bremand L, Winicki A, Huc-Anais P, Quenel P, Dussart P. Virological surveillance of dengue in Saint-Martin and Saint-Barthélemy, French West Indies, using blood samples on filter paper. Am J Trop Med Hyg. 2012 Jan;86(1):159-65
(3) Matheus S, Djossou F, Moua D, Bourbigot AM, Hommel D, Lacoste V, Dussart P, Lavergne A. Hantavirus pulmonary syndrome, French Guiana. Emerg Infect Dis. 2010 Apr;16(4):739-41.
(4) Matheus S, Lavergne A, de Thoisy B, Dussart P, Lacoste V. Complete genome sequence of a novel hantavirus variant of Rio Mamoré virus, Maripa virus, from French Guiana. J Virol. 2012 May;86(9):5399.

“Work on structural biology”

ALEJANDRO BUSCHIAZZO DIRECTOR OF THE PROTEIN CRYSTALLOGRAPHY UNIT

Determining the structure of proteins to facilitate the development of new treatments requires true team spirit.

RESEARCH PUBLIC HEALTH

What is the focus of your research work?

I have been specialised in structural biology for many years. The unit that I manage today is working on the general biological issue of cell signalling. It means understanding how cells are capable of capturing signals from their internal or external environment and reacting by developing an adapted response. To simplify, if you put your hand on a very hot object, your reflex will be to remove it when it burns. We are trying to understand why. To find out we are using various methods including biological macromolecular crystallography. Crystallography is based on the property of crystals to diffract light. The data collected enables us to reconstruct the three-dimensional structure of the molecules composing the crystal. Initially developed for small molecules, rapid technological and methodological progress in this field have enabled us to study complex molecules such as proteins or nucleic acids for several decades. For instance, the atomic structure of an enzyme shows us how it functions as a catalyst.

More specifically, what type of pathogens are you studying?

We are working on several types including unicellular trypanosomatid parasites such as trypanosome and Leishmania. We have just completed a major European project on Leishmania aimed at decrypting signalling associated with the virulence of the parasite in order to identify therapeutical targets.
In conjunction with the molecular parasitology unit run by Gérald Spaeth in Paris, we specifically focused on a family of proteins

It was a really difficult task at the beginning as we started from scratch, but little by little we began reaping the rewards, and today our unit works really well.

The main strength of the PIIN resides in the fact that it provides simplified systems for working together with a complementary rather than competitive approach.

called kinases, which are involved in detecting signals from the environment and are essential for the parasite's survival. We obtained excellent results as we have just published the structure of the Leishmania kinase, the LmaMPk10. The Pk10 structure has specific characteristics, which could accelerate the development of treatments[1]. Over the last few years, we have also started working on bacteria, particularly leptospires. We initiated research through a partnership with the spirochetes biology unit run by Mathieu Picardeau at the Institut Pasteur in Paris. There again, we focused on the family of kinases and tried to identify those that are really important for leptospire virulence. We continued this work through a Pasteur network research programme, focusing on the regulatory mechanisms of heme metabolism, of which we know very little, and which is essential for the survival of these bacteria. By producing mutant strains where certain signalling proteins are no longer expressed, Mathieu Picardeau's team revealed particularly interesting signalling paths. The mutant bacteria are no longer capable of sensing the need to produce heme and die.

Are the applications you work on highly therapeutic?

Yes, we are deeply involved in developing medicine. But of course, it isn't an isolated task. You can't find a direct therapeutic application just from the structure of a protein. Pathogens have multiple strategies for countering or circumventing the effects of drugs. It is therefore essential to work with parasitologists and bacteriologists who are familiar with the organism we are studying. On the other hand, the structure of a protein is often a very useful guide for chemists, who synthesise molecules capable of modulating the activity of the protein with functional outcomes. They are also the only ones that can assess whether potential treatments are too complex or too expensive to produce. This type of work therefore requires real team spirit.

Another aspect that we are gradually moving towards is what we call structural vaccinology. It entails using high resolution structural data to improve vaccine design. It is a high growth field in which there is little international expertise at present. It could be particularly interesting for continuing our work on leptospirose. A vaccine against this bacterium is really necessary from a public health perspective.

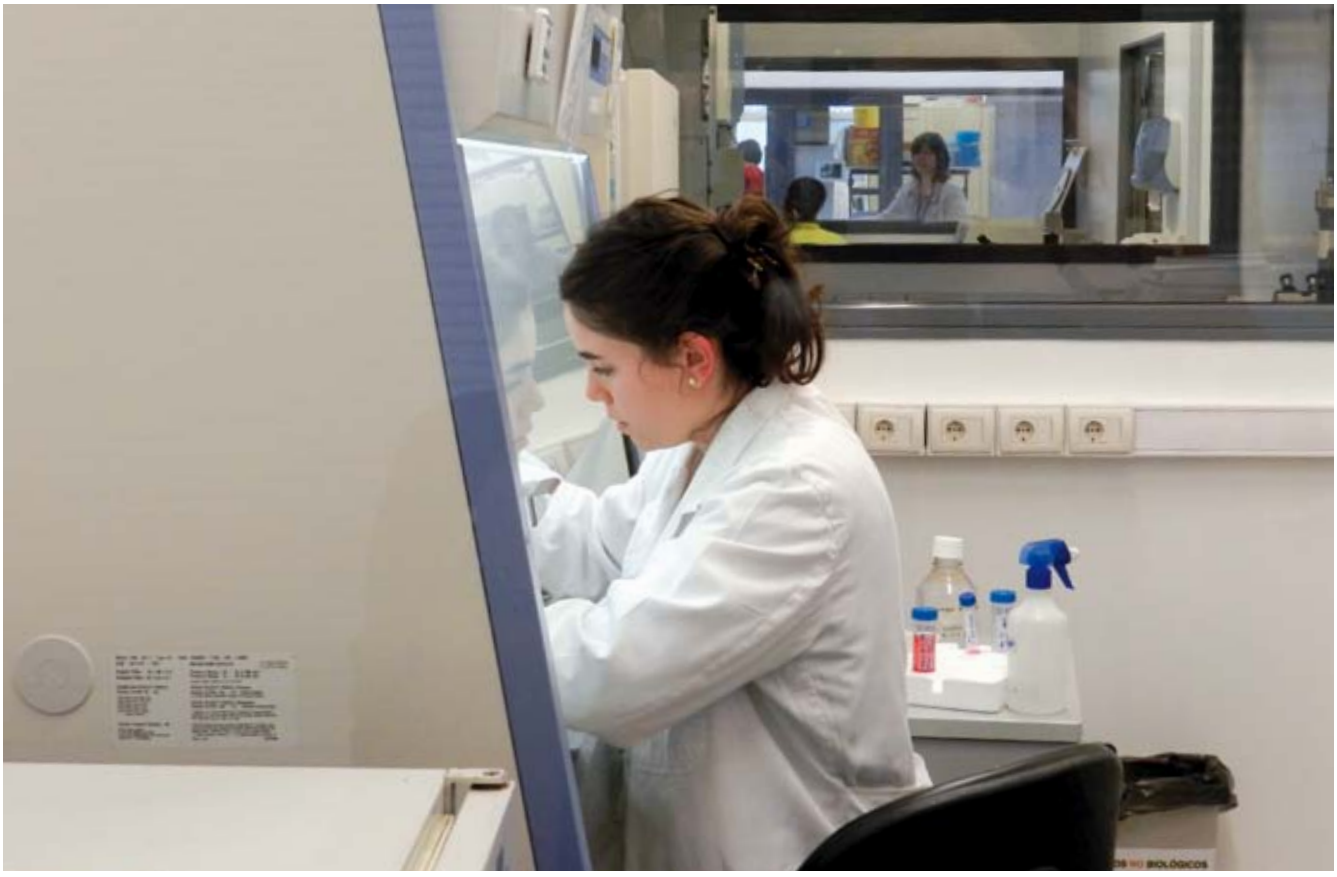
You joined the Institut Pasteur in Montevideo in 2006, what have you gained from your experience in the network?

On a personal level, the post was a turning point in my career. The fact that I am Argentinian and did my doctoral studies at Buenos Aires university was a positive point, of course. I know the region well and have a well-established network in the scientific community. The Institut Pasteur in Montevideo is relatively recent, and to work on developing structural biology here is a wonderful challenge. It was an extremely difficult task as we had to start from scratch, but little by little we began reaping the rewards and today our unit works really well.

True to Pasteur values, we are highly involved in training young researchers in structural biology. We have agreements with local universities enabling us to take on students. At a regional level, we regularly hold postdoctoral courses. It is extremely important, because structural biology has been little developed in South America. The Institut Pasteur in Montevideo has played a key role in founding the Mercosur Centre for Structural Biology[2], a fast-developing regional network aimed at training outstanding professionals in the discipline. We now intend to set up scientific and technological projects in conjunction with other institutes from the Institut Pasteur International Network on the American continent. In my mind, the main strength of the PIIN resides in the fact that it provides simplified systems for working together with a complementary rather than competitive approach, while remaining highly responsive to infectious diseases. The member institutes are directly on site in countries with emerging disease and are therefore capable of dealing with real epidemiology. The network has exceptional value and it is essential that we all provide input to make it even more dynamic in scientific and technological terms.

The Institut Pasteur in Montevideo is relatively recent, and to work on developing structural biology here is a wonderful challenge.

(1) Horjales S, Schmidt-Arras D, Limardo RR, Leclercq O, Obal G, Prina E, Turjanski AG, Späth GF, Buschiazzo A. The crystal structure of the MAP kinase LmaMPK10 from Leishmania major reveals parasite-specific features and regulatory mechanisms. Structure. 2012 Oct 10;20(10):1649-60.
(2) www.cebem.org.ar



"Understanding the interactions between host and parasite"

HARALABIA BOLETI HEAD OF INTRACELLULAR PARASITISM GROUP, MICROBIOLOGY & LIGHT MICROSCOPY UNIT

How does survive the parasite in a particular type of human immune cells, the macrophages? This is the research project of this unit which uses optical microscopy approach.

RESEARCH TRAINING PUBLIC HEALTH

What is your focus in research?

"For the last 5 years, I have been studying *Leishmania donovani,* a protozoan parasite that causes the most serious forms of the disease leishmaniasis, called Kala Azar or visceral leishmaniasis. Before, I worked on molecular and cell biology aspects of the Hepatitis C virus life cycle but I decided to switch to the cell biology of the Leishmania parasites' interaction with phagocytes and I am very grateful to Genevieve Milon whose advisory role was catalyst in that decision. Indeed as a cell biologist, I find that *Leishmania* parasites offer great scientific challenges not mentioning that any finding that could result in improvement of the current therapeutic approaches would be of extremely great benefit for public health in many Asian or African countries where it is particularly prevalent.

What are your expectations?

Basically, I am interested in understanding how the parasite survives inside one particular type of human immune cells, the macrophages. These cells have the capability to engulf pathogens that infect the body, in a membrane vesicle called phagosome whose microbicidal properties destroy the intruder. We know already that some bacterial pathogens that survive in macrophages, like *Mycobacterium tuberculosis* or *Salmonella,* secrete enzymes that alter signalling mechanisms inside the macrophages and allow the pathogens to resist our immune system's defence mechanisms. Our research projects aim at exploring whether *L. donovani* has developed similar mechanisms to prevent its killing by the macrophages. More specifically, we look at the involvement of a particular type of lipids in the cells, the phosphoinositides, that are known to play a key role in the dynamics of actin cytoskeleton, the intracellular traffic of membrane vesicles and the formation of phagosomes. The way we conduct our study is by using biotechnology and light microscopy techniques. We work with macrophage cells genetically engineered to produce different fluorescent proteins that specifically recognize phosphoinositides. Thanks to these fluorescent biomarkers we follow the lipid movement when Leishmania infects the macrophage. We are thus able to trace changes in the way specific phosphoinisitides behave in the presence of *Leishmania donovani* infection and compare it to a model of infection with Leishmania mutants that cannot survive inside the macrophage. This later model has been developed the Institut Armand Frappier who works on similar questions concerning the survival of *L. donovani* in the phagosomes of macrophages.

Optical microscopy not only allows us to obtain digital images able to visualize cellular structures, but gives us a lot of quantitative information.

Often, a study may hide another...

Another research project we are conducting concerns two groups of parasite phosphatases. One of these groups has a molecule that resides

at the surface of the parasite and one that can be secreted. For these molecules there is old biochemical data telling us that they interact with phosphoinositides. We would like to know if they affect phosphoinositide signalling in the macrophage. In these projects, we use molecular and cellular tools that we have generated to study the function of these enzymes and their importance in the parasite life cycle and survival in the host macrophages. We hope that maybe one of these phosphatases will prove to also be a virulence factor for *Leishmania* parasites. If this is the case we can then continue our studies towards the development or discovery of a drug that targets that protein.

Did you get meaningful results?

Though we are new comers in the field, I am confident that we will be successful in getting an international recognition as we have already obtained some interesting results that I hope will be published very soon. In addition, in our Light Microscopy Unit we just acquired a new microscope that will allow us to improve our work in terms of visualizing the life cycle of the parasites in live macrophages. At a regional level, our expertise in the field of light microscopy is now quite acknowledged and I feel very happy that we will host in June 2013 the first RIIP regional course focused on digital image processing and analysis in light microscopy. I had this project in my mind for quite some years now and it came to reality thanks to the help of Jean-Christophe Olivo-Marin who is head of the unit of quantitative image analysis at the Institut Pasteur in Paris and the support of my colleagues Dimitra Thomaidou and Evangelia Xingi at the Light Microscopy Unit at HPI.

We all work in a spirit of emulation and not of international competition, because we all share this vision to contribute to the improvement of public health.

Does optical microscopy plays a vital role in your approach?

What we obtain with light microscopy is not just images to see cellular structures. The digital images contain a lot of quantitative information. Today there are a number of software that help the microscopists to extract this information from the digital images. Regretfully, young scientists in the Eastern Mediterranean and Balkan region do not have the opportunity to learn much about this during their training at the university. This course will represent a unique opportunity for them to learn how to use these software correctly in order to improve the quality of their data and publications. This training is truly something that aligns with the vision and missions of Institut Pasteur which have always been very close to my heart.

Pasteur, is it a long story?

It is because of Louis Pasteur and his ideals of disseminating science everywhere and his humanitarian spirit that I was inspired to do my post-doctoral training at the Institut Pasteur in Paris in 1996-1999. Today, I feel privileged to be part of the Institut Pasteur International Network. Working with a neglected infectious disease like Leishmaniasis, it is particularly important for me to have access to valuable biological samples, rare strains of the infectious agent and share the experience of scientists that face the reality of the disease in their country. These are all possibilities that are offered within the network. I see it like a giant scientific family in which it is easier to be trusted and to establish collaborations as all members are inclined to exchange information without suspicion. We all work in a spirit of emulation instead of international rivalry because we have in common this vision of contributing to the improvement of public health wherever it is needed in the world.

"A stepping stone to becoming researcher"

CATALIN TUCUREANU RESEARCH ASSISTANT

Research of this laboratory focus on innate immunity, particularly through projects on cancer. In this area, this young researcher has now acquired a solid experience.

RESEARCH TRAINING PUBLIC HEALTH

Researcher, is it primarily a passion?

As far as I can go back in my memories, I was always fascinated with the idea of becoming a researcher. Initially, I chose to study biochemistry at the university with the idea to pursue a career in genetics. In 2006, during my second year, I had the chance to be recruited by one of my teachers for a training period of three months at the Cantacuzino National Institute for Research and Development. Before, I had basically very little knowledge about immunology and I discovered what It really was thanks to a joint course organized by the Institute in collaboration with the Institut Pasteur International Network. I immediately felt very attracted to it. I learnt most of the immunology I know during those two intensive weeks of training. Being enrolled in that course was an important step for me opening a completely new horizon, and leading to the decision of pursuing my career in immunology.

What kind of research do you work?

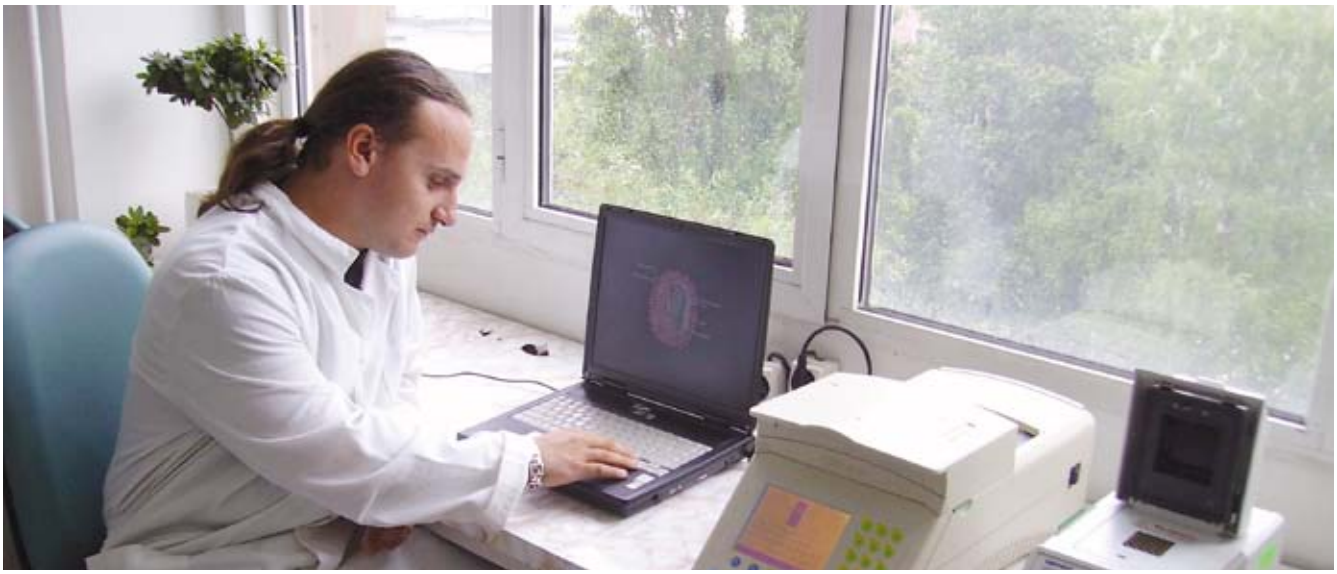
Today, I am employed as a full-time researcher. The researches in our lab are centred on innate immunity. We have a number of projects on immunity against cancer. Whereas macrophages are one of the major populations of cells present in many tumours, the role they play in tumour progression can be beneficial or deleterious depending on the functional phenotype they acquire. Using primary cells isolated from human colon cancer, we developed an in vitro model with which we recently obtained data supporting the hypothesis that tumour-secreted soluble factors are able to modulate macrophages behaviour[1]. We

My participation in this training was an important step and opened up a completely new horizon.

also aimed at examining how cancers with different levels of aggressiveness and rates of metastasis interact with the patient immune system. Adipose tissue releases a number of factors that may play a role in certain cancers, in particular colorectal ones. This might partially explained the epidemiological evidence of obesity–related carcinogenesis. We investigated the association between several blood adipocytokines levels and clinicopathological characteristics of colon cancer patients undergoing surgery and showed that some of these factors, in particular resistin and leptin, corelate with development and progression of colon cancer[2]. Finally, we did investigations to determine systemic changes in immunological profiles of cancer patients before and after surgery for tumour removal, showing increased levels of inflammatory mediators and an altered pattern of cytokine signalling in circulating immune cells.

Have you developed partnerships?

We collaborate with the Institut Pasteur in Paris and the Institute Stephan Angeloff in Bulgaria. We had a common ACIP project on the protection conferred by administration of Candida albicans DNA in both gastrointestinal bacterial infections and neonatal Candida. We will soon be starting a newly accepted accepted project on acid



modification of intravenous immunoglobulins and their immunomodulating properties.
Our partners in Bulgaria have noticed that immunoglobulins, after being exposed to extreme pH changes gain broadened specificity. Thus, commercial immunoglobulins, purified through various methods leading to their exposure to low pH have modified properties. The idea of this project is to assess the activity of these modified pooled immunoglobulin preparations in experimental severe inflammatory response syndrome and sepsis. Ultimately that kind of research can lead to better treatment of polymicrobial sepsis which is a generalized infection that happens, for example, in case of massive wounds or rupture of the intestine and is characterized by an excessive immune response that can actually be deleterious to the patient.

You also work on vaccines...

We also collaborate with a research team in the USA on a project, funded by the US Government, for technological transfer of adjuvant manufacturing processes and preclinical development of a pandemic H5N1 influenza vaccine. Finally, we are also part of project funded by WHO regarding the development of a framework for rapid vaccine development and preparedness in the event of a new influenza pandemic.

Your dream is coming alive...

We certainly have a lot of work but I am truly passionate with what I am doing. I consider myself lucky that I had the chance of entering so soon in the Cantacuzino Institute as I now have solid background as a young researcher. I still have a long road to go as I should start a PhD soon but I am confident that the Institut Pasteur International Network will offer me a great opportunities to pursue my dreams.

(1) Caras I, Tucureanu C, Lerescu L, Pitica R, Melinceanu L, Neagu S, Salageanu A. Influence of tumor cell culture supernatants on macrophage functional polarization: in vitro models of macrophage-tumor environment interaction. Tumori. 2011 Sep-Oct;97(5):647-54.
(2) Salageanu A, Tucureanu C, Lerescu L, Caras I, Pitica R, Gangura G, Costea R, Neagu S. Serum levels of adipokines resistin and leptin in patients with colon cancer. J Med Life. 2010 Oct-Dec;3(4):416-20.
(3) Caras I, Tucureanu C, Pitica R, Salageanu A. Bacterial extract cantastim activates macrophages via TLR-2. Roum Arch Microbiol Immunol. 2011 Jan-Mar;70(1):28-36.

While macrophages are one of the major populations of cells present in many tumors, their role in tumor progression may be beneficial or harmful...

"Actively involved in the students training"

ANGELA SANTONI SCIENTIFIC DIRECTOR OF THE INSTITUT PASTEUR - CENCI BOLOGNETTI FOUNDATION

Develop new therapeutic strategies capable of strengthening the response against tumors and viral infections. Such is the objective of this institute.

RESEARCH PUBLIC HEALTH

What kind of research are you leading?

I define myself as an immunologist. I am working on the basic mechanisms of the immune response directed against cancer and virus-infected cells. My main scientific interest is on the innate component of immunity and particularly on a particular population of lymphocytes, named natural killer (NK) cells. In fact, I was post-doc in 1975 in the USA, in the lab at the NIH that contributed at that time to discover this population of immune cells, and I have been working on NK cells since then. NK cells act as a first line of defence against tumours and microbial infections. But they also play a major role in the regulation of recruitment and activation of other immune cells. In our laboratory, we would like to better understand how NK cells recognize tumour or virus-infected cells. Our objective is to identify the ligands and the receptors involved in the interaction between NK cells and their targets. Ultimately, the purpose of this research is to try to develop novel therapeutic strategies that can potentiate the response against tumours and viral infections.

Have you already got results?

Recently we have established that NK cells and some innate receptors, in particular NKG2D and DNAM-1, can represent a surveillance system to sense cells undergoing a cellular stress. These cells, that are somehow damaged, in some instances can acquire a senescent phenotype. Because of this senescent phenotype they are more easily recognized by the innate receptors expressed by NK cells. Accordingly, in 2009, we published that it is possible to augment the anti-tumor NK cell response against multiple myeloma, the tumour that we have been using as a model, by treating the cancer cells with sub-lethal doses of chemotherapeutic drugs. Indeed, this treatment up-regulates the expression of the ligands for two activating NK cell receptors, NKG2D and DNAM-1, by triggering the DNA damage response. This leads to an increased sensitivity of drug-treated cancer cells to NK cell killing[1].

In our laboratory, we try to understand how NK cells recognize tumors or virus-cells infected.

NK cells may also play an important immunomodulatory role...

More recently we found that NKG2D and DNAM-1 ligands are also expressed on antigen-activated proliferating T-cells as result of the activation of DNA damage response. It means then that when normal cells like activated T-lymphocytes express the ligands of NK activating receptors, they can become target of the NK cells and be ultimately destroyed[2]. Thus, NK cells do not only play a role in the elimination of tumor and virus-infected cells, but they have also an important immunoregulatory role. They can act as a brake to limit the responses of autoreactive T cells or T cells which can be in a way

dangerous for the host. This kind of reaction is observed for example in patients that undergo a graft versus host reaction during bone marrow transplantation. If there is an incompatibility, the T cells of the donor recognize as stranger and react against the tissues of the recipient. As a consequence of the activation/proliferation process, the T cells express the ligands recognized by the NK receptors and the NK cells can kill these dangerous T cells.

Research is also synonymous with collaboration...

Within the ACIP programme, our research group has also an ongoing collaboration with the Institut Stephan Angeloff in Sofia. With the group of Petya Dimitrova, we study the interactions between NK cells and neutrophils in the pathogenesis of arthritis. This is a rather new area of research of increasing interest, suggesting that NK cells can also play a key role in the regulation of differentiation and functions of neutrophils during inflammation.

You give also great importance to teaching and training...

Beside, my research activity, I am teaching Immunology and Immunopathology at the Sapienza University of Rome. It is important for me to be actively involved in the training of undergraduate and PhD students The interaction with young people represents a continuous intellectual stimulus. It is an easy way to enlarge your vision and make you learn about other research fields.

(1) Soriani A, Zingoni A, Cerboni C, Iannitto ML, Ricciardi MR, Di Gialleonardo V, Cippitelli M, Fionda C, Petrucci MT, Guarini A, Foà R, Santoni A. ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. Blood. 2009 Apr 9;113(15):3503-11.
(2) Ardolino M, Zingoni A, Cerboni C, Cecere F, Soriani A, Iannitto ML, Santoni A. DNAM-1 ligand expression on Ag-stimulated T lymphocytes is mediated by ROS-dependent activation of DNA-damage response: relevance for NK-T cell interaction. Blood. 2011 May 5;117(18):4778-86.

NK cells not only play a role in the elimination of tumors and virus-infected cells, but they also have an important immunomodulatory role.

"Maintaining scientific awareness"

HELMI MARDASSI MANAGES THE MYCOBACTERIAL GENOTYPING UNIT

In Tunisia, surveillance of tuberculosis is essential due to the emergence of a multidrug-resistant strain.

RESEARCH PUBLIC HEALTH

You trained as a virologist, isn't it surprising that you are managing a mycobacteria laboratory?

It is true that I wasn't naturally drawn to working on tuberculosis. I focused most of my doctoral and post-doctoral work on viruses, particularly at the Armand Frappier Institute in Canada. When I returned to Tunisia in 2001, I was offered the post as head of the mycobacteria laboratory to develop both diagnostic and research activities. For me it was a real challenge, but the idea was to draw on the skills I had gained through my virology courses, particularly in molecular biology. At the time, the *Mycobacterium tuberculosis* genome had just been sequenced by Stewart Cole's team and molecular approaches were developing rapidly in tuberculosis research. So we pulled out all the stops to set up the tools needed for optimal diagnosis and characterisation of Mycobacterium strains, while initiating research projects relevant to the situation in Tunisia given our limited human resources. Tuberculosis is one of the most studied bacteria in the world, so establishing our place in this extremely competitive field was not easy, but we were able to do so thanks to the support of the Institut Pasteur International Network. At that time, there was a research group on mycobacteria run by the network. It enabled me to make contact rapidly with the unit managed by Brigitte Gicquel at the Institut Pasteur in Paris, where I was given precious help in setting up Mycobacterium genotyping.

Is tuberculosis a heavy burden in Tunisia?

With 24 cases per year for 100,000 inhabitants, Tunisia is the country with the lowest incidence in the Maghreb region and, of course, we are far from the levels found in sub-Saharan Africa. That is not to say that tuberculosis is not a public health problem though, and surveillance remains essential. When we set up our unit, we were alerted by a hospital in the Bizerte region and we rapidly discovered a multidrug-resistant tuberculosis epidemic due to a strain called Haarlem[1]. Worryingly, this strain was capable of transmitting the disease very effectively, leading to sudden epidemic outbreaks, which had never previously been observed. Using molecular cartography, we retraced the development history of the epidemic to the drug-sensitive parental strain[2]. Determining the genome sequence of the epidemic strain and comparing it with the sensitive parent strain enabled us to understand the emergence of the epidemic. It confirmed our belief that it was necessary to increase epidemiological surveillance of tuberculosis. So we used more detailed cartography of the strains present in the country and found a relatively homogenous epidemiological situation, since more than 90% of cases of tuberculosis are due to three families of *M. tuberculosis,* including Haarlem[3]. The domination of these genotypes can prob-

> *Tuberculosis is one of the bacteria the most studied in the world, so establishing our place in this extremely competitive field was not easy.*

ably be explained by positive selection, enabling them to prevail despite the high vaccination rate in our country.

So your laboratory quickly gained a prominent position in the Tunisian public health landscape?

Yes, we were the first to warn the Tunisian authorities of the multi-drug-resistant epidemic and we continue to monitor the epidemic, which re-emerges regularly. We also advise the national tuberculosis programme. We recently identified other epidemics in the same region, with transmission chains of 30-40 patients infected by the same strain. If these strains gain resistance to treatment, they can cause serious health problems. We are fully integrated into country's public health system due to our monitoring role and close relations with the authorities, hospitals and doctors. Genotyping is the best way of identifying epidemics and resistance and to guiding national programmes. The WHO has not really encouraged genotyping in the South countries as it is closely linked with research, but genotyping can provide precise responses in terms of public health.

The aim of the EuMedNet-TB project is to create a favourable environment in laboratories and improve the level of tuberculosis research.

In terms of research, what are you working on?

We are looking at developments over time in tuberculosis bacilli by studying the two gene families PE and PPE, which were discovered by sequencing *M. tuberculosis.* These genes are extremely important as they encode 10% of *M. tuberculosis,* and many are involved in antigenic variation, virulence and bacilli persistence. Our results showed that these genes are capable of exchanging parts of DNA by a gene conversion mechanism[4], opening up new perspectives for understanding the molecular events underlying the development and

recent clonal expansion of the tuberculosis bacilli. We have also shown that these gene families were frequently located where homologous recombination occurred, while it is generally accepted that the genome is relatively stable[5]. By examining these phenomena more closely, we found that deletions of PE-PPE genes from a specific secretion locus were associated with the most frequent genotype present in Tunisia. We continued our analysis to understand how deletion could give this strain a selective advantage. Other important work concerned the analysis of PE genes in soft strains of Mycobacterium isolated in patients in the Horn of Africa. Our results show the dual role of recombination and positive selection in the development of these genes and their adaptability to humans and animals[6].

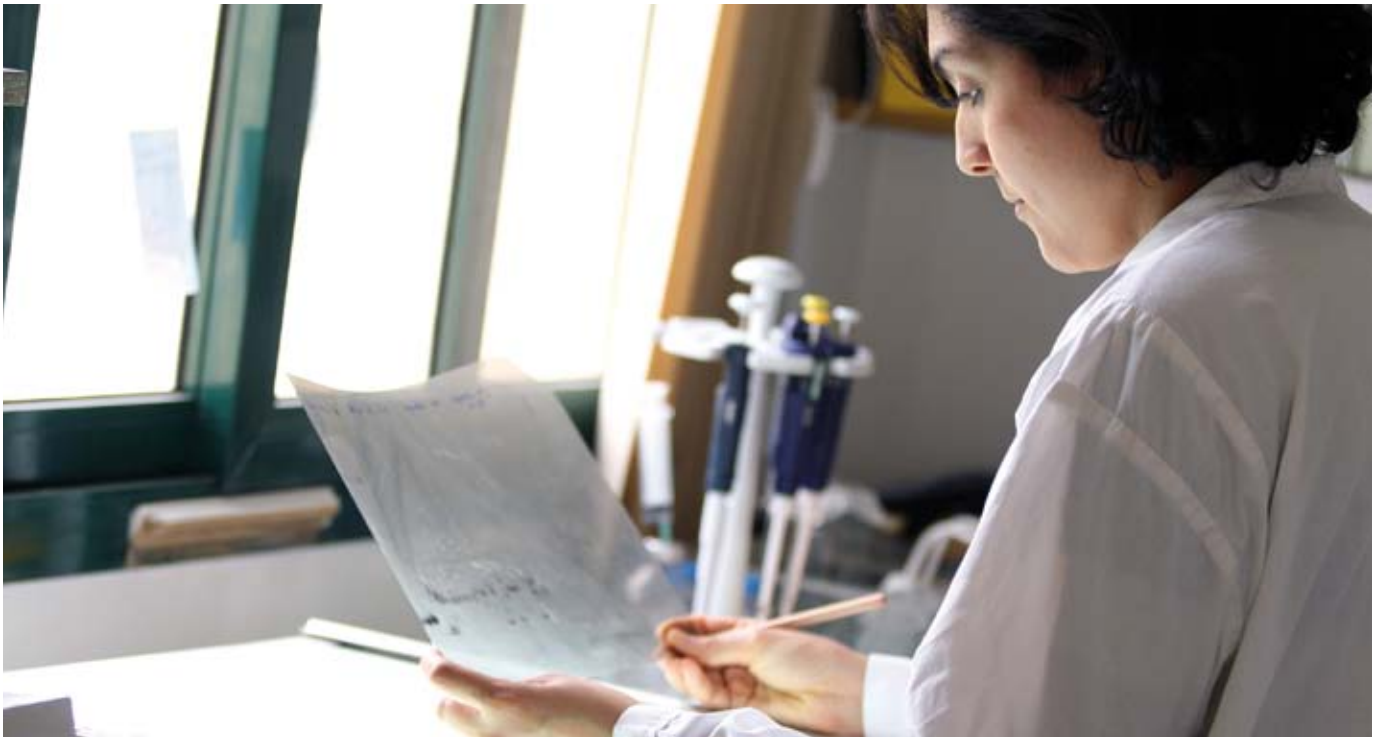
Is it important for you to maintain this research activity?

It is essential not only on a personal level but also for the Institut Pasteur of Tunis and more generally for my country. Research enables us to maintain scientific awareness, to train young people, and to improve the surveillance and control of tuberculosis. At present, we are working with the EuMedNet-TB[7] project funded by the European Commission in connection with FP7. The project is coordinated by Brigitte Gicquel and involves eight partners including the Institut Pasteur in Algeria, Guadeloupe, Paris and Tunis, as well as the Stephan Angeloff Institute in Bulgaria, the Borstel Centre in Germany and the Health Sciences Institute in Spain. The objective of EuMedNet-TB is to promote bilateral research initiatives between partner countries and to strengthen the capacity of laboratories in southern Mediterranean countries.

The idea of the project is to create a favourable environment for South laboratories to improve the level of tuberculosis research. For over two years, this project has enabled us, among other things to organise international seminars and to make contact with many internationally renowned experts. It has provided a unique opportunity for our laboratory to progress. This would not have been possible without the network, which has played a key role, and for which we are sincerely grateful.

We were the first to warn the Tunisian authorities of the multidrug-resistant epidemic and we continue to monitor the epidemic, which re-emerges regularly.

(1) Mardassi H, Namouchi A, Haltiti R, zarrouk M, Mhenni B, karboul A, khabouchi N, Gey van Pittius NC, Streicher EM, Rauzier J, Gicquel B, Dellagi k. Tuberculosis due to resistant Haarlem strain, Tunisia. Emerg Infect Dis. 2005 Jun;11(6):957-61.
(2) Namouchi A, Mardassi H. A genomic library-based amplification approach (GL-PCR) for the mapping of multiple IS6110 insertion sites and strain differentiation of *Mycobacterium tuberculosis*. J Microbiol Methods. 2006 Nov;67(2):202-11.
(3) Namouchi A, Haltiti R, Hawari D, Mardassi H. Re-emergence of the progenitors of a multidrug-resistant outbreak strain of *Mycobacterium tuberculosis* among the postoutbreak case patients. J Infect Dis. 2010 Feb 1;201(3):390-8.
(4) Namouchi A, karboul A, Mhenni B, khabouchi N, Haltiti R, Ben Hassine R, Louzir B, Chabbou A, Mardassi H. Genetic profiling of *Mycobacterium tuberculosis* in Tunisia: predominance and evidence for the establishment of a few genotypes. J Med Microbiol.2008 Jul;57(Pt 7):864-72.
(5) karboul A, Gey van Pittius NC, Namouchi A, Vincent V, Sola C, Rastogi N, Suffys P, Fabre M, Cataldi A, Huard RC, kurepina N, kreiswirth B, Ho JL, Gutierrez MC, Mardassi H. Insights into the evolutionary history of tubercle bacilli as disclosed by genetic rearrangements within a PE_PGRS duplicated gene pair. BMC Evol Biol. 2006 Dec 12;6:107
(6) karboul A, Mazza A, Gey van Pittius NC, Ho JL, Brousseau R, Mardassi H. Frequenthomologous recombination events in *Mycobacterium tuberculosis* PE/PPE multigenefamilies: potential role in antigenic variability. J Bacteriol. 2008 Dec;190(23):7838-46.
(7) Namouchi A, karboul A, Gutierrez MC, Fabre M, Mardassi H. Evolution of smooth tubercle bacilli PE and PE_PGRS genes: evidence for a prominent role of recombination and imprint of positive selection. PloS One. 2013. In press.
(8) www.eumednet-tn.com



EpiSouth Plus, a unique health surveillance network in the mediterranean region

The EpiSouth network, which was set up in 2006, comprises local focal points in the public health institutes and/or Health ministries of 27 Mediterranean countries. The Institut Pasteur joined this network as part of a new phase of activities represented by the EpiSouth Plus project (2012-2014), coordinated by the Istituto Superiore di Sanità (ISS) and financed by the European Union (DG Sanco and Devco). The objective of this second phase is "to increase health security in the Mediterranean Area and South-East Europe by enhancing and strengthening preparedness to public health threats and other bio-security risks among the 27 countries of the existing EpiSouth network". The WHO is a partner in the project and coordinates action to facilitate the implementation of International Health Regulations in the region, in conjunction with the ISS.

The Institut Pasteur, in partnership with the Turkish Public Health Institution, is responsible for one of the key phases of the EpiSouth Plus project. It entails setting up and running a Mediterranean regional laboratory network, called the MRLN, which to date comprises 24 members. The purpose of the MRLN is to facilitate the detection of infectious health risks common in Episouth region countries. The network provides support for the epidemiological surveillance already in place for three major regional emergencing priorities: West Nile, Dengue and Biosafety. In December 2012, the first meeting of the EpiSouth Plus project was held for both national focal points and heads of the MRLN laboratories. The meeting enabled participants from different countries and disciplines to gather and discuss issues, such as common emerging requirements, but also ways of ensuring the sustainability of this unique Euro-Mediterranean network in the long term.

As part of the laboratory network activities, the Institut Pasteur and Turkish Public Health Institution identified the laboratories to be involved. The heads of the MRLN laboratories met in March 2012 in Ankara, to discuss their experience and expectations. A tailored training programme was then developed. The Institut Pasteur hosted the first international training session on "Dengue & Biosafety" for all Mediterranean countries in July 2012 at its training centre. The training session, which combined both theory and practice, involved experts from the internationally renowned networks and laboratories. It enabled all participants to obtain international ISST certification, allowing them to transport infectious substances internationally. The second session on "West Nile & Biosafety II" will take place in summer 2013 after which training kits will be provided for both courses.

AFRICA – **INSTITUT PASTEUR IN MOROCCO**

"Serving the population"

SOUMAYA BENJELLOUN HEAD OF THE INFECTIOUS DISEASES DIAGNOSIS DIVISION

This division works closely with several teams from the Institut Pasteur in Paris and is involved in the viral hepatitis control programme.

RESEARCH PUBLIC HEALTH

What is your role in combatting hepatitis?

As a national reference laboratory, we are at the core of Moroccan public health. We work closely with university hospital centres to biologically monitor patients and respond to epidemiological requirements in the Kingdom. It is in this laboratory that the first molecular diagnosis of the hepatitis virus was performed in Morocco, and also the first diagnosis of hepatitis E following the epidemic declared in 1994, in collaboration with the Health ministry. Since 2010, we have participated in the programme combatting viral hepatitis set up by the Health Ministry. In Morocco, chronic liver disease associated with infection by hepatitis viruses is a heavy public health burden. Hepatitis B and C occur in relatively endemic states with prevalence estimated at 2% and 1 % respectively. We plan to conduct a survey on seroprevalence, which should enable us to reassess the situation, as part of the national programme. We conducted a similar study on co-infections of HIV and hepatitis B and C showing relatively low prevalence of around 5% compared with rates reported in European populations. As coinfection is a factor that worsens both HIV and hepatitis, it is necessary to provide patients with optimal care.

It is in this laboratory that the first molecular diagnosis of the hepatitis virus was performed in Morocco.

What is your research strategy?

Our research work is founded on the epidemiological environment specific to Morocco. Our work focuses on the variability of hepatitis B and C viruses and their involvement in the development of liver diseases such as hepatocellular carcinoma. Several of our studies have shown the predominance of genotype D, which is present in 90% of chronic cases of hepatitis B in Morocco. We have just published the results of a study showing for the first time an association between hepatitis B virus, virus genome mutation and the severity of hepatic diseases in chronic carriers[1]. In public health terms, these results are significant as therapeutic strategies will be adapted based on the presence or absence of such mutations. Moreover, some mutations lead to less expression of HBe antigen, used as a clinical indicator of viral replication and others involved in viral restriction through Apobec3 activity[2].

What strains of hepatitis C have been identified in Morocco?

Work conducted at the end of the 1990s showed the presence of two main sub-types in Morocco, 1b and 2a/2c. Today, the situation has changed with 75% of VHC strains belonging to sub-type 1b, which responds less well to treatment. The phylgoenetic analysis of the strains present suggests a probable common origin between the isolates found in Morocco and those found in Europe and the Maghreb. The similarity is due to the geographic position of Morocco and amplifying migratory flows between these countries[3]. In addition, the analysis of hepatitis C virus genes showed the presence of mutations, solely in patients with genotype 1[4].

We are partners of the European Hepacute project, which studies viral factors and the host involved in severe hepatitis C.

Through a recent analysis conducted in conjunction with the Institut Pasteur in Paris and the Pasteur Centre in Cameroon, we have determined the common ancestor of the hepatitis C virus strains present in Morocco and have shown that genotype 1b was introduced into Morocco around 1910, while genotype 2 is older, dating back to 1860[3].

Joint projects, partnerships, are you involved on all research fronts?

We work closely with several teams from the Institut Pasteur in Paris. It all began in 2003, thanks to the network setting up a network-wide research project on the etiopathology of liver cancer in the Maghreb. We showed that there was not much genetic alteration or single mutations that could explain the development of hepatic cancers. We are interested now in the polymorphism of genes involved in epigenetics, which could explain hepatic carcinogenesis in Morocco[5]. Finally, we are partners of the European Hepacute project, which studies viral factors and the host involved in severe hepatitis C. The objective is to understand why some patients heal spontaneously while others remain chronic virus carriers, and to identify new biomarkers involved in natural healing from hepatitis C virus infection. We succeeded in this case in confirming that the polymorphisms of gene IL-28B are associated with natural clearance and progression of hepatic disease[6].

For me, the interface between research and public health is essential. Our mission is to serve the population and provide new treatments and diagnostic tests to try and better understand hepatitis issues in Morocco. That is why I am proud to have worked for twenty years for the Institut Pasteur in Morocco.

(1) Kitab B, Essaid El Feydi A, Afifi R, Trepo C, Benazzouz M, Essamri W, zoulim F, Chemin I, Alj HS, Ezzikouri S, Benjelloun S. Variability in the precore and core promoter regions of HBV strains in morocco: characterization and impact on liver disease progression. PLoS One. 2012;7(8):e42891.
(2) Sayeh Ezzikouri, Bouchra kitab, khadija Rebbani, Agnès Marchio, Simon Wain-Hobson, Anne Dejean, Jean-Pierre Vartanian, Pascal Pineau, Soumaya Benjelloun. Polymorphic APOBEC3 modulates chronic Hepatitis B in North African Patients. Accepted in Genes and Immunity.
(3) Brahim I, Akil A, Mtairag el M, Pouillot R, Malki AE, Nadir S, Alaoui R, Njouom R, Pineau P, Ezzikouri S, Benjelloun S. Morocco underwent a drift of circulating hepatitis C virus subtypes in recent decades. Arch Virol. 2012 Mar;157(3):515-20.
(4) Ikram Brahim, Sayeh Ezzikouri, El Mostafa Mtairag, Rhimou Alaoui, Salwa Nadir, Pascal Pineau, Soumaya Benejlloun. Amino acid substitutions in the hepatitis C virusC ore region of genotype 1b in Moroccan patients. Infection, Genetics and Evolution. 2012 Nov ; 14 :112-104
(5) Akil A, Ezzikouri S, El Feydi AE, Benazzouz M, Afifi R, Diagne AG, Benjouad A, Dejean A, Pineau P, Benjelloun S. Associations of genetic variants in the transcriptional coactivators EP300 and PCAF with hepatocellular carcinoma. Cancer Epidemiol. 2012 Oct;36(5):e300-5.
(6) Sayeh Ezzikouri, Rhimou Alaoui, khadija Rebbani, Ikram Brahim, Fatima-zohra Fakhir, Salwa Nadir2, Helmut Diepolder, Salim I. khakoo, Mark Thursz, Soumaya Benjelloun. Genetic variation in the interleukin-28B gene is associated with spontaneous clearance and progression of hepatitis C virus in Moroccan patients. PLoS One. 2013;8(1):e54793.

Creation of 4-year groups

Attracting wide-ranging talent to serve the network

The Institut Pasteur provides support to young scientists from the South who form international research groups within the Institut Pasteur International Network. The go-ahead has just been given for the creation of the first four-year groups in Africa.

This initiative provides a wonderful opportunity for young researchers. They can set up a research group in a low income country. There are thousands of unexplored fields requiring young world-class scientists. The initiative provides them with the means to undertake their projects.

At the end of 2012, the Institut Pasteur selected the first two winners who will set up research groups within the network institutes. In the same spirit as the projects undertaken on the Institut Pasteur campus, the objective is to enable young researchers from the South countries to lead innovative research programmes on infectious diseases in their own country.

RESEARCHERS FROM THE SOUTH RETURN TO THEIR COUNTRY

The programme gives internationally-trained postdoctoral researchers with experience in renowned laboratories the opportunity to set up new research groups in one of the network institutes.

APPRECIATING THE UNIQUE CHARACTERISTICS OF DEVELOPING COUNTRIES

Over the years, the human research capacity of the international network institutes has grown. Personnel have gained skills and experience, particularly in research projects combining field expertise and applied research. With the arrival of a new generation of international researchers, local scientific assets and skills will be strengthened by the input and commitment of young people leading grounded research projects. Discovering and disseminating the new scientific findings resulting from the combination of local assets and regional and international skills, will highlight the importance of conducting research in developing regions.

G4, AN INSTRUMENT FOR INTERNATIONAL EXPOSURE

For Antoine Gessain, Chairman of the Selection Committee for the four year research groups and Head of the Oncogen Virus Epidemiology and Physiopathology Unit at the Institut Pasteur, "Research has become global and we absolutely must drive this dynamic process within the network institutes. Scientific diversity is essential for harnessing the phenomenal research potential on infectious diseases of the Institut Pasteur International Network. There are thousands of unexplored fields awaiting young world class scientists. For that we need a critical mass of high level researchers." It is clear that creating the first two four-year research groups is a response to this challenge. The G4 initiative provides the opportunity to attract dynamic international researchers who are open to setting new research partnerships. Drawing on his knowledge, the scientific team leader will naturally seek to network, particularly with universities and public and private international research institutions. These contact points will then strengthen local research programmes.

A NEW UNIFIED MODEL FOR ESTABLISHING NORTH-SOUTH AND SOUTH-SOUTH RELATIONS

In addition to financial support (€80 thousand per year), the Institut Pasteur provides the research groups with technical and scientific backing. A mentoring and monitoring committee has been set up for this purpose. Advice is given on the relevance of programmes and development perspectives generated by the new initiative. The host institute adopts a unified model, ensuring the group works as an integral part of the local scientific community and actively participates with the Institut Pasteur teams and those of the international network.

TWO YOUNG SCIENTISTS SELECTED FROM CAMEROON AND SENEGAL

Africa and malaria were given pride of place for these first two groups. Two young scientists from Cameroon and Senegal were chosen for the high quality of their training and project proposal. The two young researchers wish to pursue malaria issues further. They will provide a new perspective on the disease by creating research synergies and fostering new projects.

Teaching and training: abroad

programme!

Alongside research and public health, teaching and training is one of the three missions assigned by Louis Pasteur to the Institute that bears his name. As a strategic challenge, each institute of the Institut Pasteur International Network aims to train young researchers. Thus, the Institut Pasteur International Network contributes to the transmission of knowledge and to the training of future researchers and public health experts worldwide.

Fellowships for those wishing to train abroad

The Institut Pasteur International Network plays a significant role, as assigned by its founder, by enhancing scientific capacity and human resources through training worldwide. Training programmes are provided for this purpose, in partnership with national scientific and medical universities and local research structures. Initially aimed at network personnel, these programmes are now also open to researchers, technicians and students from other institutions.

The Pierre Ledoux Jeunesse Internationale Foundation and Institut Pasteur International Division jointly fund ten fellowships per year.

The Calmette and Yersin Program finances an ambitious training programme for international scientists and researchers. It is a unique initiative in the universe of research training. Each year, though international fellowships, the Institut Pasteur provides support to scientists from the South that wish to follow a course or participate in an internship in Paris, in an institute from the Institut Pasteur International Network or in another research institute. The programmes also give young international researchers the possibility of doing their thesis or post-doctoral training in endemic countries. The Institut Pasteur International Network also holds international courses.

SUPPORTING TRAINING THROUGH RESEARCH

Many scientists from the South have supplemented their training by taking courses or doing internships in Paris or in the Institut Pasteur International Network.

Research fellowships

The purpose of fellowships is to enable scientists (students, researchers, engineers and technicians) from the Institut Pasteur International Network to participate in training provided by the Institut Pasteur in Paris and other network institutes. The training supplements the scientist's initial training, enhancing their skills in their research field.

Each year, the Institut Pasteur training centre in Paris holds 28 advanced theoretical and practical courses on scientific research, which are attended by students and researchers from all over the world (500 students per year and 50 nationalities). Sixty-seven scientists from the Institut Pasteur International Network and nine students from Amsud-Pasteur took courses during the 2011-2012 and 2012-2013 sessions in Paris, thanks to fellowships granted by the International Division of the Institut Pasteur.

Internship fellowships

The purpose of these fellowships is to provide support to scientists (students, researchers, technicians) from the South that wish to undertake internships at the Institut Pasteur or in the Institut Pasteur International Network. The aim of the internships is to enhance scientists' skills in their field of research and strengthen the capacity of

Training: a priority for the Institut Pasteur International Network

Every year, more than 100 scientists from the Institut Pasteur International Network take courses or do internships in Paris to supplement their initial training. In 2012, thirteen courses and workshops funded by the Institut Pasteur International Network were held in eight countries, including five in Africa, four in Asia, two in Latin America and two in North Africa.

Young scientists with international fellowships from the Institut Pasteur in Montevideo, with Éliane Coëffier and Marcelo Comini.

Doctoral fellowships programme: promising results

2010 – Benjamin Bailly, French student preparing a thesis on "Drug discovery: virology, biology, biochemistry systems"at the Institut Pasteur in Shanghai under the supervision of Ralf Altmeyer in partnership with the Glycomics Institute at Griffiths university (Australia) co-supervised by Mark von Itzstein. He is registered at Griffiths university (Australia).

2011 – Anne-Claire Andries, French student preparing a thesis on "Dengue in Cambodia: surveillance and treatment of serious cases" at the Institut Pasteur in Cambodia, supervised by Philippe Buchy. She is registered with Montpellier university for a PhD in Integrated systems in biology, agronomy, geosciences, hydrosciences, environment.

2012 – Elisabeth Streit, Austrian student preparing a thesis on "*Mycobacterium tuberculosis* and other mycobacteriosis in French overseas departments in the Americas and the Caribbean: epidemiological aspects and the study of transmission by the use of molecular tools" at the Institut Pasteur in Guadeloupe under the supervision of Nalin Rastogi.

their home institutes.

Monaco International Cooperation Division fellowships

In 2011, the State of Monaco, the Prince Albert II de Monaco Foundation and the Institut Pasteur signed an agreement to set up a project entitled "Training scientists from South countries - specialised masters' in public health (option infectious disease risk) at the Pasteur School-Cnam for public health. The aim of the project is to provide fellowships to five young public health professionals from the African continent enabling them to access advanced training in the form of a specialised masters' course, funded by the government of the Principality of Monaco. The specialised masters in public health is provided through a partnership between the Institut Pasteur, the French National Conservatory for Arts and Crafts (Cnam) and more recently, the French School for Advanced Public Health Education (Ehesp). It provides public health training with a specialisation in infectious disease risk.

Congress fellowships

The purpose of the fellowships is to facilitate the participation of young scientists from the Institut Pasteur International Network (students, researchers and technicians) that have been accepted as speakers in international congresses. The fellowships enable Institut Pasteur International Network scientists to present their work at international meetings and thus increase the outreach of the Institut Pasteur International Network.

Permanents courses provided at the Institut Pasteur International Network

- Malaria workshop - Institut Pasteur in Madagascar.
- Courses at the research centre of Hong Kong university-Pasteur on cellular biology, virology and immunology.
- Global netwok course on food-borne infectious diseases and surveillance of salmonellosis - Pasteur Centre in Cameroon, Institut Pasteur in Saint Petersbourg, Madagascar and Tunis in partnership with the World Health Organization (WHO) and the Centre for Disease Control and Prevention (CDC) in the United States.
- Course on bio-data analysis in the Maghreb, Asia and Latin America.
- Data analysis with Stata software at the Institut Pasteur in Cambodia, Montevideo and Tunis.
- Theoretical and practical courses at the Institut Pasteur in Montevideo on new technologies for the scientific community in Latin America.

ATTRACTING YOUNG RESEARCHERS

Discovering the Institut Pasteur International network.
Training programmes offer researchers the possibility of preparing their theses and undertaking postdoctoral internships in the Institut Pasteur International Network, in countries situated in endemic areas and/or with limited resources.

Doctoral and postdoctoral fellowships

Every year, the International Division of the Institut Pasteur awards doctoral and postdoctoral fellowships to promote and facilitate theses and related work by researchers from Institut Pasteur International Network.

Pierre Ledoux-Jeunesse International Foundation fellowships

For more than twelve years, the Pierre Ledoux Jeunesse Internationale Foundation, under the auspices of Fondation de France, has supported training for young researchers, enabling them to gain a better understanding of the international envrionment. Through a partnership with the Institut Pasteur, the fellowships enable French students to undertake internships in biomedical research in the Institut Pasteur International Network in developing countries. As the founder, Pierre Ledoux stated, "the foundation first and foremost provides an opportunity for action and assistance to all young people interested in the world and other people. Simply by giving meaning to one's life by flourishing in an international environment". (My life has meaning, Pierre Ledoux, 2004, Éditions Atlantica.)

PROMOTING TRAINING TO ENDEMIC COUNTRIES

The purpose of the Institut Pasteur International Network is to enhance scientific capacity and human resources worldwide. In order to do so, the Institut Pasteur International Network develops regional and international courses in partnership with universities, local health authorities and professionals. The training is aimed at personnel working in the Institut Pasteur International Network, as well as external researchers, technicians and students. It enables them to acquire a skills base and knowledge that is recognised in all regional, national and international facilities.
The priority is to enhance coordination and cooperation by offering training tailored to the themes most relevant for each region. The aim is also to promote and complement scientists' education, at various stages of their career, through a wide range of courses. The training provides access to modern scientific techniques and new methods, ensuring technology skills transfer. It also strengthens scientific relations between researchers from other countries in the region and promotes the emergence of innovative regional scientific projects.

Postdoctoral fellowships: postdoctoral traineeships in the RIIP

2011 – Benoît Witkowski, French student undertaking postdoctoral research in the Malaria and Molecular Epidemiology Unit of the Institut Pasteur in Cambodia under the supervision of Didier Ménard.

2012 - Katerina Doleckova, Czech student undertaking postdoctoral research on "Generating and characterization of transgenic mice and mammalian/ trypanosomal cell lines expressing fluouresence-based redox biosensors" at the Institut Pasteur of Montevideo under the supervision of Marcelo Comini.

Key figures - 2011-2012 international fellowships set up by the Institut Pasteur International Division

163
international fellowships in 2011 and 2012

146
fellowships funded by the Institut Pasteur International Division through the Calmette and Yersin programme:

65 study grants

66 internship **fellowships** including five for three-year **doctoral grants** and two for two-year **postdoctoral grants**

15 fellowships to attend conferences

17
fellowships cofinanced by the Institut Pasteur International Division and partners:

13 fellowships from the Pierre Ledoux Jeunesse Internationale Foundation

3 fellowships from the Prince Albert II de Monaco Foundation

1 three-year **doctoral grant** from the Total Foundation

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Partners

FRENCH AND INTERNATIONAL MINISTRIES AND AGENCIES

- American Center for Disease Control (CDC)
- Department of Health and Social Services (DHSS)/APSR
- French Development Agency (AFD)
- French Ministry of Foreign Affairs
- French Ministry of Health
- French Ministry of Higher Education and Research
- Friends of the Global Fund
- Medical Research Council (MRC)
- Mexican National Council for Science and Technology (CONACYT)
- Monaco's International Cooperation Division
- National Institute of Infectious Diseases (NIID), Japan
- Japanese Research Institution for Science and Technology (RIKEN)
- Union for the Mediterranean (UfM)
- U.S. Agency for international Development (USAID)

Research institutions - CEA, CIRAD, CNES, CNRS, IFREMER, IMMI, INRA, INRIA, INSERM, INVS, IRD, IRES and agencies - AIRD, ANR, ANRS, AVIESAN in France.

INTERNATIONAL ORGANISATIONS

- World Health Organization (WHO)
- European Union (EU)
- National Health Institutes (NIH)
- European & Developing Countries Clinical Trials Partnership (EDCTP)
- Global Alliance for Vaccines and Immunization (GAVI)

FOUNDATIONS, ASSOCIATIONS AND NON-GOVERNMENTAL ORGANISATIONS

- AREVA foundation
- Bill and Melinda Gates Foundation
- BNP Paribas Foundation
- Doctors Without Borders (MSF)
- Drugs for Neglected Diseases Initiative (DNDi)
- EDF Foundation
- Fondation de France
- University Agency for Francophony (AUF)
- International Rotary Club Foundation and Rotary Clubs in France
- Mérieux Foundation
- Multilateral initiative on Malaria (MiM)
- Pierre Ledoux Jeunesse Internationale Foundation
- Preventive Medicine Agency (AMP)
- Prince Albert II de Monaco Foundation
- Rockefeller Foundation
- Sanofi Espoir Foundation
- Total Foundation
- Wellcome Trust

PRIVATE SECTOR

- Air France
- AXA
- EDF
- Mérieux Institute
- Sanofi-Pasteur
- Veolia

List of abbreviations

ACIP Inter-Institut Pasteur Concerted Action
AFD French Development Agency
ANRS French National Agency for Research on AIDS and Viral Hepatitis
BCG Bacillus Calmette-Guérin (Tuberculosis vaccine)
BSL Biosafety Laboratory Level 2 (BSL2) or Level 3 (BSL3)
CERMES Centre for Medical and Health Research (Niamey, Niger)
CDC Centre for Disease control and Prevention
CHARLI Children's Antibiotic Resistant infections in Low Income countries: an international cohort study
CIBU Laboratory for urgent response to biological threats (Institut Pasteur)
CIRAD French Agricultural Research Centre for International Development
DHHS Department of Health and Human Services
FIOCRUZ Oswaldo Cruz Foundation (Rio de Janeiro, Brazil)
FSP Priority Solidarity Fund
GLODEN Global Network for Dengue Research
IMMI Microbiology and Infectious Diseases Institute
INSERM French National Institute for Health and Medical Research.
NGO Non-governmental Organisations
NIH National Institutes for Health (Bethesda, United States)
NIHE National Institute of Hygiene and Epidemiology (Hanoi, Vietnam)
NRC National Reference Centre
OFID OPEC Fund for International Development)
OIE World Organisation for Animal Health
OPEC Organisation of the Petroleum Exporting Countries
PCR-(RT) Polymerase Chain Reaction (in real-time)
PTR Transverse Research Programme
RIIP Institut Pasteur International Network
RIKEN Japanese Research Institution for Science and Technology
WHO World Health Organization

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