2011
2019

Integrative Biology of Emerging Infectious Diseases

(LabEx IBEID)

«Science, d'où prévoyance ; prévoyance, d'où action»

Auguste Comte *in Cours de philosophie positive (1830-1842)*

Integrative Biology of Emerging Infectious Diseases
(LabEx IBEID)

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http://www.pasteur.fr/labex/ibeid

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PREFACE

The Labex IBEID, a flagship project against emerging infectious diseases

According to the World Health Organization, a new infectious disease emerges somewhere in the world every year. Even more disturbingly, we have witnessed, in recent decades, the emergence of new viral and bacterial diseases that rapidly led to widespread epidemics. These threats originate from complex and interconnected factors and are a great challenge for the medical and scientific communities.

Research on infectious agents, particularly those causing emerging infectious diseases, is for the Pasteur Institute and its partners, a traditional topic that requires excellence and synergies in basic research in microbiology, virology, immunology and epidemiology and needs sustained support due to its high relevance to public health.

The establishment of a LabEx entitled "**Integrative Biology of Emerging Infectious Diseases (IBEID)**" (2011-2019) was spurred by the urgent need to create a strong scientific coalition by bringing together a network of institutions that are at the frontline of research, surveillance, analysis and control of emerging infectious diseases in France and abroad. This LabEx thus represents for the Pasteur Institute and its partners a strong input for successful collaborative research on public health problems. It also offers, on both a national and international level, an important, original and unique tool to support policies for the surveillance, control and prevention of emerging infectious diseases.

This LabEx has been conceived to stand as a scientific and technological entity dedicated to research on emerging infectious diseases taken in the broad sense and thus including the emergence of antibiotic resistance and nosocomial infections as well as infections in immunocompromised patients, infants and elderly people. The key word in IBEID is "integrative"» because the aim is to bring together in the same consortium existing groups of various disciplines from the Pasteur Institute and partner institutions as well as new research groups that are led by top level young investigators who provide innovative expertise to the LabEx.

In addition to increasing our basic knowledge on infections, IBEID is determined to offer to the national authorities and to European and other international health institutions like the WHO an integrated "reference tool" that is rapidly able to identify an emerging infectious agent, cultivate it, study its basic pathogenic capacities and basic parameters of transmission, identify its major antigens and guide new diagnostic, therapeutic or vaccine strategies.

While all LabEx partners benefit from the outstanding scientific and technological environment of the Pasteur Institute, several LabEx groups have the opportunity to be hosted in the newly created transdisciplinary « François Jacob Center » that houses circa 300 scientists working on the topic of integrative biology of emerging infectious diseases.

The Labex IBEID is a long-term project that has unprecedented chances of success on a very important public health problem.

Members of the IBEID Scientific Advisory Board should be warmely thanked for their commitments and advices. Members of the Institut Pasteur Direction should be thanked for their enthousiastic support to the emergence of the LabEx IBEID. Members of the LabEx should be thanked for their active participation and outstanding contribution.

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I. A LabEx ON EMERGING INFECTIOUS DISEASES : CONCEPT AND MAIN OBJECTIVES

The LabEx "Integrative Biology of Emerging Infectious Diseases" (IBEID) addresses the topic of emergence and reemergence of infectious diseases in its most challenging aspects, *i.e.* conditions and anticipation of occurrence and transmission, quick identification of etiological agents, molecular mechanisms of infection, bases of species barriers crossing, mechanisms of resistance, bases of host defenses and individual variation in susceptibility. IBEID benefits from a broad and in-depth knowledge of the microbial world, developed through the Pasteur Institute's traditional research focus on bacteriology, virology, mycology, parasitology and the host immune system. **The LabEx is a great opportunity to strengthen the fundamental aspects of microbiology and immunology that are essential to meeting the challenges of emerging infections**. Epidemiology, "omics", cell biology, structural biology, host genetics and vector biology are other important disciplines of the LabEx and all benefit from the availability of cutting-edge technological facilities.

Genomics Platform

Fluorescence microscopy

To extend the diversity of expertise and fill some gaps, the IBEID planned (i) the creation of new groups led by young investigators: one in mathematical modeling of emerging epidemics and four in fundamental microbiology; and (ii) a strong reinforcement in bioinformatics as well as major investments in equipment for (meta)genomics, proteomics, imaging, and high-throughput screening. This scheme should create a critical mass that, at any given moment, is able to support and advise policy makers and health agencies when facing an emerging infectious disease crisis.

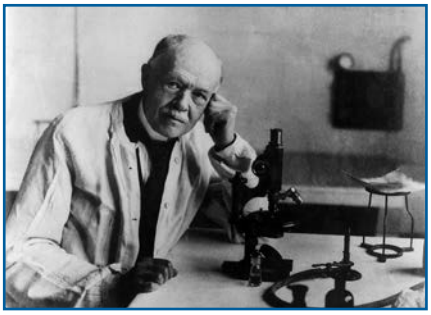
In the past 20 years, more than 70% of the emerging infectious diseases were zoonoses whereby an animal pathogen "crossed" the species barrier and caused disease in humans. Thus, it is more necessary than ever to establish or strengthen collaborations between human and veterinarian medicine centers, field and research epidemiologists, and microbiologists working on human, animal, food and environmental microbes.

The IBEID main objectives are:

- ✓ to anticipate and rapidly detect the emergence or re-emergence of infectious diseases, based on improved knowledge of new parameters and on the use of newly developed techniques and methods.
- ✓ to rapidly identify the origin and nature of the etiological agents through an optimized infrastructure and «ready to use» tools that are designed based on a considerably broader and globalized view of the microbial world, on different microbiotas and on unsuspected factors that underlie the homeostasis and the diversity/ complexity of microbial assemblies in the environment, in vectors and /or inside hosts.
- ✓ to generate tools to diagnose, treat, eradicate and also prevent the dissemination of a new infectious agent. The scientific program of the LabEx will thus encompass a strong basic research program on microbes, microbial biodiversity, vectors, host susceptibility, species barrier and on the factors involved in host-pathogens interactions. In adiditon, the LabEx IBEID includes the setting up of high performance tools for the molecular detection and rapid identification of emerging agents and the search for possible targets and new therapeutic strategies. Notably, a qualitative and quantitative upgrading of the technological facilities is an absolute requirement for this ambitious program.

The LabEx IBEID has built strong partnerships with institutions that are on the frontline of the fight against emerging infectious diseases.

II. EMERGING DISEASES : STATE OF THE ART



Charles Nicolle, 1866-1936, Director, Institut Pasteur de Tunis, Nobel Prize of Physiology or Medicine (1928)

In his visionary essay, "Naissance, vie et mort des maladies infectieuses" ('Birth, life and death of infectious diseases') published in 1930, the microbiologist Charles Nicolle wrote "*Infectious diseases, like all living phenomena, are no more today what they were yesterday and are not today what they will be tomorrow*". « The genius of infectious diseases», as he so nicely stated, still imposes and will continue to impose a permanent and global threat to public health.

Worldwide, 14 millions individuals succumb to an infection each year. Infectious diseases are essentially poverty-related, with about 90% of deaths occurring in the developing world, mainly among children. Major recognized killers are tuberculosis, AIDS, malaria, enteric and acute respiratory infections, although many other "neglected" pathogens account for a much broader set of etiologies (*i.e.* arboviroses, hemorrhagic fevers, leishmaniasis, schistosomiasis and filariasis). In addition, 16% of cancers are of infectious origin. Yet, mortality is only a partial reflection of the impact of infectious diseases on global health. In the most impoverished countries, infectious diseases have a substantial negative impact on development. Parameters such as the DALY (Disability-Adjusted Life Years) better reflect the societal impact of infectious diseases, which in developing countries account for 43% of the loss of life and working capacity. Even in industrialized countries with advanced health care systems like France, infectious diseases remain a major concern.

Superimposed upon the above endemic background, infectious emergences and resurgences occur relentlessly. Numerous factors underlie the emergence or re-emergence of diseases and can be classified into three categories: (i) the human environment: including changing ecosystems, climatic changes, war, famine and land overexploitation; (ii) the human host: their susceptibility to infection, over or inappropriate use of antibiotics, increase of international trade and travel; and (iii) the pathogen: their ability to evolve very rapidly and thereby acquire new phenotypic properties in response to host and/or environmental modifications. In addition, those factors that increase the density of either humans, pathogen vectors or pathogen reservoirs all multiply the contacts between humans and pathogens, thereby driving and promoting events of disease emergence.

Between 1940 and 2004, 335 emerging infectious diseases were detected. They were mainly zoonoses (70%) and largely acquired from wild fauna (75%). Examples are HIV, Lassa, Marburg, Ebola, West Nile, SARS, and Avian flu (H5N1, H1N1); some of which are transmitted by insect or arthropod vectors.

Many modern infectious diseases in humans are caused by pathogens that once crossed the species barrier (*i.e. Mycobacterium tuberculosis*, measles virus). We live in a global microbiological world where viruses outnumber living cells by at least ten fold. Any major change in animal flora, particularly flora of those serving as major food sources *(i.e.* cattle and poultry) will inevitably impact human health; thus the division between human and veterinary microbiology is no longer valid: **there is one world, thus one health**.

Laundry in Africa

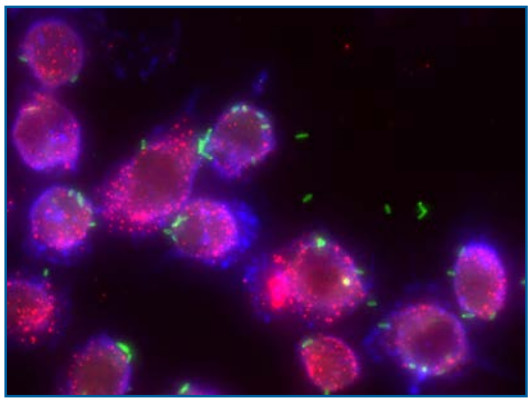
Poultry and pig in South East Asia

Sites of emergence are mainly located in the South, particularly in South America, Sub-Saharan Africa and South-East Asia. Meanwhile, it is important to note that the incidence of emerging diseases in the North has also increased by 10% to 20% in the last fifteen years.

The extraordinary size, complexity, and capacity of genetic evolution of the microbiological and viral worlds (mobile genetic elements, bacteriophages, gene exchange, lack of proof-reading for viral RNA polymerases) provide them with a potential of adaptation far superior to eukaryotic multicellular organisms. This genetic plasticity, which is reflected in the concept of virus quasipecies, facilitates crossing of the species barrier as well as inter-human dissemination, a factor of growing importance due to the massive recent increase in intercontinental exchanges.

Understanding the crossing of the species barrier requires a fully integrative approach, encompassing basic microbiology, epidemiological modeling, cell and receptor biology, molecular and cellular mechanisms of infection, and immunology. It also requires field studies, including the development of tools and methods to catalogue agents from domestic and wild fauna that may cross the species barrier and to track their adaptation to humans. Furthermore, the epidemicity of pathogens is a science yet to be invented. Considering the critical role of animal hosts in the transmission of many pathogens, the biology of insect vectors needs to be strengthened in this critical period of global warming.

Children in Burkina Faso



Cells infected by *Legionella*

Poverty and industrialization each contribute their own risk factors to emerging infections. The food industry and the architectural complexity of buildings are examples of sources of new infections (*i.e.* Legionnaire's disease). In hospitals, this complexity combined with the fragility of patients and the intensive use of anti-infectious agents makes nosocomial risk a dominant problem in infectious diseases. In developing countries, the concentration of populations at the periphery of major conurbations, the lack of education, and poor hygiene standards dominate the risk factors. At the same time, "invasion" of forest areas increases the chances of humans encountering new vectors and animal reservoirs of novel infectious agents.

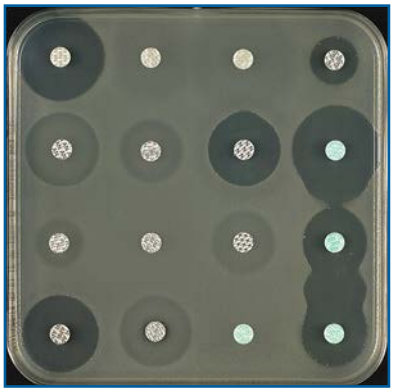
Emerging infections in Europe

Emerging infectious diseases in France and Europe share many of the characteristic traits of emerging diseases in the world:

Emerging viruses.

Global warming, modifications of biotopes leading to the modification of the distribution of vectors (e.g. presence of the mosquito Aedes albopictus in France and Italy) combined with massive intercontinental population exchanges has led to the emergence of important viral diseases (flu - H5N1 and H1N1 - Chikungunya, Dengue, West Nile). Indeed, the newly identified cases of autochtonous transmission of Dengue and chikungunya infections in southern France are important recent examples. Similarly, the presence of *Aedes albopictus* and *Aedes aegypti* mosquitoes on the American continent as well as the cohabitation of these two species in regions such as Florida, Mexico, Panama, Brazil raises great concern. It is clear that understanding the risks associated with viruses spreading throughout Europe and the North and South American continents is becoming increasingly important. **It is thus crucial to build up an interdisciplinary approach combining epidemiology, physiopathology (animal models), vector biology, as well as structural and systems biology approaches to gain insight into the mechanisms of infectious disease emergence, propagation and control.**

Antibiotic resistance and nosocomial infections.



Antibiotic susceptibility (*Klebsiella*)

Even though the positive impact of measures taken in Europe and America to limit antibiotic use in hospitals, in the community and in agriculture is evident, multiresistance remains a worldwide concern and is central to the issue of nosocomial infections. Indeed, the massive and uncontrolled use of antibiotics and antiviral drugs in emerging countries is likely to cause a renewed threat. This self-perpetuating process is a result of the selection of adaptive mutations and the increasing prevalence of pathogens acquiring mobile genetic elements carrying resistance genes from environmental microorganisms, emphasizing the globalization of our interface with the microbiological world. Recent studies have confirmed a poorer prognosis of infections caused by multiresistant microorganisms due to the acquisition of virulence genes, **making the synergy "multiresistance-pathogenicity" an emerging theme and a research priority**. In parallel to multiresistance, the negative impact of nosocomial infections has only been fully appreciated in the last 20 years. In France, one million nosocomical cases occur per year, affecting 7% of hospitalized patients and leading to the death of about 10,000 individuals. Many of these infections concern medically or surgically implanted devices and prostheses colonized by mono- and multiorganismic communities living as biofilms (60% of nosocomial infections are linked to biofilm formation). How multiorganismic bacterial communities survive in the hospital environment, how they are transmitted, and how they are able to establish in patients are key issues. It is necessary to elucidate the mechansims underlying the ability of bacteria and fungi to condition and colonize surfaces and to build a biofilm that is recalcitrant to both immune defenses and antibiotics. Beyond nosocomial infections, resistance of endemic bacterial (*i.e. Mycobacterium tuberculosis*), viral (*i.e.* HIV) and parasitic (*i.e. Plasmodium* spp.) pathogens remains a permanent threat for severe events of reemergence. It is essential to engage a multidisciplinary action encompassing novel creative approaches in epidemiology, microbial genetics/genomics, and physiology/physiopathology in order to build strong capabilities to efficiently and effectively respond to the ever-growing challenge of microbial resistance and hospital infections.

Infection in immunocompromised patients, severe sepsis and septic shock.

Intensive care medicine

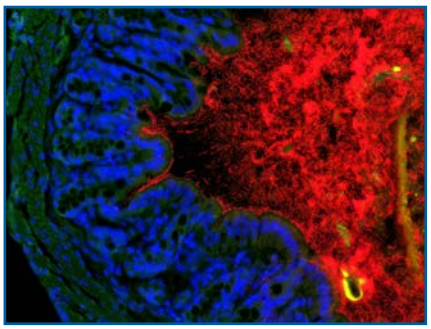
Infection is a major cause of morbidity and mortality in patients undergoing chemotherapy and/or biotherapy for leukaemia, lymphoma, and cancer; in patients with organ and bone marrow transplantation; and in patients with systemic inflammatory diseases. As a myriad of microorganisms including opportunistic bacteria, viruses (CMV, HSV, EBV), yeast/fungi (*Aspergillus* spp., *Candida* spp., *Cryptococcus* spp.) and protozoa (*Toxoplasma gondii*) are involved, a broad range of the most relevant infectious agents must be studied, particularly with regards to their interactions with the failing immune system. From the angle of severe sepsis caused by these - often opportunistic - microorganisms, a consensus seems to be emerging regarding which yeast/fungal infections dominate and keep increasing in terms of percentage of mortality. Severe sepsis represents between 2% to 4% of all hospitalizations (10% in intensive care units) and about 150,000 patients die each year in Europe from septic shock. Septic shock prevention and treatment requires strong basic and clinical research to identify the genetic bases of susceptibility, the genetic and epigenetic modulations, and the signaling cascades that lead to the situation of extreme immune activation followed by immune collapse. Only a better understanding of these processes will provide relevant predictive and monitoring biomarkers and novel targets for prevention and treatment.

Aging of the population.

Aging of the immune system has major consequences on the susceptibility of the elderly population to infection and the failure of vaccines. In 2025, ~22 % of the French population will be over 65 years of age. Similar figures are also observed in all other industrialized countries and a similar trend is quickly appearing in emerging countries and in continents such as Asia and South America. Hence, we are entering a terra incognita that raises truly novel fundamental questions regarding the mechanisms of decay of the immune system and its potential to create novel conditions for emergence of new pathogens and impair vaccine efficiency. For example, it is increasingly apparent

that persistent infections by many herpesviruses take a toll on the immune system, requiring its constant action to keep the virus in check throughout the life span of the individual. These infections thereby strongly contribute to immune system collapse in the elderly and additionally represent threats within the field of transplantation medicine. There therefore is an urgent need to explore options for prevention and intervention to combat these life-long viral infections.

Pathologies related to "mishandling" of the commensal flora.


Bacteria in the colon

Our increasing awareness of the important roles of the microbial world has led us to think of man as a "superorganism", a prokaryote-eukaryote hybrid, whose immune system has likely been forged by the dual demand to control and tolerate a huge bacterial microbiota (*i.e.* 10^{14} microorganisms in the gut), and to eliminate any incoming pathogen through quick recognition and subsequent triggering of innate immune defense mechanisms. Hence a key question arises: How does the immune system discriminate between commensal and pathogenic bacteria? We are now only beginning to anlyze the molecular and cellular mechanisms of this process and the consequences of its dysfunctions. Indeed, these dysfunctions are creating a new challenging research area in medicine with the study of inflammatory bowel diseases (IBDs) in general but also including more systemic pathologies that appear to share inflammatory components possibly related to the imbalance or lack of control of the commensal flora, such as atopy and allergy, atherosclerosis, insulin resistance, obesity and type 2 diabetes. It is time to decipher host-microbes mutualism with the degree of molecular resolution attained in the study of host-pathogens interactions.

Fundamental research towards new tools for the control of infectious diseases

In facing these major challenges, there is strong evidence that only outstanding basic research and broad knowledge of the microbiological world and host responses can lead to discoveries that will significantly contribute to progress in the control of infectious diseases. To cite a few examples:

- The discovery of HBV, HCV, and HIV, combined with the new technique of PCR, allowed the reliable diagnostics of these infections worldwide. This has, for example, provided the capacity to implement generalized viral genomic diagnostics (DGV) on transfused blood products, thereby bringing the safety of blood transfusions to an astonishing low risk of contamination of less than 1 in 2.5 million.

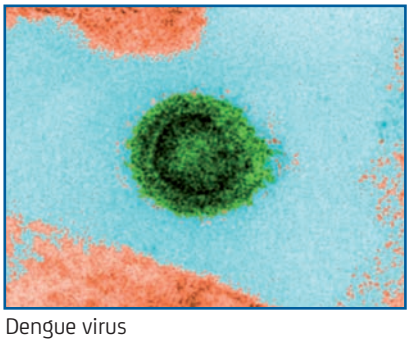
- The discovery of *Helicobacter pylori* causing gastritis, peptic ulcer and stomach cancer has created a revolution in gastroenterology, suddenly transforming a disease that often justified surgery into a disease treatable or preventable by antibiotics.

- The discovery that some HPV serotypes cause cervical cancer led to the development of vaccines able to prevent cervical cancer.

- The discovery that carrier proteins are needed to allow proper immune response to complex surface polysaccharides of encapsulated bacteria has allowed the development of long-awaited vaccines against respiratory infections and meningitis in children caused by *Streptococcus pneumoniae*, *Haemophilus Influenzae*, and *Neisseria meningitidis*.

Basic research in virology, microbiology and infection biology

Virology is at the heart of infectious emergence.


Dengue virus

A successful infection by a virus relies on the interaction of the virus with hundreds of specific host proteins of the target cell without which virus replication is impossible. The cellular host proteins and genes are collectively called the '*infectome*' of a given virus. Some components of the virus *infectome* are part of cellular networks that viruses divert to their own advantage. The subset of the *infectome* composed of proteins making direct physical contact with the virus particle or viral proteins during

infection, together with the participating viral proteins, is the so-called '*interactome*'. Some of these interactions are necessary to counteract the innate immune system of the cell. Their detailed analysis provides a window into the infected cell and illuminates processes occurring during infection.

Tremendous progress has recently been made with the advent of high resolution imaging coupled with high-throughput (HT) genome wide RNAi knock-out and cDNA knock-in screens to identify viral "*infectomes*" in various cell types. Similarly, high-throughput genome wide yeast-2-hybrid screens - combined with validation by affinity based mass spectrometry - have allowed the definition of viral *interactomes*. Integration of these data with structural studies now provides the opportunity to identify the determinants of the molecular recognition events that underlie the ensemble of virus-host interactions, providing a handle for the rational design of specific inhibitors as potential antiviral compounds. Furthermore, recent progress at the frontiers of structural and cell biology has been aided by spectacular advances in electron and light microscopy. Thus, using super-resolution light microscopy (STED, PALM/STORM) and cryo-electron microscopy - which is now reaching resolutions comparable to X-ray crystallography without requiring crystals - along with *in cellulo* correlated cryo-electron tomography and other light microscopy developments, it is now possible to bridge the resolution gap and go from the detailed picture of atomic interactions all the way to tracking these events within the cell, both temporally and spatially.

The combination of these methodologies now pave the way to understanding infection mechanisms more deeply. The knowledge generated can be applied to emerging viruses and used to devise both preventive treatments as well as antivirals that block infection at multiple stages, thereby strongly reducing the chances of resistance development.

The rise of a novel Microbiology.

Genomics has provided a new vision of the microbiological world and technological improvements in genome sequencing now allow applying this exhaustive knowledge of microbial genomes to an increasing number of species, and even to the scale of microbial communities in specific environments that include human and animal-associated microbiotas (*i.e.* metagenomics). "Post genomics" approaches such as proteomics and transcriptomics, including microarray analysis and deep sequencing of messengers and small regulatory RNAs (RNA-seq), can be used to generate a global view of the microbial physiology in various conditions. The new scale of these studies is generating an accumulation of information that requires exceptional storage and analytical capacities coupled with interpretative capabilities of competent experts in informatics who understand biology (bioinformatics). None of this new genomic-based science makes sense without a qualitative and quantitative leap in bioinformatics combined with an integrative approach currently referred to as "systems biology".


Flow Cell for Next Generation Sequencer

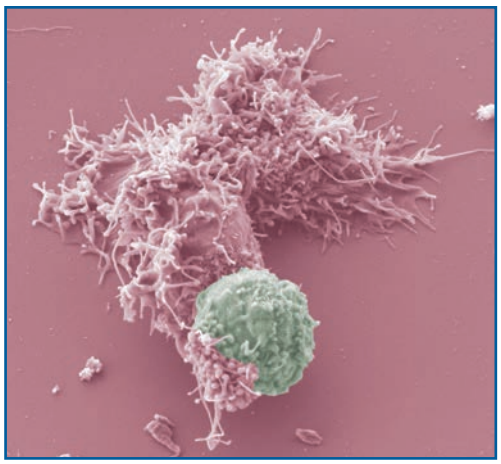
In this context, a truly novel microbiology has emerged with important new areas being actively investigated. **These include the diversity of protein secretion** strategies; the biology of bacterial envelopes dictating shape, division, spore formation, and differentiation; the processes of intra- and inter-cellular communication essential to the social life of microorganisms, and particularly fungi; the existence and role of secondary metabolites and new signaling molecules such as cyclic diGMP; the deciphering of the molecular mechanisms of quorum sensing (QS) and biofilm formation in single and complex bacterial communities; the genetic and molecular bases of microbial latency and dormancy; the mechanisms of symbiosis encompassing endosymbiotic, commensal and mutualistic microorganisms; as well as the novel aspects of transcription with the discovery of riboswitches, long antisense RNAs, small regulatory RNAs and CRISPR arrays (See G5 Group "Synthetic Biology" p. 33). **These very fundamental domains of microbiology are offering possible novel targets for therapeutic development (*e.g.* anti-quorum sensing and anti-riboswitch strategies)**.

The last two decades have also been marked by an explosion of studies deciphering the molecular cross talk established between pathogenic microorganisms and their target cells in the course of infections. Thanks to the phenomenal progress in both photonic and electron microscopy, imaging has become a major component of the research process, not only revealing the morphological characteristics of interaction steps, but also the microbial effectors and the signaling cascades they affect in infected cells and tissues. In combining "post-genomic tools" applied to infected cells and tissues, with biochemistry and structural biology, one can now obtain, with high

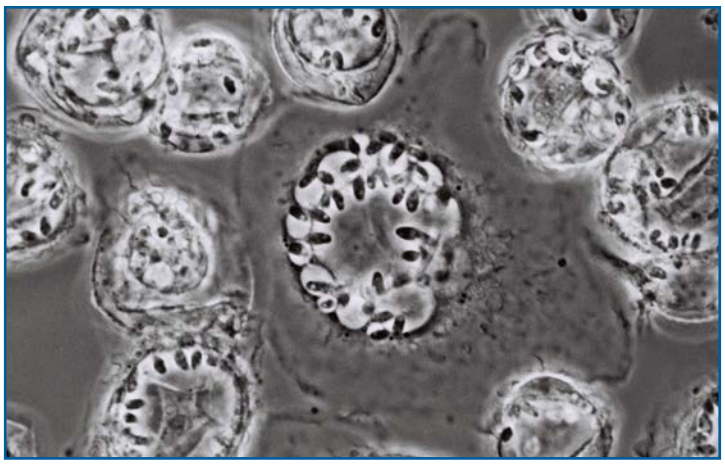
molecular resolution, a global 3D and even 4D analysis of the progression of an infectious process. This involves the study of critical steps of infections like the passage of important host barriers (*i.e.* intestinal epithelial barrier, skin barrier, respiratory barrier, blood brain barrier, etc...), and engagement of the immune system by the pathogens seen at the global level of the innate and adaptive immune response and at the level of the interaction of the microbes with immune cells and organs (*i.e.* lymph nodes, Peyer's patches). Similar approaches – although less advanced - are currently being used to analyze the homeostatic mechanisms that govern the human interface with its microbiota. Only the fine deciphering of the cross talks between microbes and their host targets will provide relevant targets to generate novel anti-infectious drugs attacking the disease mechanisms instead of the microbes.

In parallel, major progress has occurred in immunology,

including both the now well-established concept of innate immunity as the basis of the inflammatory program that helps the host to quickly confront microbial intruders, and the signaling networks that support and orient the adaptive/protective immune responses. The development of "alternative animal models" (*i.e. Drosophila*, *C. elegans*, Zebrafish, etc...) has been very useful in this regard. In addition, new areas are quickly developing such as the deciphering of the genetic bases of susceptibility to infectious agents and to severe forms of infections. Understanding the genetic bases of what Louis Pasteur called "le terrain" is a necessary step forward to personalized medicine in infectious disease prevention and cares.



Dendritic cell interacting with HTLV-1 infected lymphocyte



Leishmania amazonensis amastigotes in Macrophages

From academic research to diagnostics, therapeutics and vaccines:

it is the right time and it is ethically desirable to start converting the massive amount of basic knowledge acquired on the mechanisms of infectious diseases into innovative diagnostics, therapeutics and prophylactic tools in order to improve the control of infectious diseases. The consequences of the ever evolving infectious diseases should become major items on the agenda of biopharmaceutical companies again. It is likely that their declining investment in this area is not simply due to the taken-for-granted statement that anti-infectious drugs no longer represent a profitable market. It is also largely caused by a series of failed attempts at developing new molecules. Indeed, even the concept that the knowledge of microbial genomes would reveal "secrets" that could be quickly converted into novel antimicrobials fell short of everyone's expectation.

One should therefore not miss the window of opportunity for academic institutions and pharmaceutical companies to get together in an unprecedented joint venture. This necessitates efforts of communication, adaptation, and coordination, but at the end, it is the quality and originality of the basic research that will drive its success. In this, we are faithful to Louis Pasteur's legacy and vision: *"Basic and applied research are linked like the fruit to its branch".*

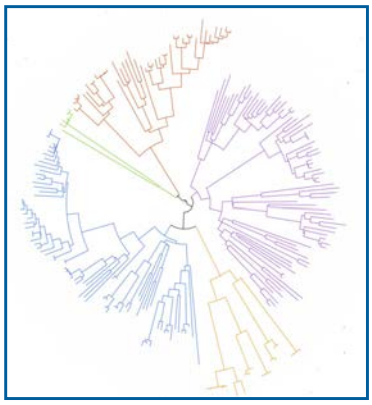
III. PRIORITY RESEARCH AVENUES

In order to fulfill its goals, IBEID benefits from the wide range of expertise and the broad knowledge of both the diversity of the microbial world and the host immune system available at the Pasteur Institute. IBEID provides a great opportunity to strengthen some fundamental aspects of microbiology and immunology that are essential to meet the important challenges faced in combating emerging infectious disesase. This improvement will be achieved through the network of partners whose groups are offering complementary expertise. Thereby, the convergence of a great variety of skills creates a critical scientific mass on major topics. The physical proximity of the groups and the availability of cutting-edge technological platforms naturally create the conditions for synergistic and highly productive interactions.

The research topics follow four major orientations:

1. Exploring microbial diversity and complexity and detecting emergences

Biodiversity and complex flora in man and his environment



Streptococcus agalactiae phylogenetic tree

Microbial biodiversity is breathtaking and our knowledge of it is still in its infancy. The number of microbial species present on Earth is estimated to be between 10 million and one billion and less than 1% have been identified. Each human being is thought to harbor more than 1,000 bacterial species. In addition, a vast genetic and functional diversity might be present among different isolates of the same species and this is observed even at a cellular level in apparently homogeneous populations. The biodiversity present in environmental niches has been neglected. However, pathogens that evolve from environmental bacteria live together with commensals in communities, influencing each other. Thus, understanding the mechanisms of evolution leading to the emergence of pathogens and the factors of pathogenicity is a great challenge. It is important to gain knowledge about these bacterial communities by identifying and characterizing their diversity and to understand the complex interactions present within these communities.

In the LabEx, analysis of microbial diversity is based on genomics approaches and is focused on two main aspects: (i) Pathogen diversity and evolution are investigated at the level of microbial communities and within individually infected patients (in vivo evolution and adaptation) making use of single-cell genomics in providing access to the non-cultivatable bacteria. High priority is given to the study of the dynamics and evolution of microbial populations in a changing climate and biosphere (including vector or host-range shifts); and (ii) An in-depth analysis of the microevolution allowing adaptation of microorganisms to the hospital environment and the study of the underlying mechanisms of this adaptation with the perspective of enabling better management of nosocomial infections. The bacterium *Legionella* is, for example, a privileged model to study evolution of virulence and to explain the emergence of human pathogens from the environment.

These studies greatly benefit from the availability of high-throughput sequencing and analyses of single DNA molecules, two technologies that have revolutionized the fields of microbial genome sequencing and pathogen discovery.

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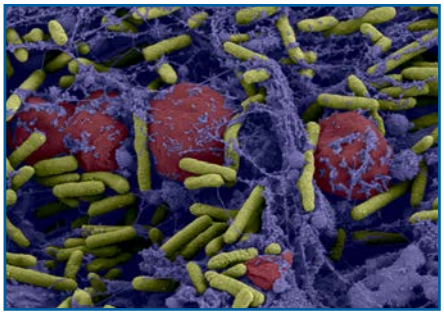
Basic microbial genetics, physiology and metabolism with emphasis on the novel aspects of microbiology

Recent progress in the study of microbes under conditions reflecting their natural environment has revealed that they live in complex multi-organism communities and that their physiology relies on much more complex regulatory mechanisms than previously thought. It appears that regulatory RNAs play a major role in the control of the expression program of all organisms.

In the LabEx, the new discipline of "multispecies molecular microbiology" is highly fostered through the investigation of inter-microbial communication, cell differentiation, growth, and dormancy in mixed-species bacteria and fungi communities that mimic in vivo situations. A significant effort concerns the exploration of novel regulatory mechanisms in bacteria (*e.g. Listeria*) and fungi (*e.g. Candida albicans*) and the ability of both commensal and pathogenic microbes to form biofilms. Research on the role of the metabolism in the composition of microbial communities on different surfaces and also on cell-shape formation in relation with cellular growth is conducted.



Pseudomonas aeruginosa biofilm

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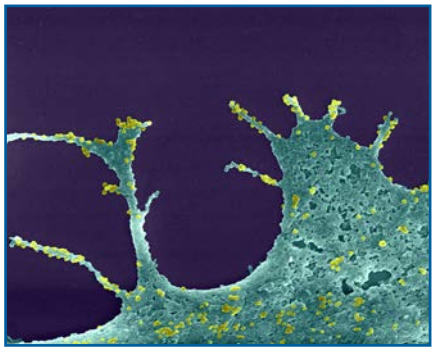
Diagnostic of emerging microorganisms and of the microbiological etiology of diseases

High throughput sequencing and microarrays applied to human and animal biological samples are now used to detect known pathogens and to discover new pathogens, even when their DNA sequences are distant from those of known microorganisms. Such tools are combined with bioinformatics to become the cornerstones of the identification and full-genomic characterization of emerging pathogens responsible for future global crises similar to the AIDS and SARS pandemics. Other applications include the identification of infectious agents responsible for clinical syndromes of unknown origin or the identification of infectious agents associated with conditions of putative infectious origin, including cancer (*e.g. Helicobacter pylori* and gastric cancer, and HPV and cervical cancer).

In the LabEx, tracking of emerging pathogens within hospital settings on a national and international scale is addressed by first developing real time genome sequencing and cutting-edge bioinformatics database systems. The goal is to significantly upgrade and definitively formalize the pathogen discovery program that is already involving research groups of the Pasteur Institute and its 15 National Reference Centers, four associated laboratories, the WHO-collaborative centers, institutes of the Pasteur International Network, and the IBEID partners, the InVS (Institut National de Veille Sanitaire), the ENVA (Ecole Nationale Vétérinaire de Maison-Alfort) and ANSES (Agence

Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail). This network of strong partnerships involves molecular biologists, bio-informaticians, epidemiologists, clinicians, and veterinarians and constitutes an operational pipeline that goes from the collection of samples, to the identification of microbes, the demonstration of novel causal relationships between microbes and diseases, and the development of new diagnostic tools to identify the novel microorganisms.



Budding of Chikungunya virus

These studies will allow the rapid (and hopefully immediate) identification of abnormal epidemiological situations caused by putative new infectious agents. In such cases, the first aim will be to identify the transmission modes of the new agent using case-control studies and collecting samples for the microbiology teams involved in the "discovery" process. Once the agent is identified, field studies will confirm its causal role in the disease by investigating its presence in a series of cases and controls and will evaluate the sensitivity and specificity of the new diagnostic tools developed by the microbiology team. Mathematical models will predict the potential for large-scale epidemics or pandemics. Cohort studies will be launched to describe the natural history of the infection and to identify factors associated with the development of clinical disease among infected individuals. In some situations, clinical trials will be undertaken to evaluate the efficacy of existing drugs if the newly discovered agent shares similarities with other treatable agents.

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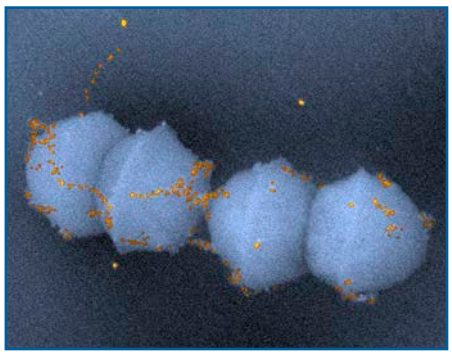
Resistance to anti-infectious agents

Resistance to antimicrobials is a major threat to public health and veterinary medicine and concerns bacteria, viruses, fungi and parasites. Resistance results from the selection of novel mutations and horizontal gene transfer. While current efforts focus on the characterization of accessible reservoirs using, for example, metagenomics, little is known about the mechanisms and the physiological conditions triggering the emergence of resistance. Most often we completely ignore the nature of the ecological niche in which resistance emerges and the dynamics of the transfer.

The underlying problem raised by the emergence of resistance is the heterogeneity of microbial populations that determines distinct outcomes under selection. This heterogeneity is found at two levels: (i) the physiological states of different individuals of a single species, and (ii) the diversity within microbial communities. It is now urgent to sort and characterize at the single cell level the intra-specific population response to antimicrobial exposure. The aim is to identify specific signatures associated with the ability to acquire and/or express resistance to antimicrobials in a population. This information is essential to guide future rapid diagnostic tools and, most importantly, the development of new antimicrobials targeting the sub-populations central to the emergence of resistance. Unfortunately, the pharmaceutical industry has been unable to generate a significant amount of new molecules for the market and there is a drastic shortage of antimicrobials to which there is no described resistance mechanisms. Resistance has also appeared in parasites (*e.g.* malaria) where, in contrast to antibacterials, the mechanisms and molecular bases of resistance to most antimalarial drugs have until recently remained poorly understood.



Streptococcus agalactiae pili

In the LabEx, the following key issues are addressed: 1) reinforcing the analysis of the molecular basis of resistance to antimicrobials, 2) understanding the epidemiological conditions favoring selection of resistant microbes and their subsequent spreading, 3) identifying specific signatures associated with the ability to acquire and/or express resistance to antimicrobials in a population, 4) developing novel tools to monitor the rapidly changing patterns of drug resistance, and 5) developing novel antimicrobials.

Some of the most successful classes of antibiotics such as β–lactams and glycopeptides target the assembly of the bacterial peptidoglycan (PG) that is the major bacterial "Achilles' heal". Therefore, one aim of this part of the program is to investigate how the PG is assembled in order to identify new targets. To understand better the emergence and the mechanisms of antibiotic resistance, resistance is being studied in relevant in vivo models in which selection occurs, as opposed to *in vitro* selection, as well as in clinical strains, as these two situations on their own only give partial snapshots of the evolutionary mechanisms underlying selection. Epidemiological research is conducted to better understand the intrinsic epidemicity of antimicrobial resistant bacteria (AMR).

Research on resistance to antimalarials is focused on the emerging resistance to artemisinins. High content imaging is used to decipher the dynamics of the parasite response to artemisinins in various host cells. High throughput parasite genome sequencing serves to identify the genetic alterations associated with artemisinin resistance identified in isolates from Cambodia and French Guinea. Through a population genetic approach, genetic sweeps are being searched in a set of parasites collected during the last twelve years in the regions where artemisinin resistance is currently emerging.

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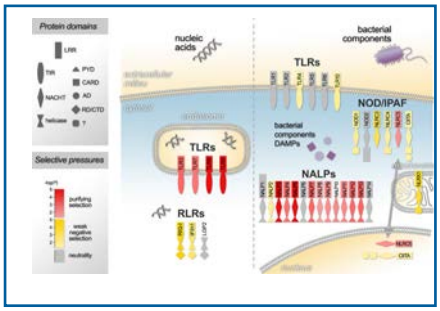
2. Exploring host diversity/complexity upon confrontation with microbes

Medicine of tomorrow will become increasingly "personalized". Genetic, environmental and physiological (*i.e.* age) parameters will be incorporated in preventive and therapeutic schemes. This will be true as well for emerging infectious diseases, since recent epidemics have revealed differences between individuals when confronted with the same infectious agent. Some individuals are experiencing subclinical or mild forms of a disease while others suffer from severe sepsis and eventually death. Age, pregnancy, and associated pathologies are essential factors, but also genetic traits are increasingly recognized as major parameters of host susceptibility to infection. This concept is also true for the emerging diseases appearing when tolerance of individuals to their symbiotic microflora is disrupted. Some situations, like aging of the immune system, might also create a new reservoir for infectious emergence. Research is conducted along three major lines:

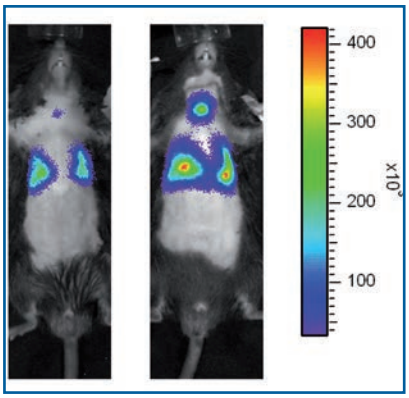


Evolutionary dynamics of innate immunity microbial sensor

Genetics of host susceptibility to infectious agents and to severity of infections. Building a coherent and complementary approach in mice and men

Understanding the way in which host genetic factors are involved in the differential susceptibility to infection and the severity and clinical outcome of emerging infectious diseases (*e.g.* Dengue, Influenza, Rift Valley fever) requires the integration of data from mouse models and humans. Human genetic studies combine Mendelian approaches searching for rare mutations with large effects (in particular using deep-sequencing techniques) that might account for susceptibility to the most severe clinical forms (*e.g.*, in life-threatening Dengue or flu), and population genetics approaches (in particular genome-wide association studies) searching for polymorphisms that could be involved in more common phenotypes (*e.g.*, in Dengue or HCV infection). This genetic dissection of human immunity to infection *in natura* has already provided unique immunological insights into several diseases. To develop new therapies and vaccines, we need to have a detailed understanding of the events that are triggered in the host after a bacterial, viral or parasitic infection. The mouse is an ideal organism to understand human infectious diseases. Deletion, modification and insertion of genes (including human genes) are possible through transgenic and gene replacement techniques of embryonic stem cell cultures. Despite some differences, the immune systems of mice and humans are similar and they can often be challenged with the same, or similar, pathogens.

In the LabEx, the different approaches mentioned above are used to unravel (i) how natural selection in humans has shaped the genetic architecture of host defense genes (i.e. distinguishing Mendelian vs. complex disease genes); (ii) how the genetic and epigenetic diversity of the human host can contribute to the different susceptibility to, or severity of, emerging infectious diseases; and (iii) how variable the microRNA repertoire is after infection and how this variability is genetically controlled by the host.



Mice infected with bioluminescent bacteria

The integration of genome wide data into a clinical and epidemiological framework will provide new insights into host genes and pathways of major biological relevance for host survival against infection. In parallel, knock-in or transgenic mice are developed to directly test how polymorphisms modify gene function. These results should help to identify the cell type and functions affected in humans. Experimental mouse populations composed of inter-specific hybrids, which are currently developed at the Pasteur Institute and elsewhere, should help to identify additional genes and signaling pathways whose relevance will be tested in genomic studies of human populations, thus feeding back into human genetic research. This is likely to uncover fundamental and general regulatory mechanisms for the efficacy of the host response to infection and to create a new paradigm in host genetics control of infectious diseases.

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Age-dependent susceptibility to infections: the very young and the elderly

Regardless of host genetic factors, extremes of age are characterized by higher susceptibility to some infections. However, this issue remains elusive due to a poor knowledge of the immune system of the newborn and the elderly. In fact, these populations constitute privileged targets and reservoirs for emerging diseases. In the elderly, pathogens such as CMV lead to chronic inflammatory states that strongly interfere with vaccines and favor co-infections by (re)emerging pathogens. Therefore, strategies designed for healthy young adults are clearly inappropriate since vaccine efficacy severely drops at the two age extremes.

In the LabEx, the objective is to establish a map of immunological signatures defining age-dependent susceptibility to infections at the molecular and cellular levels by linking immune cell-specific gene expression, phenotypes and functions. Host immuno-reactomes to pathogens are studied in neo-natal mice infection models and in a second step in the elderly immune system. An integrated platform combining experimental tools and models is appropriate to investigate susceptibility and immunity in emerging infectious diseases for which early and late life populations are at risk.

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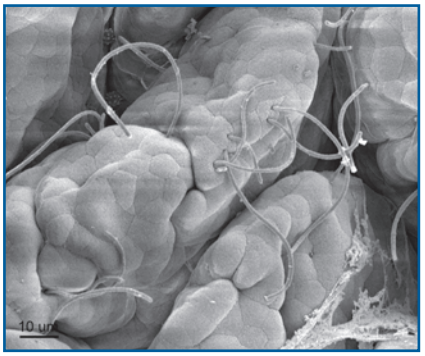
Microbiota in health and disease

After birth, microbes colonize all surfaces of the human body, including the skin, mouth, digestive tract, upper respiratory tract and vagina. These symbionts establish a mutualistic relationship with their host. In the intestine, bacterial and archaeal species complement the host in metabolic pathways for digestion and synthesis of essential vitamins, as well as in protection from pathogens. It was recently shown that symbiotic bacteria induce a level of immune activity, termed «physiological inflammation», that protects the host from opportunistic infections, and at the same time these bacteria form a balanced community that prevents "pathologic inflammation". Given the rapid evolution of nutritional and hygienic behavior of the human population, we suggest that the resulting changes in the symbiotic microbiota expose us to an array of common and emerging infectious diseases.



Segmented filamentous bacteria in intestine

In the LabEx, the search is mainly focused on the nature and the mechanisms of the «forced ménage à trois» between the host, its symbiotic microbiota, and emerging enteropathogens, taking advantage of the expertise in human and mouse mucosal immunology, gnotobiotic mouse models and the cutting-edge infrastructures in metagenomics, proteomics and microbiology. Sequencing the symbiotic microbiota of mice intestine during homestasis allows the deciphering of their intestinal metagenome and metabolome. Then, the same approach will be performed on mice during infection with model pathogens, such as *Citrobacter rodentium*, *Listeria monocytogenes* and *Salmonella* sp. The role of probiotics/ commensals on the infection by *Listeria* using germfree mice is currently under investigation. Another project aims at understanding how symbiotic and pathogenic bacteria affect the homeostatic balance that governs the constant epithelial renewal of the gut, particularly in the colon. Three major zones of the crypt villous axis are being considered: the crypt where stem cells are constantly dividing and generating the four major lineages of intestinal epithelial cells, the proliferative compartment, and the differentiating compartment. At each of these levels, the effect of a model symbiont, *Lactobacillus casei*, and a pathogen, *Shigella flexneri*, is being analyzed with regards to alteration of stem cell pluripotency, regulation of the cell cycle and thus proliferation, and cell differentiation. Another team is studying the molecular mechanisms underlying the potent immunostimulatory effect of Segmented Filamentous Bacterium, a symbiont found in mice and humans that has recently raised considerable interest due to its highly potent and unique inducing role on the post-natal maturation of host mucosal immune responses.

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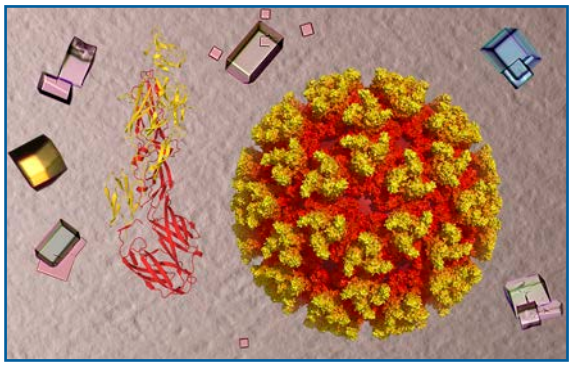
3. Exploring host-microbe interactions, defining the species barrier to transmission of infectious agents, vector biology and finding novel targets for vaccinology and therapeutics

Understanding the disease mechanisms and the dynamics of epidemics is key to understanding emergence and the mechanisms of crossing of the species barriers, an integrative topic that requires a very multidisciplinary task force such as the one the LabEx can assemble with rapidity and flexibility. Particular effort is invested into vector research, a key issue regarding inter-human, animal-human, and inter-animal transmission of a large number of emerging viruses. Last but not least, only very basic analysis of virus infectious processes will bring the necessary hits required to develop novel therapeutic agents and vaccines. Basic and applied research is made along four lines:

Exploring the disease mechanisms of emerging viruses (HIV, HCV, Flu, Dengue)



Structural study of Chikungunya virus envelope glycoproteins

Understanding the physiopathological features associated with emerging viruses, (e.g. HIV, Influenza virus, Dengue virus, Chikungunya virus, HCV) requires a trans-disciplinary approach in order to integrate the various spatial and temporal dimensions of virus-host interactions. Viral replication is the result of a constant conflict between viral and cellular components. Cellular restriction factors protect the cell against infection and viral countermeasures block these factors. Viruses also manipulate the behavior of infected cells and their ability to communicate with neighboring cells. Studying host and viral protein interactions is compulsory to identify and characterize cellular proteins affecting viral replication positively or negatively.

In the LabEx, the genetic evolution of respiratory viruses, particularly Influenza virus, is being investigated, applying deep-sequencing methodologies that provide a global vision of the viral diversity found in infected hosts and a better understanding of the mechanisms of selection of drug-resistant viruses or immune-escape variants. Identification of host components that interact with the viral ribonucleoproteins helps to understand their role in virus replication and their contribution to Influenza virus host range and pathogenicity. Special attention is given to links with the innate host response and the relation with genetic evolution of the virus. These will provide potential targets for the development of new antivirals.

High-resolution structural studies by X-ray crystallography and NMR are the only way to identify the determinants of molecular recognition underlying initial interactions between the pathogen and components of the cell surface - in particular, virus-receptor interactions - that are essential for entry into the host cell. Viral and immunological synapses, formed between cells, target cells, and cells of the immune system are analyzed by high content imaging technologies and videomicroscopy in order to assess, in real time, cell-to-cell virus spread and the immune response of the host. Structural studies are conducted on viruses in the Bunyaviridae family-hantaviruses, Rift Valley fever virus, Congo-Crimea hemorrhagic fever virus, and bunyamwera virus, all of which are important human pathogens.

One group is investigating how HIV shapes the host's intracellular environment to optimize both cell survival and viral propagation. Another group focuses its research on the study of the HIV-1 tropism evolution and usage of co-receptors by viruses isolated sequentially throughout several years (from primo-infection to AIDS) from infected human patients. This research investigates: (i) the mechanisms that permit the resistance and escape of HIV-1 during the natural infection to chemokines binding specifically major co-receptors CXCR4 and CCR5, (ii) the molecular basis determining the preponderance of CCR5 co-receptor in both the transmission and evolution of HIV-1 infection, (iii) the regulation of cell trafficking and sorting of CCR5, and (iv) the pharmacological inhibitory properties of low molecular weight CCR5 antagonists.

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Crossing the species barrier

The majority of emerging viral diseases, including HIV-1, SARS, Ebola, H1N1 and H5N1 Influenza viruses, result from cross-species transmission from wild or domestic fauna to humans. Recent advances in the detection and surveillance of this phenomenon indicates that the emergence of zoonoses, *i.e.* viral diseases of animal origin, will continue to increase in the near future. Consequently, a centralized response network is crucial to address new emergence events at the national level and beyond. Such a framework coalesced at the Pasteur Institute through the HIV crisis and was utilized most recently during the Chikungunya outbreak in the Indian Ocean for which numerous laboratories of the Pasteur Institute were mobilized.

In the LabEx, to analyze how pathogens cross the species barrier, field samples are dispatched between (i) groups devoted to the discovery, identification and molecular characterization of emerging viruses using high throughput sequencing and pan-virological DNA chips. These methods are already well established at the Pasteur Institute through collaborative projects such as the "Detection of Viral Emerging Agents" program; (ii) units working on host-cell interactions, viral adaptation and restriction, as well as structural virology; and (iii) expert teams for the development of animal models. Such a network of skills is essential to identify the agent, to decipher why the cross-species transmission and viral emergence occurred, to gain insights into the physiopathology of viral infection, to develop specific diagnostics and therapeutics tools and finally to predict further viral adaptation to humans (epidemic, pandemic) of other zoonotic agents. The collaboration between medical and veterinary research has been reinforced through the joint creation, by ENVA and ANSES, of the junior team "Innate Immunity, Interactomics and Interspecies transmission of viral Infection".

As RNA viruses comprise the majority of emerging virus infections, approaches are being developed to manipulate the genetic potential of RNA viruses, by either restricting or accelerating their evolution, and to generate significantly different mutant distributions derived from the same genotype, using members of the picornavirus, alphavirus and flavivirus families. Next Generation Sequencing is then used for in-depth (10,000X genome coverage) analysis of the frequency at which minority variants exist and are enriched within the population. The evolutionary trajectories and genetic fluctuations of these populations are characterized during infection of mammalian and/or insect hosts to identify the key variants responsible for tissue tropism, transmission, host-switching and emergence.

Ebola virus

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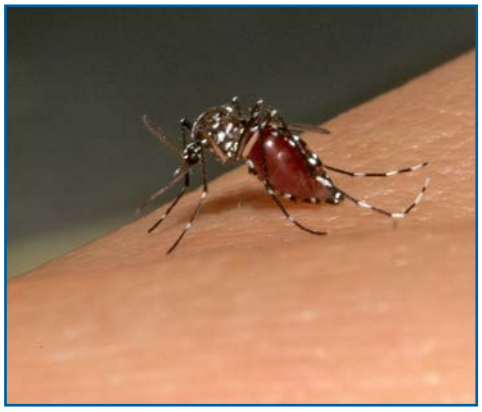
Biology of vectors

Important infectious diseases such as Dengue, Chikungunya, Lyme disease and malaria are transmitted to humans by mosquito and tick vectors. One of the key factors that modulates whether an insect is competent or not to transmit a given pathogen is the innate immune response of the insect. Understanding how the infection is controlled within the insect before its crossover to the human host could generate crucial new strategies to disrupt pathogen transmission.



Aedes albopictus blood meal

In the LabEx, a comprehensive dissection of insect innate immunity is developed through combined studies of natural vector mosquitoes and the model insect *Drosophila melanogaster*. The tools of genomics, biochemistry and cell biology are being used to analyze, particularly for malaria, the interactions between pathogens and the insect immune response that operate by pathways involving small RNAs. Known pathways involving small RNAs and canonical immune responses such as Toll and Imd are investigated, and non-hypothesis driven global approaches are taken in search for undescribed pathways. One practical outcome is an improved risk prediction through the acquired knowledge of factors that allow insects to serve as vectors of human pathogens. This knowledge will help improve public health surveillance of vector-borne diseases in France and is a field that has to be reinforced. A new five year group (G5) "Insect-Virus Interactions" has been created and aims to shed a new light on the genetics of vector-virus interactions to understand their role in arboviruses emergence and evolution.

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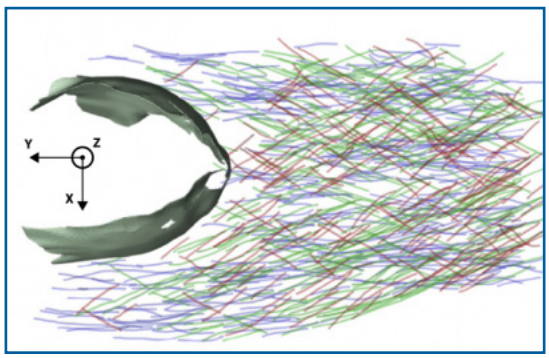
Revisiting disease mechanisms to find novel targets for vaccinology and therapeutics



Cryo-electron tomography of *Listeria* actin tail

Understanding the mechanisms of infectious diseases is key to the development of specific therapeutic or preventive measures. However, even for the most-studied infectious diseases, our comprehension of disease physiopathology largely derives from reductionist experimental systems that provide only snapshots of the complex infectious processes within the living host. Recent technological developments now offer the opportunity to move into an era of integration of the biological processes taking place when a pathogen encounters its host. Of particular interest are the co-evolutionary mechanisms that allow the pathogen to counteract the host immune defenses. Tapping into these escape strategies represents a substantial source of innovation in therapeutics and vaccine development.

In the LabEx, in parallel to non hypothesis-driven approaches, such as random screening of molecules of the pharmacopoeia, a systems biology approach is applied to infectious diseases by integrating complementary levels of analysis:

(i) the atomic level, via the structural analysis of the key host-pathogen interactions involving super-resolution light microscopy, state of the art electron microscopy, X-ray crystallography and NMR analyses.

(ii) the traditional molecular and cellular levels, extended to high-throughput and systematic screens for identifying novel pathogen key-effectors and/or host molecules involved in the infectious process.

(iii) the host cell level, by capitalizing on the extraordinary development of real time in vivo imaging techniques that provide an unprecedented view of both the dynamic interplay of pathogen and host cell populations over time and the developmental biology of eukaryotic parasites in the host.

This unique combination should bring a better understanding of the underlying mechanisms in several pathological situations: emerging viruses (Chikungunya, HIV, HCV, Flu, Dengue), *Listeria monocytogenes* and group B streptococcus pathogenesis, the host immune response to infection by *Shigella*, and the identification of the host and parasite actors involved in the Irradiation-attenuated sporozoites (IS)-induced protection in malaria. This integrated approach is directly applicable to finding novel targets for prevention and therapeutics.

Teams involved

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4. Creating a cutting edge technological environment to support advances in research on emerging infectious diseases

None of the above domains can be addressed with the level of ambition set forth in the LabEx without an unprecedented effort to establish state of the art technological platforms and conditions of data management and integration. Hence, the following four priorities:

Strengthening and diversifying the Genomics Platform at the Institut Pasteur

The Genomics Platform is organized into four groups tightly interacting with complementary missions and skills: (i) Genomics, (ii) Transcription and epigenesis, (iii) Eukaryotic genotypying, and (iv) Pathogen genotyping and public health. These four groups are interacting with informatics and bioinformatics teams from the Pasteur Institute and they share the equipment and the expertise required to perform genetics, genomics, epigenetics and transcriptomics studies. The major research area of the platforms deals with all aspects of infectious diseases from the biology of the pathogen (viruses, bacteria, parasites or fungi) to the host response. The group “Genotyping of

Genomics Platform (NGS)

pathogens and public health" had a major contribution in the characterization of the Chikungunya virus and its diversity and, in collaboration with the two national reference centres, in the management of the recent flu pandemics.

High throughput sequencing (HTS), using the so-called NGS (Next generation sequencing) techniques has a profound impact on all aspects of infectious diseases, from fundamental questions to clinical and industrial applications. For example, large-scale population genomics studies allow the identification of genetic traits associated with the transition from commensalism to virulence, with host specificity, and with the emergence of highly virulent clones. Genome level epidemiology of multi-resistant clones allows the tracking of their origin and their spreading and the assisting in their control. Genome sequencing and high-density genotyping allows one to identify genes involved in human and animal susceptibility to infections. The number of applications of these HTS increases continuously, producing masses of information that require an extraordinary effort in informatics and bioinformatics. Adequate organization, integration, and data mining of heterogeneous information is a pivotal issue in tackling a system-level understanding of infectious diseases.

In the LabEx: We will significantly improve both the quantitative and qualitative aspects of the Genopole sequencing facilities. All of the different major technologies will be implemented, as each has its own special advantages for specific tasks. This will allow us to apply metagenome sequencing to the discovery of emerging pathogens, and to study the impact of microbiomes in human health and diseases. Improved HTS will improve expression studies (transcriptomics) and aid the characterization of the epigenome, and the analysis of the binding of proteins to DNA and RNA. These technologies, applied to both the pathogens and the hosts, are fundamental to the analysis of host-pathogen interactions under special cicumstances and on a temporal level. Significant improvements in informatics will be implemented. The hardware will have to be adapted to cope with the data and the complexity issues (data collection size, computational resources). An important aim in this LabEx is to promote strong interactions between bioinformaticians and biologists. Advanced visual representations, data models, analysis tools, and user interfaces should be easily and readily accessible to help biologists interpret massive and complex data.

Teams involved

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Building up proteomics

Proteomics platform (mass spectrometry)

Human infection by pathogens is driven by a variety of microbial virulence factors able to subvert and evade host defense mechanisms. Proteomics, fueled by the ever-growing information on host, vector, and microbial genomes, represents today the most powerful tool to identify these factors and to unravel regulatory networks underlying host-pathogen interactions and disease progression on a global scale. The SILAC (Stable Isotope Labeling by Amino acids in Culture) technique has been a revolution in allowing one to distinguish, quantify and identify differences between samples after metabolic labeling. A significant scaling up of the existing proteomic facilities will allow the tackling of relevant issues such as:

- Investigating the host post-translational modifications during infection of cells with a pathogen or during cell contact with commensals / probiotics regardless of whether these are viral, bacterial, parasitic or fungal in nature.

- Visualizing (MALDI imaging) of microbial infections at a proteomics scale by revealing the spatial distribution and abundance of hundreds of host- and pathogen-derived proteins and metabolites. This novel approach allows a global view of the infection process and provides important new incentives for translational research relevant for the development of efficacious human vaccines, therapeutics and diagnostics.

Teams involved

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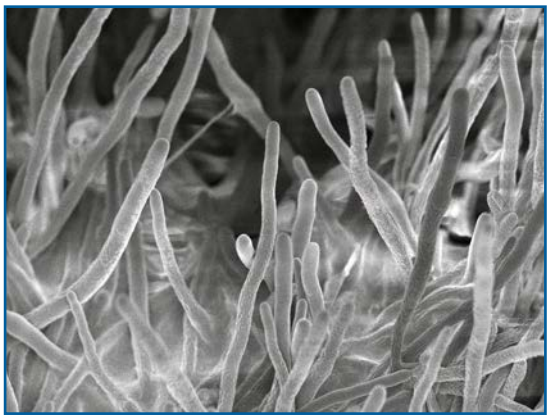
Developing imaging in tandem with high-throughput screening

Modern cell biology of infectious diseases relies heavily on the availability of sophisticated imaging technologies including multi-dimensional high-resolution techniques such as FRET, FRAP, and 4D high-speed confocal microscopy. The Platform of Dynamic Imaging enables investigations of cell/tissue-biology processes and its usurpation by infection and disease. It allows the integration of multidimensional observations, quantification of biological systems, and analysis of *in situ* spatio-temporal dynamics. Precise quantification is now an absolute requirement for rigorous evaluation of these events. Indeed, pathogenesis involves highly dynamic processes at the molecular, cell, tissue, and whole organism level and understanding the mechanisms of host-pathogen infection requires live cell imaging of these host-pathogen interactions *in vitro*, *ex vivo* and *in vivo*.



Aspergillus fumigatus (cryo scanning electron microscopy)

Advanced microscopy combined with high throughput automation for massive data acquisition and quantification is crucial for the development of new drugs and strategies against infectious diseases. Members of the LabEx benefit from access to the Ultrastructural Microscopy Plateform that brings its strength and expertise in transmission electron microscopy (TEM), scanning electron microscopy (SEM), correlative electron light microscopy (CLEM), and corresponding chemical and cryo-fixation/cryo-microtome sample preparation. Coordinated efforts employing expertises of these two platforms should leverage a high added value to the objectives of the LabEx.

Teams involved

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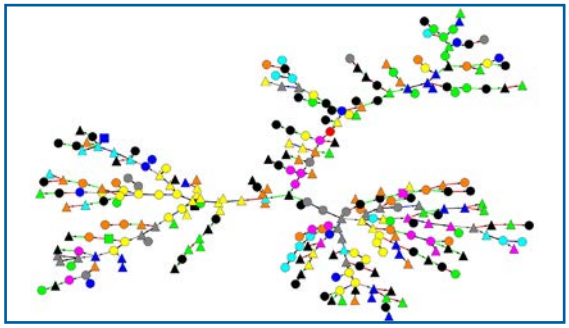
Integrating complex systems in biology, boosting bioinformatics and mathematical models



Transmission tree of outbreak of pandemic influenza

Understanding a disease requires the integration of an impressively large amount of information gathered from HTS and a variety of cutting-edge technologies or approaches including proteomics, in vivo and in vitro 4D imaging approaches and RNAi screening. New high-throughput technologies produce masses of information that require an extraordinary effort in informatics and bioinformatics. Adequate organization, integration, and data mining of heterogeneous information is a pivotal issue in tackling a systems-level understanding of infectious diseases. Therefore "Next-generation" bioinformatics environments are needed to represent conceptually and interpret functionally the information generated by HTS in infectious disease studies, and in particular, the multiple genome sequences of related isolates (population genomics and associated evolutionary questions), gene expression data (mapping of promoters, regulators), host genetics (association studies) and epidemiological and phenotypic data. Using these bioinformatics tools, systems biology tries to question and interpret these massive raw data by means of an iterated application of large-scale experimental technologies, data mining, and computational modeling. In support of this approach, a new Unit entitled "Mathematical Modelling of Infectious Diseases" has been created. It constitutes a core capacity that is able to quickly provide real-time analysis and predictive modeling to support evidence-based decision making (**See Chapter V**).

Teams involved

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IV. PARTNERSHIP AND GOUVERNANCE

Partnership

IBEID partnership is made of six main entities:

- ✓ - Pasteur Institute (**Box 1**)
- ✓ - Two Health agencies InVS (**Box 2**) and ANSES **(Box 3**); these national agencies are on the frontline of emerging infections among humans and animals, respectively
- ✓ - École Nationale Vétérinaire de Maisons-Alfort (ENVA) (**Box 4**); considering the unicity of human and veterinary microbiology and the fact that the majority of emergences occur following species barrier crossing by animal commensal and pathogenic microbes. “One world, one health” must be kept in mind.
- ✓ - Hopital Necker-APHP (**Box 5**)
- ✓ - INSERM, the medical research institution dedicated to human health (**Box 6**)

The research orientations collectively conceived by the LabEx partners are implemented in a way that facilitates strong synergies between academic research in human and veterinary medicine and public health agencies/ schools. The truly novel and innovative program of IBEID intends to exploit, for the first time, the unique, outstanding, and complementary competences existing among the different partners; to attract and/or create several new groups critical to support its ambitious program; to upgrade significantly the existing technological platforms; and to merge all these forces into a center of excellence.

In addition to performing top-level science and building a strong response capacity to emerging infectious diseases crises, this LabEx, together with the above partners, is now in a position to innovate on:

(i) the theoretical modeling of the dynamics of epidemics,

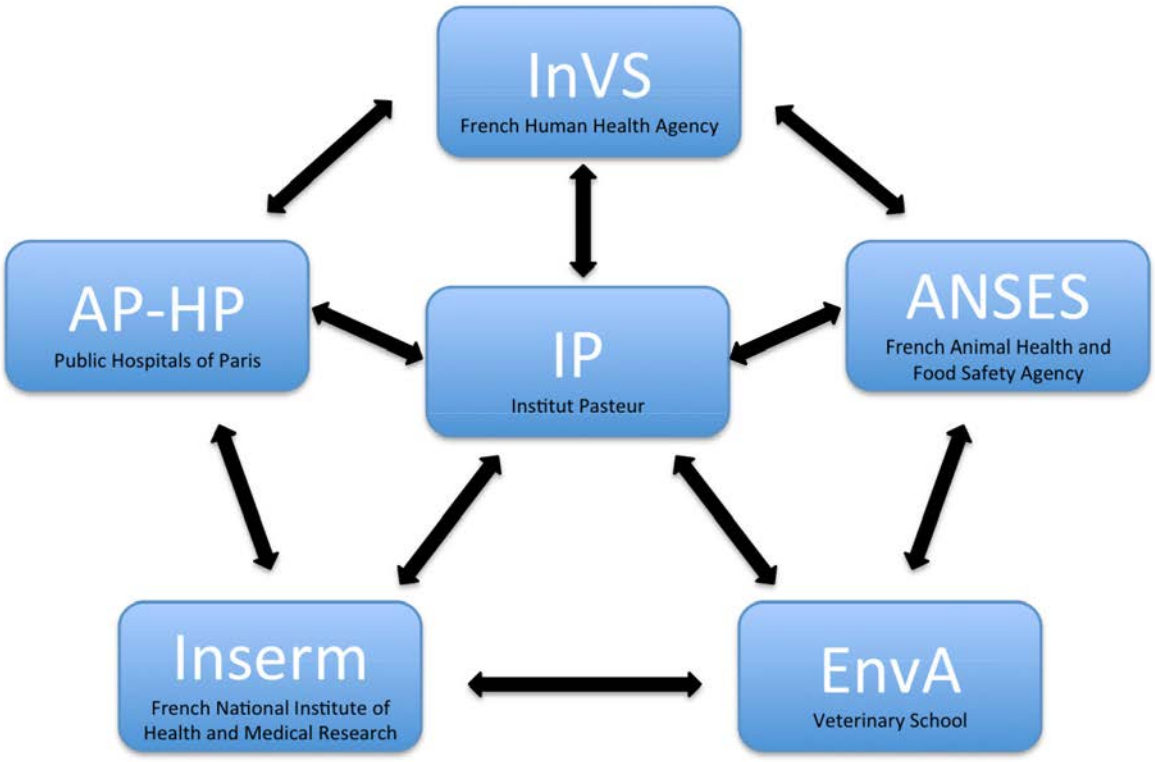
(ii) the methodologies of molecular diagnostic of novel/unknown microorganisms,

and

(iii) the development of innovative approaches to treat or immunize against infectious diseases.

Several of the novel topics introduced in the LabEx are of outstanding importance to fill the translational research gap with the industry. This includes upgrading the already existing “high tech” platforms and acquiring the additional competencies outlined in this project.

IBEID Consortium



A straightforward and efficient gouvernance

The idea and the concept of this LabEx were conceived at the Pasteur Institute by the two coordinators, Pascale Cossart and Philippe Sansonetti. Together with the assistance of a LabEx manager, they have defined and presently maintain its strategy and orientations. Groups of experts who are members of the LabEx and scientists from the Pasteur Institute or from partner research centers are responsible for the scientific evaluation and recruitment of post-doctoral scientists and the attribution of grants to PhD students and post-docs. The Pasteur Institute Scientific Council validates their proposals for recruitment of new PIs and the Directorate of the Pasteur Institute establishes their research groups. The LabEx manager, Thierry Planchenault supports Pascale Cossart and Philippe Sansonetti in the IBEID scientific coordination.

In order to maintain its coherence and identify the new challenges in its fields of expertise, the LabEx benefits from an International Scientific Advisory Board (ISAB) chaired by the two coordinators. The ISAB is composed of outstanding experts and helps to orient the medical and scientific policies of the LabEx and to define the priority areas to be strengthened. It also helps to integrate the LabEx in its environment by facilitating and advocating its presence in the relevant fields. In case of an emerging crisis, an ad hoc committee will be assembled.

ISAB conclusions and advices are transmitted by the coordinators to the Direction and the Scientific Councils of the Pasteur Institute and partner institutions.

ISAB Members

Ruedi Aebersold	ETH Zürich, CH
Jeff Almond	Sanofi-Pasteur Lyon, FR
Fernando Baquero	IRYCIS Madrid, ES
Jean-François Delfraissy	AVIESAN Paris, FR
Gérard Dénariaz	Danone Palaiseau, FR
Vincent Deubel	Institut Pasteur du Cambodge Phnom-Penh, KH
Anne Fagot-Largeault	Collège de France Paris, FR
Alain Fischer	Hôpital Necker Paris, FR
Antoine Flahault	Institut de Santé Globale Genève, CH
Laurent Fraisse	Sanofi Toulouse, FR
George Griffin	SGUL London, UK
Antonio Lanzavecchia	IRB Bellinzona, CH
Marc Mortureux	ANSES Maison-Alfort, FR
Bruno Coignard	InVS Saint-Maurice, FR
Jacques Schrenzel	Hôpitaux Universitaires Genève, CH

BOX 1

Institut Pasteur

Institut Pasteur
25 rue du Docteur Roux
75015 Paris
www.pasteur.fr

The Pasteur Institute is a recognized public benefit organization with three core missions: research, public health and teaching. Founded over a century ago and still faithful to the humanist ideals of Louis Pasteur, the institute of today stands at the forefront of biomedical research.

Setting the international standard of excellence in infectious diseases, its scientists strive daily to move research forward and to fight the microorganisms that cause disease, whether these are viruses, bacteria, fungi or parasites. Widely recognized as the birthplace of microbiology and a cradle of many other disciplines, the institute also helped lay the foundations of immunology and molecular biology. Nowadays pasteurian research has extended to neuroscience, developmental and stem cell biology, genomics and systems biology. Since its creation, ten Pasteur Institute scientists have been awarded the Nobel Prize in Physiology or Medicine.

The Pasteur Institute is at the center of an international network of 32 institutes located on every continent worldwide. They have all signed a charter declaring their commitment to Pasteurian values, and are all united in the fight against infectious diseases.

In September 2012, the Pasteur Institute and the World Health Organization (WHO) signed a cooperation agreement to help countries to manage the risks of epidemic outbreaks. The programme should strengthen, in countries at risk, the surveillance, alert, and detection capabilities by applying the principles set out in the WHO's International Health Regulations

BOX 2

InVS

INSTITUT
DE VEILLE SANITAIRE
12, rue du Val d'Osne
94415 Saint-Maurice cedex
www.invs.sante.fr/

The French Institute for Public Health Surveillance or Institut de Veille Sanitaire

The French Institute for Public Health Surveillance (InVS) is a public agency falling under the supervision of the Ministry of Health. It is responsible for the surveillance, early warning and alert of all public health-related threats that occur.

Created following on from a 1998 law strengthening health surveillance and the control of the safety of all products targeting human beings, the InVS competences were reinforced by the 2004 public health law.

The French Institute for Public Health Surveillance has a broad range of missions :

- ✓ The continuous observation and surveillance of the population's health status
- ✓ Health surveillance
- ✓ Alert to decision makers
- ✓ Contribution to the management of health crisis

These missions apply to infectious diseases, chronic diseases and injuries, environmental health as well as occupational health. The InVS works in close cooperation with a broad range of partners, including a network of 46 infectious disease-specific national reference centres, 15 of them being located at the Institut Pasteur.

BOX 3

ANSES

27-31 avenue du Général Leclerc
94701 Maisons-Alfort Cedex
www.anses.fr

French Agency for Food, Environmental and Occupational Health & Safety

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) was created as an independent scientific body. It was created in July 2010 through the merger of the French Food Safety Agency (AFSSA) and the French Agency for Environmental and Occupational Health Safety (AFSSET). Its primary role is to assess health risks and inform public policy, thus contributing to the safety of the general public, workers and consumers. It is a public administrative body working mainly with the French Ministries of Health, Agriculture, the Environment, Labour and Consumer Affairs. It is an original and innovative health agency based on the deployment of independent, pluralistic scientific expert assessment by groups made up of external scientists.

The Agency relies on a network of 11 reference and research laboratories located in 16 different parts of the country, that are internationally recognised in several areas or disciplines. This Agency plays a leading role in Europe with a broad sphere of expertise encompassing human, animal and plant health which considers human beings in their environment taken in the broad sense of the term.

BOX 4

ENVA

7 Avenue du Général de Gaulle,
94704 Maisons-Alfort
www.vet-alfort.fr/

The Alfort Veterinary School / École Nationale Vétérinaire d'Alfort

By its own missions, the EnvA is conducting research in the main fields of veterinary sciences. A first research axis is devoted to animal infectious and zoonotic diseases while the second axis regards muscular, locomotor and reproduction biology and medicine. On the one hand, the study of infectious diseases is of major importance regarding the biology and transmission pathways of viruses, bacteria and parasites which are present in animals and foodstuffs potentially transmissible to humans. On the other hand, the research in physiopathology is critical to offer new diagnostic tools and therapeutic strategies in locomotor, muscular and reproductive or developmental diseases. All these research activities open promising perspectives for both animal and human medicines. This is directly linked to the "one world-one health initiative", which was even already applied by Louis Pasteur who worked in the EnvA during the 19th century.

The original strategy of the EnvA is supported by 8 major joint research units co-supervised with French research institutes (INRA, INSERM, CNRS), regulatory agency (ANSES) and universities (UPEC, College of Medicine). This offers a unique opportunity of collaboration between scientists from different topics including veterinarians, agronomists, basic scientists, pharmacists and medical doctors. This is the ideal scientific network to offer original solutions and innovations to the incredible challenges that the veterinarians will need to overcome in the next decades over the world.

BOX 5

Hôpital Necker

149, rue de Sèvres
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http://hopital-necker.aphp.fr

The Necker-Pasteur Centre for Infectious Diseases (NPCID)

The Necker Pasteur Centre for Infectious Diseases (NPCID) was born in 2005 from a convention signed between the Pasteur Institute Medical Center and the infectious and tropical diseases of Necker Hospital Department (Service des maladies infectieuses et tropicales). It has become a unique reference structure in infectiology with complementary expertises in clinics, microbiology and epidemiology.

This Center studies the pathogenesis of opportunistic infections in immuno-compromised hosts and develops innovative diagnostic and therapeutic approaches, with a special focus on bone marrow, stem cells and organ transplant recipient patients and patients with primary immune deficiencies.

One area of investigation is the study of emerging pathogens and of the infectious origin of the orphan human diseases. In the framework of the biomedical activities of the NPCID, its staff members are either affiliated or head of the following reference centers: National Reference Center for Hereditary Immunodeficiency, National Reference Center Mycology and Antifungals, and National Reference Center and WHO collaborating Center on *Listeria*.

BOX 6

INSERM

Institut national
de la santé et de la recherche médicale
101 rue de Tolbiac
75654 Paris Cedex 13
www.inserm.fr

Founded in 1964, the French National Health and Medical Research Institute (Inserm,) is a public science and technology institute, jointly supervised by the French Ministry of Higher Education and Research and the Ministry of Health. The mission of its scientists is to study all diseases, from the most common to the rarest, through their work in biological, medical and public health research.

Inserm supports more than 300 laboratories across France. In total, the teams include nearly 13,000 researchers, engineers, technicians and administrative staff, etc.

Inserm is a member of the National Alliance for Life and Health Sciences, founded in April 2009 with CNRS, Inserm, the CEA, INRA, INRIA, the IRD, the Institut Pasteur, the Conference of University Presidents - Conférence des Présidents d'Université (CPU) and the Conference of Chairmen of The Regional and University Hospital Centres - Conférence des directeurs généraux de centres hospitaliers régionaux and universitaires. This alliance forms part of the policy to reform the research system by better coordinating the parts played by those involved and by strengthening the position of French research in this field through a concerted plan.

For more information on Inserm visit www.inserm.fr

V. EARLY ACHIEVEMENTS: NEW GROUPS AND FELLOWS

IIBEID aims at improving capacities to anticipate and manage future emerging infectious diseases. It has been conceived and constructed on existing research groups both inside and outside the Pasteur Institute that collaborate through the partnership. This strong core of scientific expertises represents a springboard for the creation of new groups bringing original competencies that are deemed essential to reach the LabEx objectives. The recruitment of these young scientists together with the attribution of PhD and post doctorate fellowships reinforce and enlarge the assortment of skills, thereby creating dynamics that will be sustained during the whole LabEx lifetime (**See Box**: IBEID 2011-2014).

New skills, training and diffusion of knowledge

Creation of research groups

IBEID has recruited outstanding young scientists to improve its capacity to respond to the newly emerging infectious agents. Among them are the three 5-year junior groups (G5), a junior team created jointly by ANSES and ENVA, and a research unit in epidemiology on mathematical modeling of epidemics.

The G5 group called "**Morphogenesis and microbial growth**" (Sven Van Teeffelen, group leader) studies the mechanistic and fundamental bases of macroscopic cell-shape formation in relation with cellular growth. The problem of bacterial morphogenesis is approached from a biophysics and a systemic point of view. An improved understanding of cell-wall synthesis and remodeling is crucial to conceive future generations of antibiotics.

The G5 group "**Mosquito-Virus Interactions**" (Louis Lambrechts, group leader) aims to shed a new light on the genetics of vector-virus interactions in order to understand their role in arbovirus emergence and evolution. Dengue, Chikungunya and West Nile fever are examples of arboviral diseases that have re-emerged in the last decades. Dengue, for which vectors are Aedes aegypti and Aedes albopictus, is the most prevalent arboviral infection worldwide. Uncovering of the genetic determinants will help to evaluate the relative epidemic risk of a given arbovirus in a particular vector species.

The third G5 group "**Synthetic biology**" (David Bikard, group leader) focus on the application of a synthetic system (CRISPR) to study and fight pathogenic bacteria. CRISPR loci and the associated Cas genes are the adaptive immune system of archeae and bacteria. They are able to capture pieces of DNA from viruses and other invading genetic elements and can then use this information to cleave foreign DNA sequences through Cas proteins that act as RNA-guided nucleases. This restriction system can be programmed against bacterial populations in order to kill bacteria carrying antibiotic resistance or virulence genes, leaving the rest of the microbiota intact. One important application is the fight against *Staphyloccus aureus* strains that are a major source of respiratory tract and skin infections as well as a common cause of nosocomial infections.

The innate immune response is the first line of defense against viruses, resulting in the production of type-1 interferon (IFN) and other pro-inflammatory cytokines that control infections. As the interferon response is detrimental for viruses, it is counterbalanced by the antagonist effect of proteins induced by viruses. The junior team **"Innate Immunity, Interactomics and Interspecies transmission of viral Infection"** (Damien Vitour, group leader) created within JRU Virology (ENVA-ANSES) is focusing its research program on innate antiviral immunity, pathogenesis and interspecies transmission during Bluetongue virus (BTV) infection. This insect-borne virus (serotype-8) is responsible for unexpected major epizootic diseases in Noth-western Europe livestock during the last decade.

While pathogen identification, diagnostics, and treatments progress ever more quickly due to fundamental research and technological improvements, policy makers have the responsibility to determine the most appropriate type and level of response when facing an emergent threat. In this regard, the "**Mathematical Modelling of Infectious Diseases**" Unit at the Pasteur Institute (Simon Cauchemez, group leader) is developing statistical and mathematical models that can be applied at different stages of the emergence in order to increase the scientific knowledge on the dynamics, the transmission, and the control of an epidemic.

Launching of new research projects and training of young investigators

For the IBEID community, the most important investment is undoubtedly intellectual. It is embodied in two major actions: the creation of new research groups led by outstanding scientists (**see above**) and the training of young investigators in numerous disciplines all relevant to research in emerging infectious diseases. The Labex has attracted high level students, both of French and foreign origin, through PhD and postdoctoral fellowships. These young scientists are working in the best conditions on this new facet of microbiology: "The microbiology of emerging diseases". Subject priorities are:

(i) in microbiology: the molecular mechanisms of resistance to antibiotics, regulatory mechanisms of gene expression in bacteria and mechanisms of homeostasis and communication in complex microbial communities

(ii) in virology: viruses with strong potential of emergence, such as arboviruses.

By belonging to IBEID, they benefit from the cutting edge multidisciplinary environment provided by the Institut Pasteur and its partners. They all have the great opportunity to collaborate with outstanding group leaders all having been ranked top level (A+) by the French evaluation Agency (AERES) and for some of them (8) awarded an ERC either Advanced or Young investigator grant.

At present, highly competitive fellowships have been awarded to post-doctoral scientists and PhD students. Up to now, 8 three-year post-doctoral and 7 PhD thesis projects are funded by IBEID. Other fellowships will be awarded along the LabEX ten years period.

The 8 post-doctoral projects all tackle important issues that are highly relevant to IBEID's main objectives:

- ✓ "Bayesian monitoring of the pandemic risk of emerging infectious diseases"
- ✓ "Comparative genomics and phylogeographic analysis of two epidemic and multidrug resistant bacterial populations : *Shigella dysenteriae* type1 (Shiga's bacillus) and *Salmonella kentucky* ST198"
- ✓ "Identification of tick molecules that contribute to tick-borne pathogens transmission".
- ✓ "Pathogenesis of enterovirus 71, a human emerging encephalitogenic virus"
- ✓ "Importance of trypanosome motility during early infection in the mammalian host"
- ✓ "*Legionella pneumophila* nucleomodulins: characterizarion and identification of their targets in the host"
- ✓ "Experimental evolution of arboviruses during natural transmission: identifying evolutionary trajectories and predicting emergence events"
- ✓ "Study of Chikungunya virus replication and entry into mammalian cells"

The 7 PhD thesis projects are studying:

- ✓ the emergence of neonatal Group B *Streptococcus* infections,
- ✓ the abilities of commensal and pathogenic bacteria to form anaerobic biofilms.
- ✓ an integrative network analysis of genome-wide association studies of dengue
- ✓ the role of a RNA-interference pathway (piRNA) in antiviral immunity in insect vectors
- ✓ the early steps of Chikungunya virus entry into the host cell
- ✓ the specific immune responses in humans infected by the simian Foamy viruses
- ✓ the identification of viral factors that determine the ability of influenza A viruses to cross the species barrier

Initiating a top level training on emergent infectious diseases

The LabEx has a strong potential for high-level training of master, PhD, and post-doctoral scientists and for the generation of new knowledge that can be integrated into the various advanced courses offered at the Pasteur Institute and in the lessons delivered by Philippe Sansonetti through his Chair of Microbiology and Infectious Diseases at the Collège de France. Advanced courses cover multiple facets of emerging infectious diseases such as epidemiology, microbiology, virology, immunology, and infectious diseases and they are taught using the most advanced concepts and cutting-edge technologies.

Regarding LabEx trainees, PhD students are largely affiliated to the major Doctoral Schools of Paris Universities, and post-doctoral scientists are in general supported by the most prestigious international granting institutions (*i.e,* EMBO, HSFP, Marie Curie, Pasteur Foundation.). They receive mentoring by LabEx group leaders and benefit from a large number of seminars, conferences, and workshops held at the Pasteur Institute and at other partner sites.

In addition, the LabEx has decided to put a strong emphasis on risk evaluation. A major expression of this focus is the yearly organization, back to back with a LabEx Day, of an international symposium covering a particular and possibly original aspect of the risk of infectious disease emergence. As an example, in September 2014, the Symposium's topic is: "Can one anticipate the next emerging infectious diseases in Europe". It is organized by a scientific committee of LabEx members.

Fostering valorization and Diffusion of knowledge

The LabEx is in complete agreement with the strong pasteurian tradition of valorization of research. Members of the LabEx will benefit from the experience of the "Service des Brevets et Inventions" of the Pasteur Institute to protect their discoveries. The Pasteur Institute has agreements with other scientific institutions and universities, particularly with INSERM, to treat patent applications according to the respective contributions when discoverers belong to different institutions. In a sensitive area for the public like emerging infectious diseases, it is vital that scientists provide accurate and accessible information on a phenomenon that is complex and prone to unrealistic interpretations and behaviors.

The LabEx will represent a central reference to help generate the objective information to be disseminated to authorities and to the public. The issue of communication will be a major theme, with a group of scientists, epidemiologists, medical doctors, and representatives of communication offices of partner institutions meeting regularly and during crisis periods to integrate updated information and optimize its dissemination.

First achievements / first publications

Among the scientific articles already published by partners in the framework of the IBEID project, the studies summarized below highlight some of the specific contributions of this LabEx in the fields of emerging infectious diseases.

Encephalitis in Vietnam

Acute encephalitis syndrome (AES) is a major public health problem in Asia. The main etiologic agent is the Japanese encephalitis virus (JEV), a flavivirus transmitted by *Culex* spp. mosquitoes. Since 1999, the Bac Giang province of northern Vietnam has had unexplained outbreaks of non JE-acute encephalitis that occur specifically during the months of May and July. These outbreaks affect mainly children under 15 years and result in severe clinical features in terms of morbidy and case fatality. Emergence of these AES is attributed to the strong intensification of litchi cultivation in this particular province with a short 1-month harvest period that coincides with the epidemic season of these outbreaks. This suspected association has been investigated by conducting a retrospective ecologic analysis in the Bac Giang province for the years 2004–2009, involving various environmental, agronomic, and climatic factors. This group has found evidence for a spatiotemporal association between the outbreaks of encephalitis in the province and litchi harvest period. Other studies are being conducted to identify the causative agent.

Paireau J1, Tuan NH, Lefrançois R, Buckwalter MR, Nghia ND, Hien NT, Lortholary O, Poirée S, Manuguerra JC, Gessain A, Albert ML, Brey PT, Nga PT, Fontanet A. Litchi-associated acute encephalitis in children, Northern Vietnam, 2004-2009. Emerg Infect Dis. 2012 Nov;18(11):1817-24

The Chikungunya virus (CHIKV)

During the 2005–2006 outbreak, the mosquito *Aedes albopictus* was the predominant vector in la Reunion and Mayotte whereas the usual CHIKV vector Aedes aegypti was absent or very scarce. The complete genome sequence of six viral isolates has resulted in the identification of one amino-acid substitution in the E1 viral glycoprotein (polymorphism E1-A226V) that was responsible for the shift between the two vectors. This substitution is directly responsible for a significant increase in infectivity, dissemination and transmission by *Ae. albopictus*. A group has discovered the underlying molecular mechanism leading to the selection of the E1-226V variant. It showed that the midgut barrier favors the dissemination of the E1-226V variant in *Ae. albopictus* and could explain why this variant was able to so rapidly emerge as soon as the vector *Ae. albopictus* was present.

Arias-Goeta C., Mousson L., Rougeon F., Failloux A.-B.. Dissemination and transmission of the E1-226V variant of Chikungunya virus in Aedes albopictus are controlled at the midgut barrier level. PLoS ONE 2013; 8(2):e57548

In September 2010, a few cases of Dengue (DEN) and Chikungunya (CHIK) were reported in the southeast of France. Since the affected patients had not traveled outside of France, an autochthonous transmission of both viruses by the mosquito Aedes albopictus was suggested. This species has expanded all over the world during the past decades, including to the south of Europe. Since its first report in Albania in 1979, Aedes albopictus has been found in 20 European countries. In France, this mosquito was first detected in 2004 in the city of Menton and has gained ground each year. It is now established in seven French departments. This study assessed whether the temperate counterpart of Aedes albopictus collected in southeastern France shows a high ability to transmit CHIKV and DENV when compared to Aedes aegypti. It was shown that this mosquito is very efficient in transmitting both CHIK and DEN and that it can sustain epidemic outbreaks during favorable seasons in France and in continental Europe.

In December 2013, the Pasteur Institute of Guyane alerted the Pasteur Institute, Paris, about the emergence of an outbreak of Chikungunya virus infection in the French Caribbean islands and Guyana and called IBEID for help. Within 2 weeks, the LabEx mobilized a task force to identify the needs of health authorities and hospitals of the area and to propose a fast answer at the scientific level. A call for projects on the most relevant research topics identified was immediately published within the LabEx and in February, two scientific projects were selected and funded.

Vega-Rua A., Zouache K., Caro V., Diancourt L., Delaunay P., Grandadam M., Failloux A.-B. High Efficiency of Temperate Aedes albopictus to Transmit Chikungunya and Dengue Viruses in the Southeast of France. PLoS ONE, 2013; 8(3): e59716

The Zika virus epidemics

In October 2013, an outbreak of febrile rashs linked to the Zika virus was identified in French Polynesia. *Aedes* mosquito is the vector of this flavirus identified in 1947 in Ouganda. In January 2014, 6,630 suspected cases were reported with some patients suffering from severe neurological syndromes, mainly Guillain-Barré syndromes. As the epidemic reached New Caledonia, IBEID was alerted by health authorities in French Polynesia and New Caledonia to set up and fund relevant research projects aimed at studying the virus epidemicity and its fitness within its mosquito vector.

The Middle East Respiratory Syndrome coronavirus (MERS-CoV)

The Middle East Respiratory Syndrome coronavirus is a respiratory virus that belongs to the same family as the SARS coronavirus which struck in 2003. Infection by the MERS-CoV causes respiratory distress with a high mortality rate (around 60%). The patients tend to suffer from pre-existing chronic diseases or are immunodeficient. Today MERS-CoV is considered an emerging virus. The first confirmed case of infection was in April 2012 in Jordan and since April 2014, the WHO has been notified of 156 cases of MERS-CoV infection although the world assessment amounts to 417 cases and 123 deaths. The Epidemiology of Emerging Diseases Unit at the Pasteur Institute in Paris, led by Arnaud Fontanet, has estimated the virus transmissibility and the epidemic potential of this virus and has compared the results with similar findings obtained for pre-pandemic SARS. By drawing on the analysis of known cases within the literature, the scientists indicate that the virus, in its current form, does not yet have pandemic potential but might one day. This group recommends enhanced surveillance, active contact tracing, and vigorous searches for the MERS-CoV animal hosts and transmission routes to human beings.

Breban R, Riou J, Fontanet A. Interhuman transmissibility of Middle East respiratory syndrome coronavirus: estimation of pandemic risk. Lancet. 2013;382:694-9

Another study reported the first two French cases of MERS-CoV infection with a case of patient-to-patient nosocomial transmission in a hospital. One patient visited Dubai in April 2013 and the second patient lives in France and did not travel abroad but the two patients shared the same room for 3 days. Both patients had underlying immunosuppressive disorders and showed very similar clinical features. The virus' incubation period could reach 9–12 days, a longer period than what was previously recorded and with clinical implications for the duration of quarantine. The authors of this study recommend that patients with respiratory symptoms returning from the Middle East or exposed to a confirmed case should be isolated and investigated for MERS-CoV with lower respiratory tract sample analysis and an assumed incubation period of 12 days. Immunosuppression should also be taken into account as a risk factor.

Guery B, Poissy J, El Mansouf L, Séjourné C, Ettahar N, Lemaire X, Vuotto F, Goffard A, Behillil S, Enouf V, Caro V, Mailles A, Che D, Manuguerra JC, Mathieu D, Fontanet A, van der Werf S; the MERS-CoV study group. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. Lancet. 2013;381:2265-72

Prediction of arbovirus mutation with epidemic potential

During the process of virus RNA replication, mutation events can take place that lead to the production of new viruses. Since these mutations are frequent, a viral population from a single strain is actually composed of a mix of variants, with diverse mutations. Among these mutations, some will confer a selective advantage to a given variant in the population: in the case of arboviruses, such as Dengue, Chikungunya, West Nile, and yellow fever, which cycle between insects and vertebrates, these mutations can, for example, improve a virus' ability to replicate in mosquitoes and transmit to mammals, rendering it more likely to spread than other variants. The new strain thus bears a stronger likelihood to cause a new epidemic. Using the 2005-2006 Chikungunya virus epidemic that occurred in the Indian Ocean islands as a model study, researchers in the Marco Vignuzzi's unit at the Pasteur Institute have succeeded in developing an approach that can predict the virus mutations that have a strong epidemic potential and are most likely to emerge in the short-term. Their method relies on monitoring the natural, rather than the forced, evolution of a virus during a transmission cycle between mosquitoes and mammals. This work has strong implications for improving surveillance of ongoing epidemics and the potential to strengthen vaccine strategies against emerging viral diseases.

Stapleford KA, Coffey LL, Lay S, Borderia AV, Duong V, Isakov O, Rozen-Gagnon K, Arias-Goeta C, Blanc H, Beaucourt S, Haliloglu T, Schmitt C, Bonne I, Ben-Tal N, Shomron N, Failloux AB, Buchy P, Vignuzzi M. Emergence and transmission of arbovirus evolutionary intermediates with epidemic potential. Cell Host Microbe. 2014 Jun 11;15(6):706-16

IBEID 2011-2014

IBEID Funding

- ✓ **November, 2010**
  Application to the call for proposal published by the French Government
- ✓ **April, 2011**
  The IBEID project is selected for funding by an International Board of Experts

IBEID Meetings

- ✓ **Kick-off meeting**: September 6th 2011
- ✓ **2nd annual meeting**: September 6th 2012
- ✓ **Scientific Advisory Board and 3rd annual meetings**: June 20-21st 2013
- ✓ **Workshop "Can one anticipate the next emerging infectious diseases in Europe?"**: September 15th 2014
- ✓ **4th annual meeting**: September 16th 2014

IBEID fellowships

- ✓ **PhD fellowship, 1st call**: September 2012 – 7 projects funded
- ✓ **Post-doctoral fellowship, 1st call**: June 2013 – 8 projects funded
- ✓ **Post-doctoral fellowship, 2nd call**: June 2014

Creation of new Research Groups

Following the publication of International Calls for Candidatures, 5 new young scientists were selected and offered to head research groups in the framework of IBEID.

Within Institut Pasteur:

- ✓ **"Mathematical Modelling of Infectious Diseases"** Simon CAUCHEMEZ
- ✓ **"Microbial Morphogenesis and Growth"** Sven van TEEFFELEN
- ✓ **"Insect-Virus Interactions"** Louis LAMBRECHTS
- ✓ **"Synthetic Biology"** David BIKARD

Within ANSES/ENVA:

- ✓ **"Innate Immunity, Interatomics and Interspecies transmission of viral Infections"** Damien Vitour

VI. GETTING READY TO FACE AN EMERGING DISEASE CRISIS ?

The recent epidemics of viral pathogens such as SARS, Avian Flu, Ebola, Chikungunya, and Zika, as well as of multidrug-resistant bacterial pathogens are a constant reminder to the permanent threat of emerging infectious diseases to public health. By gathering experts at the frontline of research, surveillance, and control of emerging infectious diseases, IBEID aims to develop synergies to improve our knowledge of the pathogens and their physiopathology, and to provide tools (i.e. detection, risk evaluation, diagnosis, vaccine, therapeutic targets) to face future emerging crises.

How does the LabEx operate when faced with an emerging infectious disease crisis ?

The LabEx concept is to provide a broad array of expertise and technical facilities that can be mobilized to quickly respond to the crisis.

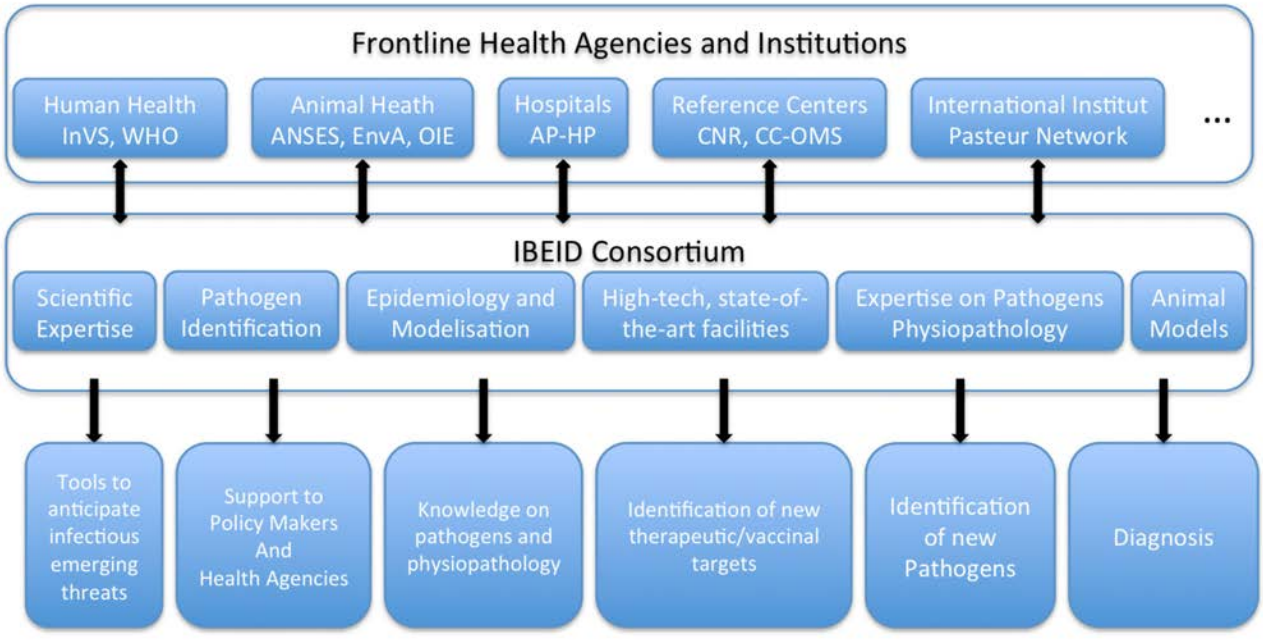
Health agencies involved at the front line, detect the infectious disease agent, evaluate the risk, and collect epidemiological and clinical data and biological samples. Several health agencies are LabEx partners (*i.e.* ANSES, AP-HP, EnvA, InVS) or directly collaborate with LabEx partners (e.g. WHO, ECDC, OIE, Pasteur Institute International Network (**Box 7**), Reference Centers for Pathogens) and can therefore call upon the expertise and technical skills of IBEID.

In response to a crisis, IBEID can quickly mobilize a task force of experts that will support policy makers and health agencies by initiating studies on various aspects of the emerging pathogen, such as:

- ✓ Identification of pathogens, mutations, drug resistance
- ✓ Vector identification and its biology
- ✓ Physiopathology, species barrier crossing, development of animal models
- ✓ Epidemiology and modeling
- ✓ Immune response, biomarkers of infection and protection (*i.e.* serology)
- ✓ Genetic and immunological susceptibility of the host

In return, data, samples and strains from the field are very fruitful for academic research and allow development of new concepts, improvement of knowledge on pathogens and physiopathology and identication of new therapeutic and vaccinal targets.

Getting ready to face an emerging disease crisis ?



BOX 7

The Institut Pasteur International Network

The «"Réseau International des Instituts Pasteurs" (RIIP) constitutes a unique and original model of international scientific cooperation that primarily aims to protect the health of populations in the most impoverished areas of the planet. It is a worldwide partnership of 32 research and public health institutes. They globally encompass more than 12,000 people who contribute to the three key Pasteurian missions: research, training and public health.

The network has a 123-year long history that began with the creation of the Pasteur Institute in Saïgon by Albert Calmette in 1891, just four years after the founding of the Pasteur Institute in Paris. The legacy is still going on with the creation in 2010 of a biotechnology business incubator in the new Pasteur Institute of Shanghaï and the inauguration in 2012 of the new Pasteur Institute in Vientiane, Laos. These expansions, in addition to the very recent opening of a hub platform of virological expertise at the Pasteur Institute of Phnom Penh in Cambodia, considerably enhance the capacity in research and prevention of risks of pandemics in South East Asia.

Thanks to its worldwide presence and the high level expertise of its scientists and technicians, the network plays a major role in monitoring infectious diseases, launching alerts, and participating in the global response to recurrent emerging crises. The network hosts a large number of national and WHO reference centers that serve as microbiological observatories in their respective countries/regions and carry out the continunous surveillance of emerging, epidemic, and pandemic infectious diseases. Teaching and training activities are also a priority.

Research articles published by RIIP scientists are available online on its own portal:

http://hal-riip.archives-ouvertes.fr

Management of emerging infectious diseases crises:

Among the IBEID teams ready to be mobilized to face a crisis is the Laboratory for Urgent Response to Biological Threats (Centre d'intervention biologique d'urgence, CIBU) created in 2002 to respond to «special biological emergencies» such as epidemics, major accidents, or bioterrorist attacks using biological weapons that can endanger public health.

The LabEx is at the center of a network that may, at any time, connect with: (i) national and international health authorities and institutions, both in the industrialized and developing world; (ii) hospitals, which permanently face infectious emergences; and (iii) the pharmaceutical and vaccine industry.

A state of preparedness needs to be set up and maintained during «peaceful times» by tightening the links between health agencies and research institutions and by setting up collaborations, workshops, and round tables to identify the threats, the challenges, and the needs to respond efficiently and effectively.

It is expected that IBEID will face several crises during the ten-year project. Indeed, these will reveal the validity of the whole concept. Management of emerging infectious disease crises is immediately activated by a panel composed of relevant members of IBEID and ad hoc experts, whenever necessary. The RIIP (**See box 7**) is represented in the Scientific Advisory Board, as infectious emergences are more likely to occur initially outside France/Europe.

As a matter of fact, at the time this document was completed, an epidemic of Ebola virus infection of unprecedented dimension had emerged and was quickly spreading over several countries in Western Africa, a major challenge to the international community and to LabEx IBEID.

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POUR LA RECHERCHE, POUR LA SANTÉ
POUR DEMAIN

Institut Pasteur