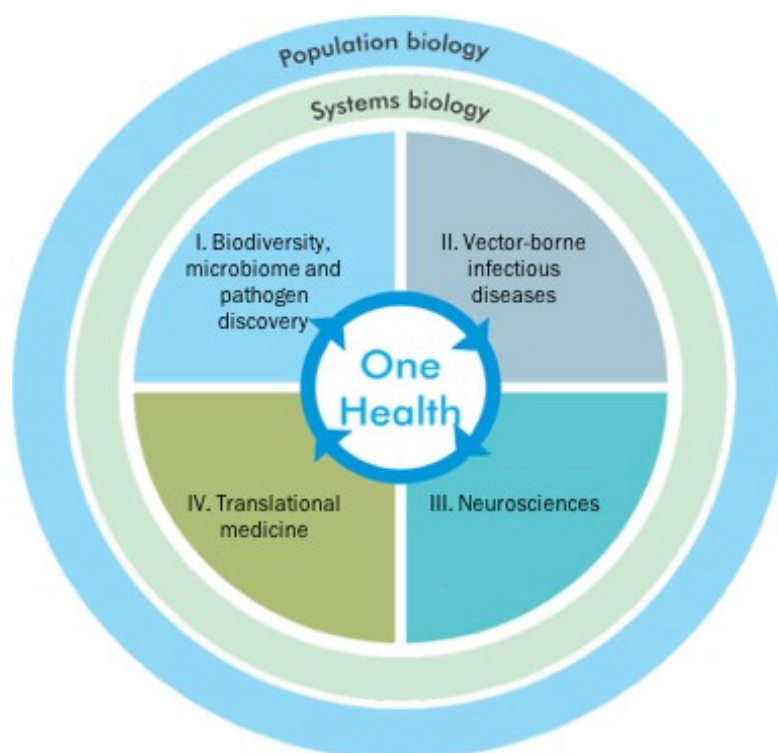


# SCIENTIFIC PLATFORM PASTEUR-USP: THE SCIENTIFIC STRATEGY “AN INTEGRATIVE APPROACH TO TACKLE MAJOR COMMUNICABLE AND NON-COMMUNICABLE DISEASES OF REGIONAL OR GLOBAL IMPACT”

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In the first step of the "Brazil Project" the attention of the partners will be concentrated in the "Sao Paulo Site" and the set up of the Technical, Scientific, Educational Platform, to be installed in the USP Campus. A multifaceted successful relationship is a palpable result of the complementarity of the partners, as concerns basic and applied initiatives to public and animal health issues, increasing performance. Short, medium and long term complementary and interdisciplinary initiatives will be set in motion, offering a unique opportunity to develop cutting edge scientific cooperation on transmissible and non-transmissible diseases in a context of rapid environmental changes and the emergency of new ecosystems created by man. Four main program priorities and 2 transversal methodologies (see Figure below) show how these approaches will be integrated into the “One Health” concept.



## IV.A.BIODIVERSITY, MICROBIOME AND PATHOGEN DISCOVERY

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Brazil is the most prominent of the tropical nations. With 6 ecosystems the country is considered the country with the highest biodiversity in the world. Its climate and humidity factors favor the proliferation of insects, which hugely increase the incidence of several vector-borne

diseases, such as Dengue, Chagas disease, Malaria, Rabies, Granular conjunctivitis, Leishmaniasis, Cysticercosis, Schistosomiasis, Tapeworm and "river blindness". These diseases that were once

common in rural areas, are now "urbanized" due to the migration of people from the countryside to the outskirts of cities.

The climatic changes observed in recent years in Brazil associated with global warming and the increase in rainfall have had a highly significant impact on the spatial and temporal distribution of insect vectors of pathogens and consequently on the infectious diseases they transmit, increasing transmission. Importantly, insect breeding sites and inadequately stored water during periods of drought have contributed to the expansion of these populations, which has contributed to the deforestation which together with the poverty of urban areas as a real problem for the emergence of human and animal diseases. Climate changes and the impact on the environment also have contributed to the spread of these diseases to non-tropical countries.

Some priorities of this project aim are briefly summarized here :

- Evaluate the impact of environmental changes on the interactions between vector, pathogen, reservoir and microbiome, certainly having an effect on the dynamics of pathogen transmission and disease;
- Assess microbiology surveillance and pathogen discovery by investigating the risk of pathogen emergence, including zoonoses in the different Brazilian ecosystems;
- Use highthroughput technologies to study the wild fauna and consequently evaluate the potential for behaving as new (introduced? endemic?) reservoir of emerging or re-emerging pathogens;
- Investigate the mechanisms of pathogen spill over at the interface of vectors, wild and domestic fauna and man and
- Undertake genetic diversity and genoma evolution of pathogens issued from the different ecosystems (Brazil and RIIP).

#### IV.B. VECTOR-BORNE INFECTIOUS DISEASES

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Studying the interactions between vector-borne pathogens and their vertebrate and invertebrate hosts is a matter of the utmost importance. The partnership wants to focus on major vector-transmitted diseases, such as Leishmaniasis, Chagas, Malaria and several emergent arbovirus diseases (Dengue, Zika, Chikungunya, etc). Dengue virus alone, which is transmitted by *Aedes sp* mosquitoes, causes great impact on public health of Latin American countries. Brazil leads the world in the number of dengue cases, with 3.2 million cases and 800 deaths reported in the 2009-14 period. Suspected cases of Dengue in the first 10 weeks of 2017 reaches 70 thousand. USP, Fiocruz and Instituto Butantan (in Sao Paulo) are presently engaged on an effort to test dengue vaccine candidates at clinical conditions as well as looking for new tools and formulations presently tested in clinical phases (III to IV). Considered a major health threat by the end of 2015, the Zika outbreak has affected thousands of newborns that have been affected by microcephaly, Brazil has declared the end of its public health emergency in May 2017. However, the World Health Organisation (WHO) has warned that ZIKV, transmitted by *Aedes albopictus* and *A. aegypti*, is still a major problem in Brazil and, despite the decline in cases, continued efforts are needed to fight the disease.

*Aedes spp* also transmit other important Flaviviruses such as the re-emerging Yellow Fever Virus. Although a vaccine against this virus has been used for several decades, regular outbreaks are still occurring each year in South America, and Brazil has just been facing an important outbreak in early 2017. The YFV continue to expand toward the Atlantic coast of Brazil in areas not deemed to be at risk. Beyond the impact on Public Health, vector-borne diseases also impede on the economy: millions of people are invalid, and fertile regions located near water plans are regularly left out. New tools are urgently needed to control *Aedes spp*, which is growing exponentially despite all the efforts

made in recent decades to control it by conventional methods.

Very solid cartography studies on, for instance, Chikungunya virus and vector spread, revealed the impact of mosquito microbiome and fitness on virus transmission in South America. This study, performed by a joint effort between Institut Pasteur and the Fiocruz-Rio Janeiro has called the attention of the authorities for the epidemic risks of the virus in the American continent. In view of these, better knowledge of the disease transmission mechanisms is urgently needed. Some priorities should be considered:

- Vector-borne disease transmission is complex. It does not result from a simple relation between the pathogen and its host, but involves interactions among the three different actors - vector, pathogen and host - that are, in addition, regulated by environmental factors. Only the complete understanding of all these interactions will allow contemplating vector-borne disease prevention and control.
- The generation of phylogenetic data of those microorganisms will inform about their diversity and evolution. It will also allow tracing the microbial expansion in different areas and open new avenues of research for the identification and validation of innovative targets for diagnosis, prognosis, drug design and/or vaccine development.
- Progresses have been made to better understand the function of genes of interest, using genomics, proteomics and metabolomics, which together with powerful tools and nanotechnology (RNAi, biochips, etc), or advanced imaging techniques will surely lead to a better understanding of the effects of different mediators in the saliva of insect vectors and their interactions with the immune system of their hosts. Therefore, the prospect of developing new vaccines targeting antigens to a given phase of the microbial cell cycle, without interfering with the host cells, is not a utopia.

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#### IV.C.NEUROSCIENCES

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The partners will be committed in elaborating advanced projects on neurosciences and communicable and non-communicable diseases. These projects should be modern and broad, and encompass different aspects of neurosciences.

One attractive subject deals with the connections between the microbiome and the brain and how gut bacteria can influence the brain and behavior. Bacteria from the skin and the gastrointestinal tract modulate the immune system, and have been described as playing an important role in autoimmune diseases. Several disciplines have approached this topic that may link neurosciences, immune system dynamics and microbiology. Additionally, they have been associated to the regulation of stress hormones, which control the expression of genes in the brain, mostly associated to the development of neurodevelopmental and behavioral disorders, such as anxiety and autism. The appreciation of epigenetic mechanisms in informing host-microbe dialogue calls the attention of the partnership: how gut microbial products can have an impact in chromatin plasticity and alteration in host behavior? The microbial composition has significantly contributed to the comprehension of the microbiota of the gut and its relationship with health and disease.

Also, a large numbers of unrelated viruses (cytomegalovirus, lymphocytic choriomeningitis virus, Borna, Zika, etc) and parasites (Plasmodia, Trypanosomes, Leishmanias, etc) can cause serious abnormalities and brain dysfunctions. The immune response to these pathogens is complex and deserves interest, and a single mutation can also dramatically alter a virus's ability to subvert host antiviral defenses. These topics open new avenues of research identified by the partners such as studying :

- The impact of brain infections on major neurological diseases, mental illnesses and lytic effect of brain cells;
- The breakdown of blood brain barrier during infectious processes;

- The relationship between the immune responses triggered by infectious processes and brain damage;
- Co-morbidities : infections and neurological chronic diseases/mental illnesses;
- Microbioma & brain health and behavior
- Influence of bacterial moieties, enzymes and metabolites on the immune responses and neurotransmission, sleep, stress and memory.

However, although advances in neuroscience research, specifically neuroimaging and neuromarkers, are occurring at a large pace, there are still many difficulties in understanding the causes and mechanisms leading to brain pathology.

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#### IV.D. TRANSLATIONAL MEDICINE

The implementation of technological platforms can effectively do a scientific cross talk between complementary disciplines. The "Brazil Project" at the Sao Paulo site will promote the advancement of innovative approaches dealing with the development of vaccines, immunotherapies, diagnostic methods and drugs for the control of infectious or degenerative diseases. This will require the setting up of translational research network on pre-clinical and clinical trials, and the reinforcement of translational programs to approach infections and diseases. Clinical studies will count on unique cohorts embracing the diversity of genetic backgrounds, microbiomes, environment and life-styles.

The proposal related to translational medicine will count on the development of an automated screening platform of Institute of Biomedical Sciences/USP in partnership with Butantan Institute. This platform will be used for discovery of new bioactive compounds, that can later evolve to drug candidates or molecular probes to study complex biological phenomena in a disease-relevant context. In addition it will be dealing with the discovery of new drug targets and elucidation of drug mechanism of action by means of genome-wide RNAi screening. The platform will be composed by a technological core, which involves the equipment for both cell-based and target-based screening, and the resources core, which involves the management of compound and siRNA libraries.

A platform of OMICS and nanotechnology and innovative tools (real time imaging, biochips, etc) will be useful for the identification of genes and molecules interacting with the host, as well as to analyse the impact of the microbiome in the immune responses.

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#### IV.E. SYSTEMS BIOLOGY AND POPULATION BIOLOGY

High-throughput technologies have revolutionized biological sciences. With the immense volume of data generated by these technologies, bioinformatics became an essential part in many strategic areas of research, from experimental molecular biology to immunology. It involves not only analyzing data but also creating the tools and databases which will be used to perform such analyses. In genomics, bioinformatics aids in sequencing, annotating and comparing genomes of different organisms, as well as in providing the means to analyze whole transcriptome, metabolome and proteome data. It can also be applied to image processing, text mining, evolution, and in the interpretation of various types of data.

The development of drugs and effective vaccines is severely impaired by our lack of mechanistic understanding of immune responses induced by vaccination or infectious diseases. It is clear that such mechanisms involve several pathways that are intimately connected through genes, metabolites, and proteins found inside and outside the cells. Systems biology provides the only way of integrating and analyzing the behavior of the biological components within these intricate networks. Thus,

"Brazil Project" will focus in applying systems biology approaches to study several infectious diseases and vaccines, that are particularly relevant to Brazil.

In 2013, France and Brazil agreed to implement a High Performance Computing Infrastructure and to contribute to place Brazil among the leaders in 2016. The National Laboratory of Computing Science and the Bioinformatic group - CEBIO of Fiocruz in Belo Horizonte in Brazil and the CEA and Bull in France have been contributing to this goal.

So far, bioinformatics has been proposing new forms of very dynamic science-based *in silico* experimentation that provides the basis for generating new data and knowledge. Bioinformatics resources have been applied to Omics sciences (genomics, transcriptomics, proteomics, interatomic, metabolomics, pharmacogenomics, among others) and have enabled the prediction of structures, the simulation of different cell metabolisms, the building of evolutionary trees, the appreciation of three-dimensional structures of molecules, the analyzes of images and biological signals, and even uncovered the biological function of particular DNA sequences.

Some approaches have been identified and efforts will be put together to create a common teaching in Bioinformatics implicating FIOCRUZ, USP and Institut Pasteur. The recently created International Group for Data Analysis (IGDA) at the Institut Pasteur may boost international cooperation for big data handling with the Brazilian partners.

As mentioned in the previous section, infections are complex dynamical phenomena and as such change with time. Hence, the partners will focus on descriptive and quantitative epidemiology, particularly in the context of epidemics, with mathematical modelling of pathogen transmission and evolution of epidemics. Brazil is one of the fastest aging populations in the world. Consequently, behavioral, neuropsychological, environmental and economic interventions are necessary to attend the increase in life expectancy. One of the Brazilian priorities will be focused on noncommunicable diseases (NCD) and new actions have already been settled centered on health diets, physical activity and reduction of alcohol taking and smoking. In addition, regulatory initiatives may contribute to respond to the challenge represented by chronic diseases. Nevertheless, more than political support for preventive actions, it is of utmost importance to reduce chronic diseases and the risk factors. NCD are and will continue to be obstacles to the economic growth of Brazil. As for HIV/AIDS, the universal and free access to treatment for infected population that had allowed an impressive decline of the morbidity and mortality, the Brazilian government recognizes that research and development and availability of new products for NCD are priorities.

Moreover, the goals of the partnership are oriented to address the prevention and the control of NCD, promoting high-quality research of biomarkers for early diagnosis (prognosis) and treatment (and/or monitoring of treatment), as well as the development of better and affordable technologies and medicines to treat NCD or to stop the progress of some of those diseases (i.e. diabetes, obesity, hypertension, mental depression).