Institut Pasteur

**FRAMEWORK AGREEMENT FOR SCIENTIFIC COOPERATION**

**USP- INSTITUT PASTEUR- FUSP**

**PASTEUR-USP SCIENTIFIC PLATFORM**

**UNIVERSIDADE DE SAO PAULO,** public institution, governed by special statute, approved by Resolution No. 3461 of October 7, 1988 and the General Regulations approved by Resolution No. 3745 of 19 October 1990, herein referred to as **USP**, based in the Rua da Reitoria, 374, Cidade Universitaria, Sao Paulo, SP, Brazil, represented by its Rector **Prof. Dr. Marco Antonio Zago**;

**INSTITUT PASTEUR**, a non-profit foundation, herein referred to as **INSTITUT PASTEUR**, based in 25-28 Rue du Docteur Roux, 75015 Paris, France, represented by its General Director **Prof.Christian Bréchot**, and

Together being called **SCIENTIFIC PARTNERS** and individually **SCIENTIFIC PARTNER**

**FUNDAÇÃO DE APOIO À UNIVERSIDADE DE SÃO PAULO**, herein referred to as **FUSP** legal entity of private law, non-profit and non - economic, whose head office and venue is in the city of Sao Paulo, Av. Afrânio Peixoto, 14 – Butantã, São Paulo, SP – CEP 05507-000, enrolled with the National Registry of Legal Entieties of The Ministry of Finances (CNPJ/MF) n° 68.314.830/0001-27, bearering the titles of public utility in the Federal, State and Municipal spheres, represented by its Executive Director, **Prof. Dr. Antonio Figueira**, Executive President, with the approval of the Curator Council,

herein individually referred to as **PARTY** and collectively referred to as **PARTIES**,

In order to conclude this Framework Agreement for scientific collaboration (hereafter the "Framework agreement"), the following is taken into account:

*I.* The FIOCRUZ / PASTEUR / USP Scientific Cooperation Tripartite Agreement signed on 08 June 2015 (hereafter the "Tripartite agreement") sets an object "*to develop, in Brazil, a technical-scientific-educational platform tripartite between FIOCRUZ-USP-INSTITUT PASTEUR, aiming at promoting the activities of the Parties in a joint and integrated way in the fields of science, technology, innovation and training of human resources in health*". Such technical-scientific-educational platform (defined in the Tripartite agreement as "***a set of concerted actions, shared equipment and projects around which the system of cooperation of the [three parties] is structured***") is "*a set of tripartite*

*initiatives with the aim to:*

i. *Initially: expand and qualify the scientific interaction of the [three parties] and consolidate the foundations of the previous cooperation during the transitional period [...],*

ii. *In the next stage: delineate in a specific document the conditions which might, ultimately, lead to further implement an "Institut Pasteur do Brasil" and its membership in the RIIP"*

II. In the view of implementing the object of the Tripartite agreement and as a first step towards such implementation, the intent of the **SCIENTIFIC PARTNERS** through the present Framework Agreement is to organize and join efforts to promote bilateral scientific and institutional cooperation.

III. **FUSP** is a private organisation offering support to **USP**, pursuant to the Cooperation Agreement signed between them and aimed at supporting teaching, research, outreach, institutional development, scientific and technological projects of interest to the latter, creating more suitable conditions for establishing relationships with civil society.

IV. The formal approval of the present Framework agreement by the relevant authorities of each **PARTY** is regularly obtained.

**THEREFORE, IT HAS BEEN AGREED:**

**Article 1. Object and principles**

**1.1.** The object of this Framework agreement is to:

- describe the scientific cooperation activities to be developed between the **SCIENTIFIC PARTNERS** and, possibly, third parties (notably their partner from the Tripartite agreement – FIOCRUZ) and the set-up of a bilateral **PASTEUR-USP SCIENTIFIC PLATFORM**, within the meaning of the term "Platform" as it has been defined in the Tripartite agreement and in line with the same Tripartite agreement;

- describe the contributions, means and resources in terms of premises, finance, human resources, equipment, administrative support etc., put in place by the **PARTIES** in order to allow the implement of these scientific cooperation activities and the functioning of the **PASTEUR-USP SCIENTIFIC PLATFORM**.

**1.2.** In order to realize the object of this Framework agreement, and as stated in the Tripartite agreement, the **SCIENTIFIC PARTNERS** intend to use convergent efforts to consolidate the cooperation among them, as regards the exchange of knowledge and contributions to scientific research, according to their respective legal form, statutes and rules of functioning.

**1.3.** The actions developed under this Framework agreement will be oriented to promote the scientific development of the **SCIENTIFIC PARTNERS**, in line with the Tripartite agreement's objects, considering also the importance of the social diffusion of science and the respect to the national and international ethical standards related to the scientific activity.

**1.4.** The cooperation and the projects developed between **INSTITUT PASTEUR** and **USP** under this Framework agreement will follow the guidelines, methodologies and objectives set out in the Scientific Strategies described in the Annex I - WORK PLAN - "*Uma abordagem integral para atacar as principais doenças comunicáveis e não-comunicáveis de impacto regional ou global*", "*An integrative approach to tackle major communicable and non-communicable diseases of regional ou global impact.*", elaborated on 31st of August, 2016 in the framework of the Tripartite agreement .

**1.5.** As stated in the Tripartite agreement, whenever possible, the **SCIENTIFC PARTNERS** will attempt to develop new concepts and technologies in the area of health for the benefit of the world population, and especially of the Brazilian population, defining the priority fields of action, guided by the Scientific Strategies described in the Annex I - WORK PLAN.

**1.6.** Nothing in this Framework agreement shall be considered as a restriction for the **SCIENTIFIC PARTNERS** to conduct other research projects in the field of this Framework agreement, alone or with third parties.

**Article 2. Activities under this Framework agreement**

**2.1.** The cooperation between the **SCIENTIFIC PARTNERS**, based on the common scientific strategy described in the Annexe I- WORK PLAN, consists in implementing common research projects on the basis of project calls and developing of high level teaching in the areas of the cooperation, and will be performed through actions described as "Forms of the Cooperation" in the Tripartite agreement, namely:

i. Implementation of Joint Chairs and Pasteur International Joint Units involving scientists from the **SCIENTIFIC PARTNERS**, following their respective activities and organizing new joint calls, notably between the SCIENTIFIC PARTNERS and FIOCRUZ;
ii. Promotion of scientific symposia and cultural events of interest to the **SCIENTIFIC PARTNERS**, with the participation of third institutions , whenever appropriate and agreed by the **SCIENTIFIC PARTNERS**;
iii. Implementation of conditions for the establishment of high-level skills aiming at the teaching and training of professionals in Bioinformatics involving the **SCIENTIFIC PARTNERS**.
iv. Assistance to teaching and incentives to the mobility of researchers, particularly for personnel exchange and training;
v. Promotion of technology transfer and the consequent establishment of actions aimed at the appropriate protection of intellectual property, in partnership with the business sector.

vi. Creation of a network of collaboration gathering together the laboratories of the **SCIENTIFIC PARTNERS**, ideally including the third party of the Tripartite agreement - FIOCRUZ;

vii. Exchange of experiences in the areas of public health, notably in the areas of communicable and non-communicable diseases, emerging diseases, neurosciences, bioinformatics, health and environment and population aging;

viii. Organization and dissemination of specialized training in the areas of public, translational research in the medicine and biomedicine fields, Biotechnology, Systems Biology, Management of Technology Transfer and Innovation;

ix. Exchange and/or mobility of personnel with scientific or medical training;

x. Joint implementation of research projects, conditioned to the respect of existing agreements between the **SCIENTIFIC PARTNERS**, possibly extended to third parties and notably with the third party of the Tripartite agreement - FIOCRUZ;

xi. Exchange of information, particularly in the form of specialized publications.

**2.2.** The organisation and the implementation of the collaborative activities described in 2.1. must be detailed on case by case basis in specific research collaboration agreements signed by the **SCIENTIFIC PARTNERS**, possibly with the participation of third parties (hereafter the "Specific Collaboration Agreements"). The Specific Collaboration Agreements are expected to set forth, notably, the respective responsibilities and, as appropriate, include provisions with respect to technical works, financial matters, liability and insurance (where relevant), the ownership and exploitation of intellectual property rights, the monitoring of the collaborative project, communication and publications, confidentiality, as well as the dissemination of results.

**2.3.** The **PARTIES** intend to make their best efforts to:

i. Develop the bilateral initiative **PASTEUR-USP SCIENTIFIC PLATFORM** as an intermediary step towards the possible implementation of a "Institut Pasteur do Brasil", in respect of the Tripartite agreement;

ii. Support or find external support for the activities implemented by the **SCIENTIFIC PARTNERS** and within the **PASTEUR-USP SCIENTIFIC PLATFORM**, as well as, when possible, the dissemination of the activities' results;

iii. Collaborate, where appropriate and possible, for the institutional promotion and strengthening of the activities and objectives of the Tripartite agreement and this Framework agreement.

**2.4. Fundamental rules for the implementation of the activities under this Framework agreement within the PASTEUR-USP SCIENTIFIC PLATFORM**

The activities under this Framework agreement shall be conducted in accordance with all applicable laws, rules and regulations. Each **PARTY** shall notify the other in writing of any deviations from the applicable regulatory or legal requirements. In particular, when required by **INSTITUT PASTEUR**, **USP** and **FUSP** shall provide **INSTITUT PASTEUR** with all necessary information about the Brazilian legislation and regulations in relation to the activities performed under this Framework agreement.

**a) Material - Data**

Any biological and chemical material and all associated data, necessary to the performance of the Framework agreement and the subsequent Specific Collaboration Agreements, owned or controlled by a **SCIENTIFIC PARNER** outside the scope of said agreements and listed in each Specific Collaboration Agreement (referred to as the "Material") may be made accessible on a non-exclusive basis for use by the other **SCIENTIFIC PARTNER** to perform the scientific activities, subject to the prior signature of specific material transfer agreements negotiated between the **SCIENTIFIC PARTNERS** ("MTA").

All Material provided by one **SCIENTIFIC PARTNER** to another pursuant to the above-mentioned MTA, for the performance of this Framework agreement and the subsequent Specific Collaboration Agreements, is to be used by the recipient **SCIENTIFIC PARTNER** for the sole purpose of performing the scientific activities within the framework of the Framework agreement and each relevant Specific Collaboration Agreement. In addition, the recipient **SCIENTIFIC PARTNER** undertakes that:

- Material shall not be distributed or released to any third party or entities without prior written approval of the providing **SCIENTIFIC PARTNER**;
- Material shall be used in compliance with all applicable laws and regulations ;
- Material shall not be used in connection with human experimentation of any kind.

Material provided in the performance of the scientific activities under this Framework agreement and the subsequent Specific Collaboration Agreements shall remain the property of the providing **SCIENTIFIC PARTNER**.

The above obligations, in material form, though not necessarily using identical language, will be included in writing in every Specific Collaboration Agreement and in any MTA.

**b) Human biological material**

In case of collecting, sampling and use of human biological material and related information ("HBM"), the providing **SCIENTIFIC PARTNER** represents that:

- the collection and use of such materials and related information as contemplated hereunder has been approved in writing to the extent required by the institutional review board (IRB) of each **SCIENTIFIC PARTNER** that shall have possession of such materials and/or information hereunder or that is providing such materials and/or information hereunder;

- the human biological material has been collected, obtained and processed in full compliance with the applicable law;

- adequate consent or opting in form has been obtained from patients participating in the scientific activities detailed in each Specific Collaboration Agreement to prior information of the said patients and/or appropriate authorization from the relevant committee/authority has been obtained to permit the providing **SCIENTIFIC PARTNER** to supply HBM to a receiving **SCIENTIFIC PARTNER**;

- to transfer any necessary document for the file of statement of the collection of HBM;

- the HBM and information related thereto is provided by the providing **SCIENTIFIC PARTNER** to the receiving **SCIENTIFIC PARTNER** in de-identified (as "de-identified" is defined by the Health Insurance Portability and Accountability Act of 1996, as amended together with all related regulations), so that under no circumstances recipient **SCIENTIFIC PARTNER** will be supplied with the identity of the patients participating in the research or any basic clinical information or any personal data which could identify the patients participating in the scientific activities under any Specific Collaboration Agreement;

- it will make no attempt to re-identify any such HBM or related information received;

- it will promptly within ten (10) business days destroy or return all such HBM and related information upon expiration or termination of this Framework agreement or of the relevant Specific Collaboration Agreement (whatever more appropriate), or sooner upon the written request of the providing **SCIENTIFIC PARTNER**, and if destroyed will confirm such destruction in writing to the providing **SCIENTIFIC PARTNER**. The **SCIENTIFIC PARTNER** returning or destroying the same will also follow any instructions from disclosing **SCIENTIFIC PARTNER** with respect to the manner of returning such material and/or information.

In addition, the receiving **SCIENTIFIC PARTNER** undertakes that:

- the HBM shall not be distributed or released to any third party or entities without prior written approval of the providing **SCIENTIFIC PARTNER**;

- the HBM shall be used in compliance with all laws and regulations applicable to the scientific activities implemented;

- the HBM shall not be used in connection with human experimentation of any kind.

**c)** The providing **SCIENTIFIC PARTNER** undertakes to have packaged and have transported the HBM until received at the receiving **SCIENTIFIC PARTNER's** offices. The transport of HBM shall comply with any applicable regulations and in particular the UN Guidelines of infectious or potentially infectious Material.

**d)** To the extent a **SCIENTIFIC PARTNER** may provide to the other **SCIENTIFIC PARTNER** information containing "Personal Data" as that term is defined in the Data Protection Directive 95/46/EC and applicable legislation enacted under the same or equivalent/similar national legislation (collectively "Data Privacy Legislation") about the subjects in connection with the scientific activities and/or Material, the disclosing **SCIENTIFIC PARTNER** agrees to obtain any consents or authorizations, as may be necessary in accordance with applicable Data Privacy Legislation, for the transfer of any Personal Data or processing of such Data provided to the other **SCIENTIFIC PARTNER**. The **SCIENTIFIC PARTNERS** shall handle all such information in accordance with all applicable law or contractual obligations.

**e)** The **SCIENTIFIC PARTNERS** undertake to respect the provisions resulting from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity, where applicable.

**f)** The **SCIENTIFIC PARTNERS** undertake to respect applicable law on animal experimentation and, if applicable to submit research protocols requiring animal experimentation to a competent ethics committee.

**g) Biomedical researches**

In the case where the **SCIENTIFIC PARTNERS** wish to conduct or sponsor a biomedical research using human subjects hereunder, they commit to perform the research in accordance with a defined protocol and with any applicable state or local legislation, statutes, regulation, rules and other authoritative sources of law pertaining to the activities of the biomedical research or the regulation of the scientific activities/researches including, without limitation the following requirements of European Union law, including without limitation those specified in EU Regulation 536/2014 and Directive 95/46/EC, requirements of the applicable Institutional Review Board ("**IRB**"), the WMA Declaration of Helsinki , ICH Harmonized Tripartite Guidelines for Good Clinical Practice ("**ICH GCP**") and generally accepted professional standards for professional, clinical and research standard of care, and only with approval of the relevant **SCIENTIFIC PARTNERS**' IRB (or equivalent office) and in compliance with all relevant patient consents. No such research using human subjects will take place prior to such research being memorialized in a legally binding written

agreement negotiated between, and fully executed by, the **SCIENTIFIC PARTNERS**.

**Article 3. Contributions, means and resources for the implementation of the objectives of the Framework agreement**

**3.1. Premises and physical space**

**USP** dedicates, free of charge, to the collaboration activities and the **PASTEUR-USP SCIENTIFIC PLATFORM** under this Framework agreement, the premises which plans and description are in ANNEXE II.

This building is currently under construction by **USP**. The proper completion of the works and the **USP** guarantee for those premises according to all construction and scientific standards are a condition for the duration of this Framework agreement (see Article 14.2)

**USP** is the owner of those premises, remains their sole manager and supports all and any costs in terms of construction/building, installations and equipment, maintenance, hygiene and security measures, provision of any services related to their proper functioning (notably and not limited to water, electricity, gases and liquids necessary for the activities, phone and internet connexions, waste management, cleaning etc.) The premises shall be fully operating for the implementation of the activities under this Framework agreement and the subsequent Specific Collaboration Agreements.

The **INSTITUT PASTEUR**'s personnel participating to the activities under this Framework agreement and the subsequent Specific Collaboration Agreements will be hosted and allowed to use those premises by **USP** for this purpose. The **INSTITUT PASTEUR**'s personnel will respect the internal regulations of USP, provided by the latter, with regard to the use of the premises.

Only third parties participating to the activities performed under the present Framework agreement and the subsequent Specific Collaboration Agreements may be invited/hosted in the premises dedicated by the **USP** to the **PASTEUR-USP SCIENTIFIC PLATFORM,** temporarily or permanently, upon the joint decision of the **SCIENTIFIC PARTNERS**.

Such third parties shall be obliged by USP to obey by its internal regulations through specific agreements signed between **USP** and such third parties.

The **INSTITUT PASTEUR** 1/ shall only have its own responsibility in relation to the use of those premises and 2/ shall not have whatsoever responsibility about third parties participating in the activities under this Framework agreement and the subsequent Specific Collaboration Agreements and allowed by **USP** to use the premises.

### 3.2. Financing and Management of Financial Resources

3.2.1.. The **PARTIES** undertake to seek the financial resources required for fulfilling the objectives of this Framework agreement. There is no obligation for any **PARTY** to commit funds to the activities under this Framework agreement. Each Party shall individually agree with the funds it is requested to provide.

3.2.2. The Specific Collaboration Agreements that must be signed between the **SCIENTIFIC PARTNERS** for each activity (see Article 2.2 above) shall detail the financial resources, their origin, their split and the conditions of expenditure.

~~4.3.~~ 3.2.3. There won't be any financial transfer between **USP** and **FUSP**.

### 3.3. Human resources

Each **SCIENTIFIC PARTNER** decides to appoint, on short-term or long-term basis, according to its own internal rules, the competent personnel to the activities developed under this Framework agreement.

Each **SCIENTIFIC PARTNER** shall bear all expenses incurred and take complete responsibility associated to its personnel.

Each **SCIENTIFIC PARTNER**'s personnel shall remain the employee of this **SCIENTIFIC PARTNER**, which shall continue to pay its remuneration package, any social security contributions (occupational injuries or accidents, travel and medical insurance). Each **SCIENTIFIC PARTNER** shall also ensure the coverage of its personnel with respect to accidents in the workplace and occupational illnesses without prejudice to legal actions, as the case may be, against the responsible third parties.

Each personnel shall be informed about and shall comply with all **USP**'s internal regulations in matters of work organisation, working hours, hygiene and security, as well as, when applicable, provisions regarding bioethics.

Each **SCIENTIFIC PARTNER** shall have at all times and communicate to the other **SCIENTIFIC PARTNER** an updated list of the personnel dedicated to the activities performed under this Framework agreement. In addition, **USP** shall, at all times, have an updated list of the personnel of third parties involved in the activities under the present Framework agreement.

Each **SCIENTIFIC PARTNER** pledges, on behalf of its personnel, not to take any clinical sample or material or data out of the **USP**'s premises dedicated to the activities under this Framework agreement, without the written approval of the Coordinating Committee and an appropriate material transfer agreement (MTA).

During **INSTITUT PASTEUR**'s personnel stay at **USP**, **INSTITUT PASTEUR** shall be responsible for purchasing their own civil liability, physical injury and repatriation insurances and maintaining worker's compensation insurance and general liability insurance. The certificate evidencing such insurance will be provided to **USP** (the "Certificate") at its request.

For the avoidance of doubt, **INSTITUT PASTEUR** shall not be liable in any manner whatsoever for any loss and damage as far as such loss and damage is caused by gross negligence or wilful misconduct of **USP**.

**FUSP** will be responsible for the recruitment, payment and management of staff who is not personnel of the **SCIENTIFIC PARTNERS** (see Article 3.5).

### 3.4. Equipment

3.4.1. Each **SCIENTIFIC PARTNER** remains the owner of its equipment purchased/brought/installed in the premises dedicated to the activities under this Framework agreement and the **PASTEUR-USP SCIENTIFIC PLATFORM**.

3.4.2. For the equipment purchased with funding from third parties/agencies etc., the ownership will be either the one determined by the funding institution, or, if such rules do not exist, should be clearly determined in writing between the **PARTIES.**

In any case, the **PARTIES** commit that, if the "Institut Pasteur do Brasil" is created in the future with proper legal status, the **PARTY** to which the ownership of such equipment is vested in the meantime, shall transfer this ownership free of charge to Institut Pasteur do Brasil.

3.4.3. The **USP** shall host the equipment in premises suitable to the proper installation of the latter, including all utilities necessary for its proper functioning (including but not limited to power, water, drainage and ventilation systems). The **SCIENTIFIC PARTNERS** shall only grant access to the equipment to those of their employees, consultants, students and other persons working under their supervision who have been trained to use the equipment, and who have been made aware of the terms of this Framework agreement and relevant Specific Collaboration Agreements.

3.4.4.
I. **USP** is responsible for the damages occurred to any equipment in its premises.
II. **USP** will not be responsible for the damages occurred to any equipment in this premises, when it is caused by Institut Pasteur's personnel.

3.4.5. Each **SCIENTIFIC PARTNER** is responsible for the damages occurred to the other or to third parties by its own equipment.

### 3.5. FUSP support to the SCIENTIFC PARTNERS's activities and to the PASTEUR-USP SCIENTIFIC PLATFORM

**FUSP** will be entrusted with the following activities:

i. Support and execute the administrative and financial management of **USP** and **INSTITUT PASTEUR** activities related to the **PASTEUR-USP SCIENTIFIC PLATFORM**. A specific detailed agreement on the role of the **FUSP**, the relations between **USP**, **FUSP** and **INSTITUT PASTEUR** and the procedures and functioning of those relations must be signed

within 6 months of the execution of this Framework agreement.

ii. Report on the expenditures effected within a period not exceeding 30 (thirty) days, and present an annual financial statement. The resources needed for the development of projects should be detailed in each. Specific Collaboration Agreement.

The relationship between **FUSP, USP** and **INSTITUT PASTEUR** will be exclusively focused on the execution of the present Framework agreement and the subsequent Specific Cooperation Agreements and any administrative support cannot serve to profit or business purposes.

**FUSP** will not give financial support to the **INSTITUT PASTEUR**, restricting the foundation's actions to administrative support for the execution of this convention Framework agreement.

### 3.6. Third parties' participation to the activities under this Framework agreement

The participation of third parties (notably FIOCRUZ) to the activities under the present Framework agreement shall be formalised on case by case basis in the subsequent Specific Collaboration Agreements.

Concerning the presence, activities and operation of such third parties (and their personnel, equipment, etc.) invited/hosted in the premises dedicated by **USP** to the activities under the present Framework agreement, by joint decision of the **SCIENTIFIC PARTNERS** as stated in Article 3.1, respective liabilities, insurance and other issues shall be settled between **USP** and this/these party(ies) in specific agreements, without **INSTITUT PASTEUR**'s involvement.

## Article 4. Governance

**4.1.** The implementation of this Framework agreement and the coordination of the activities necessary to the full completion of its objectives, thus - the functioning of the **PASTEUR-USP SCIENTIFIC PLATFORM,** will be ensured by a Coordinating Committee.

**4.2.** The Coordinating Committee is to perform the following tasks:

I. Ensure the respect and proper enforcement of the present Framework agreement and the subsequent Specific Collaboration Agreements;
II. In accordance with the applicable legislation and USP's rules as owner of the premises, validate common norms, criteria and standards for the activities under the present Framework agreement proposed by the Executive Coordinators ;
III. Define the actions, monitoring and objectives of this Framework agreement and respective methodologies that have previously been formally approved and agreed by the relevant authorities of each **PARTY**;

IV. Validate, for each activity under the present Framework agreement and in order to finalise every Specific Collaboration Agreement, the work plans, the costs, the funding origin, split of finances, human resources, equipment and other means necessary for the activities, duration etc.;
V. Ensure the smooth progress of cooperation under this Framework agreement;
VI. Assess the activities' implementation, discuss and decide modifications;
VII. Assess financing opportunities and steps to be taken in order to secure financing of the activities under this Framework agreement;
Discuss any issue or dispute related to the Framework agreement or the Specific Collaboration Agreements in the view of amicable settlement
VIII. Be accountable to the **PARTIES.**

**4.3.** The Coordinating Committee shall consist of 4 (four) members, 2 (two) designated by each **SCIENTIFIC PARTNER** and one (1) alternate member for each of them who will act in the absence and impediments of the holders. One representative of FUSP is invited to the Coordinating Committee without voting right.

The Coordinating Committee will have a Chairman who will be elected by the members for 12 months, on a rotating basis.

**4.5.** Each **SCIENTIFIC PARTNER** will appoint one (1) Executive Coordinator who is not member of the Coordinating Committee but will be invited to all its meetings.

**4.6.** The two Executive Coordinators are to perform the following tasks:

I. Make proposals to the Coordinating Committee for the latter to be able to take decisions in all the matters mentioned in Article 4.2.
II. Implement the decisions of the Coordinating Committee and take the appropriate actions
III. Be accountable to the Coordinating Committee

The rules and procedures that will allow the executive coordinators to fulfil their attributions will be defined by the coordinating committee

**4.7.** The Coordinating Committee can create a **Platform Scientific Commission**, composed of 5 (five) members, composed by the 2 (two) Executive Coordinators and 3 scientists of the **PLATFORM** to contribute to the scientific daily life of the platform.

If the Coordinating Committee creates the **Platform Scientific Commission,** it will examine the proposal for common projects to be submitted in regular basis by the scientists of the platform, analyse the application forms of candidates to fellowships or technical positions related to the projects.

If the Coordinating Committee creates the **Platform Scientific Commission** it will agree on the choice of the selected projects and candidates, in accordance

and respecting the tasks validated by the Coordinating Committee and been formally approved and agreed by the relevant authorities of each **PARTY.**

**4.8**. A **Scientific Advisory Board**, composed of 6 (six) members will advise the coordinating Committee on the **PASTEUR-USP SCIENTIFIC PLATFORM**'s scientific strategies and joint initiatives.
The members will be external to the **PARTIES** and will be appointed in the following way: 2 members by each **SCIENTIFIC PARTNER** and 2 (two) members indicated by Tripartite FIOCRUZ/PASTEUR/USP Steering Committee.

**4.9 Meetings**

I. The Coordinating Committee will meet every 12 (twelve) months and whenever requested by one of the **SCIENTIFIC PARTNERS**.

Meetings will be called by the Chairman by email or fax at least 48 hours in advance. Meeting may be held in person or by visio conference.

- The summons should contain the agenda and all documents allowing to the Coordinating Committee's members to take enlightened decisions.

- Matters indicated in a supplementary agenda may be included in emergency cases, at the discretion of any member of the Coordinating Committee, through justification and information on said matters.

- Reports containing clarifications that may supply further knowledge on matters contained on the agenda may be distributed.

The Coordinating Committee may decide to invite and hear any person of interest for the activities under this Framework agreement, and the subsequent Specific Collaboration Agreements, provided that such person accepts to be submitted to secrecy.

For the meetings of the Coordinating Committee at least 3 out of 4 of its members should be present in person. The absent member may give a proxy to another member for the decisions to be taken.

A decision by the Coordinating Committee requires the unanimous consent of the 4 members (thus – the agreement of both **SCIENTIFIC PARTNERS**).

The Chairman of the Coordinating Committee will produce minutes of each of its meetings and make them available to all the members.

In case of impossibility to reach an agreement, the Coordinating Committee will submit the issue to the General Directors of the two **SCIENTIFIC PARTNERS** who will decide together and state the decision by writing.

II. The Executive Coordinators will meet every two months and whenever requested by the Chairman of the Coordinating Committee and by themselves.

Meetings will be called by email or fax at least 48 hours in advance. Meeting may be held in person, by visio conference or by call conference.

A decision by the Executive Coordinators requires the consensus.

The Executive Coordinators will produce minutes of each of their meetings and make them available to the Coordinating Committee.

In case of impossibility to reach an agreement, the Executive Coordinators will submit the issue to the Coordinating Committee and the latter will state the decision by writing.

The Executive Coordinators will participate in the meetings organized by the Superior Council and the Executive Council of Inova-USP.
Inova-USP is the "Innovation Center of University of São Paulo", linked to the Dean's office, gathering 4 platforms, including the "Pasteur – USP Scientific Platform". It will be administrated by its Executive Council, following the direction given by its Superior Council, both created by USP resolution n°7338 of May 12th, 2017.

III. The **Scientific Advisory Board** of the **PASTEUR-USP SCIENTIFIC PLATFORM** will meet every 24 (twenty-four) months and whenever requested by the Chairman of the Coordinating Committee.

Meetings will be called by email or fax at least 48 hours in advance. Meeting may be held in person, by visio conference or by call conference.

The **Scientific Advisory Board** of the **PASTEUR-USP SCIENTIFIC PLATFORM** will produce minutes of each of its meetings and make them available to the Coordinating Committee.

**Article 5. Confidentiality**

The **PARTIES** undertake to ensure that the information of any kind and on any support exchanged, acquired or shared in connection with any activity performed under this Framework agreement and the subsequent Specific Collaboration Agreements (hereinafter referred to as the "Confidential Information"):

a) is kept strictly confidential and is protected to the same extent as their own confidential information;

b) is only provided to their staff members requiring knowledge thereof and is only used in application of this Framework agreement, for its duration.

c) is not used for any other purpose than the performance of this Framework agreement and the subsequent Specific Collaboration Agreements, in particular, for any industrial or commercial purpose or for regulatory or patent filing purposes, or for initiation or pursuit of any proceeding to challenge the patentability, validity, or enforceability of any patent application or issued patent (or any portion thereof) that is owned or controlled by the disclosing **PARTY** (including e.g. via pre-issuance submissions, post grant review, or inter parts review).

d) is not disclosed partly or totally to any third party without the written prior consent of the disclosing **PARTY**.

Any and all other communication or use of the Confidential Information is subject to the prior and written authorization of the communicating **PARTY**.

Each **PARTY** undertakes to ensure that its personnel comply with the provisions of this Framework agreement.

Notwithstanding the previous provisions, each **PARTY** may disclose Confidential Information for which it is able to prove:

- that it was in the public domain prior to its communication or subsequent thereto, but without any breach being attributable to it;
- that it was received legally from a third party non bound by a non-disclosure agreement;
- that it was already in its possession prior to the execution of the Framework agreement;
- that it was developed independently and in good faith by its personnel who did not have access to said Confidential Information.

Moreover, these provisions may not preclude:

- either the obligation for all personnel involved in the activities to provide an activity report to its institution, such communication not representing disclosure within the meaning of intellectual property rules;
- or the defense of a thesis related to the activities of this Framework agreement, such defense being held in camera whenever necessary so as to guarantee, in compliance with effective university regulations, the confidentiality of certain results of the works carried-out.

Nothing herein shall prevent a receiving **PARTY** from disclosing other **PARTY**'s Confidential Information to the extent and for the purpose required by court order or other governmental authority with jurisdiction, provided the receiving **PARTY** promptly informs the disclosing **PARTY** of such obligation and comply, at the disclosing **PARTY**'s written request, with the disclosing **PARTY**'s requirements to prevent or limit the scope of the required disclosure.

Nothing in this Framework agreement will affect the ownership rights of the Confidential Information. This Framework agreement does not transfer to the receiving **PARTY** any license or other right to use the Confidential Information other than for the purpose of the performance of this Framework agreement,

and does not obligate the disclosing Party to provide any such rights in the future.

The rights and obligations arising out of his Article 5 shall remain valid for the duration of the Frameworkagreement and for an additional period of five (5) years following itsexpiration or termination for any reason whatsoever.

**Article 6. Communication**

All public communications regarding the Framework agreement are to be made in common between the **PARTIES**. Any proposed public communication to be made individually by either **PARTY** will be subject to prior review by the other **PARTIES** for 10 working days. The **PARTIES** undertake in any event to mention the other **PARTIES'** involvement, to refer to and include that other **PARTIES'** distinctive signs (name, brand, and logo) in compliance with the latter's graphic charters.

Each Specific Collaboration Agreement will, in addition, specify its rules for communications and publications.

Except as expressly stated in the Framework Agreement, all **PARTIES** hereto will refrain from making any references to the cooperation relationship between them without prior review, as well as using in any other manner the other **PARTIES'** name, acronym, emblem, brand, logo and/or trademarks, without the owner's written permission.

Each **PARTY** commits not to harm the other **PARTIES'** reputation, renown, image, name or trademarks.

**Article 7. Intellectual Property Rights**

**7.1 Own Knowledge**

For the purpose of this Framework agreement, "Own Knowledge" shall mean any result, data, database, information, know-how, discovery, invention, method, process, software, whichever their nature, their format or their support, including the Material (defined in Article 2.4 a)) and Confidential Information, owned or controlled by a **SCIENTIFIC PARTNER** prior to the Effective Date of this Framework agreement or developed by a **SCIENTIFIC PARTNER** outside the scope of the Framework Agreement.

The Own Knowledge relevant for the performance of each Specific Collaboration Agreement which is owned by each **SCIENTIFIC PARTNER** or licensed to such **SCIENTIFIC PARTNER**, with due rights to sub-license, at the date of signature of each Specific Collaboration Agreement, shall be listed in said agreement. Each **SCIENTIFIC PARTNER** retains ownership of its Own Knowledge. Said **SCIENTIFIC PARTNER** remains free to protect and exploit its Own Knowledge, included outside the present Framework agreement and the Specific Collaboration Agreements unless they specify the contrary.

Unless otherwise stipulated in the Framework agreement or in the Specific Cooperation Agreements, nothing in said agreements shall be interpreted as granting to a **SCIENTIFIC PARTNER** any right or license on the other **SCIENTIFIC PARTNER**'s Own Knowledge.

Notwithstanding the above, as far as necessary for the performance of the Framework agreement and the Specific Collaboration Agreements, each **SCIENTIFIC PARTNER** grants to the other a non-exclusive non-sub-licensable and non-transferable license under its Own Knowledge to be listed in each Specific Collaboration Agreement, for the sole performance of the said Specific Collaboration Agreement. Upon completion of the scientific activities or upon termination or expiration of the Specific Collaboration Agreement, whichever occurs earlier, such license shall automatically terminate.

**7.2. Results**

For the purpose of this Framework agreement and the subsequent Specific Collaboration Agreements, "Results" shall mean all results, whether patentable or not, patented or not, which are obtained pursuant to the present Framework agreement and the subsequent Specific Collaboration Agreements, including but not limited to reports, experimental data, information, inventions, discoveries, methods, process, materials, database, software and software extensions, and know-how. The Results shall be the joint property of the **SCIENTIFIC PARTNERS** (hereinafter the "**Co-Owners**"), possibly with the third parties when such participate to the activities, on a pro rata basis in proportion of their respective inventive or intellectual contributions.

Each **SCIENTIFIC PARTNER** shall be in charge of the remuneration of its own inventors according to the applicable laws and regulations.

Each **SCIENTIFIC PARTNER** shall notify to the other **SCIENTIFIC PARTNER** any Result, within one (1) month of said Result's issuance ("Notification").

Each **SCIENTIFIC PARTNER** is entitled to use, free-of-charge, the Results for the sole purposes of its internal research activities and for research collaboration with academic third parties, provided that it informs the other **SCIENTIFIC PARTNER** prior to any such collaboration and that the terms of the collaboration do not jeopardize the **SCIENTIFIC PARTNER**'s rights and the potential to negotiate exploitation agreements.
The **SCIENTIFIC PARTNERS** shall not make any other direct and/or indirect use of the Results, including for commercial purposes.

A co-ownership agreement on the Results ("**Co-ownership agreement**") shall be executed between the **SCIENTIFIC PARTNERS** within one (1) month of Notification, and in any case prior to any industrial or commercial exploitation of said Results. Such Co-ownership agreement shall detail the rules relating to the protection and exploitation of the Results by the **SCIENTIFIC PARTNERS**, in accordance with the provisions of this Framework agreement and the Specific Collaboration Agreements.

### *7.2.1. Patentable Results*

The Co-ownership agreement will specify the **SCIENTIFIC PARTNER** to be in charge of the protection and the exploitation of the Results on behalf of both **SCIENTIFIC PARTNER**S, as well as of any legal proceeding related to the patents on the Results (the "**Administrator**").

### *7.2.2. Exploitation of the Results for commercial purposes*

The Administrator will receive in the Co-ownership agreement an express mandate from the other Co-Owner, to carry-out all commercial exploitation-related work and sign on behalf of both Co-Owners all confidentiality agreements, material transfer agreements, patent and/or know-how and/or software licenses, license option agreements and term sheets.

## Article 8. Publications

The scientific publications of the Results shall take place according to common practice in the scientific community and the following rules. None of the **SCIENTIFIC PARTNERS** may disclose any Results unless such publication is jointly authored by both **SCIENTIFIC PARTNERS**.

The publications originating from the activities carried-out under the present Framework agreement and the Specific Collaboration Agreements within the **PASTEUR-USP SCIENTIFIC PLATFORM** shall mention the relation of the **SCIENTIFIC PARTNERS.** They shall include the words ***"Research conducted within the context of the PASTEUR-USP SCIENTIFIC PLATFORM in Sao Paolo, Brazil"...."*** and mention the contribution of each **SCIENTIFIC PARTNER**.

A draft manuscript of any and all publication or other public disclosure to be made by a **SCIENTIFIC PARTNER** of the work that has been carried-out under the present Framework agreement or the subsequent Specific Collaboration Agreements within the **PASTEUR-USP SCIENTIFIC PLATFORM** shall be provided to the other **SCIENTIFIC PARTNER** for review, and shall be held strictly confidential by the reviewing **SCIENTIFIC PARTNER**. Within thirty (30) days of receipt the reviewing **SCIENTIFIC PARTNER** will inform the submitting **SCIENTIFIC PARTNER** if such manuscript contains its Confidential Information, identifying where such Confidential Information appears and requesting its removal. If such timely request is made in writing, the submitting **SCIENTIFIC PARTNER** will remove such Confidential Information of the other **SCIENTIFIC PARTNER** before submitting such manuscript for publication or other public disclosure.

In addition, the reviewing **SCIENTIFIC PARTNER** within the same aforementioned thirty (30) days may request a delay in publication or public presentation of such manuscript for a maximum of sixty (60) additional days in order that a patent application(s) on an invention disclosed therein may be filed.

**Article 9. Liability**

In no event shall either **PARTY** be liable for breach by the other **PARTIES** of any applicable laws and regulations.

Each **PARTY** shall be liable for any damage and loss caused by it to another **PARTY**'s property, owing to, or during the performance of Framework agreement and the subsequent Specific Collaboration Agreements.

Each **PARTY** shall bear all the financial consequences of the civil liability that it incurs under law, owing to any and all bodily injury or physical damage such **PARTY** causes to third parties during the activities performed pursuant to this Framework agreement and the subsequent Specific Collaboration Agreements.

Each **PARTY** shall be liable of its personnel in accordance with applicable laws and regulations in respect of social security, accident and disease schemes to which it is affiliated, and shall carry out the associated formalities.

Each **PARTY** shall always act in harmony with the national and international provisions adopted in connection with biomedical research, if any.

**Article 10. Insurance**

Each **PARTY** undertakes to take all measures necessary to ensure the coverage of its responsibility.

**INSTITUT PASTEUR** represents it has subscribed and will maintain all necessary insurance, including a professional liability insurance, covering adequately its potential contractual liability and its obligations under this Framework Agreement.

**FUSP** represents it has subscribed and will maintain all necessary insurance, including a professional liability insurance, covering adequately its potential contractual liability and its obligations under this Framework Agreement.

As a public entity, **USP** shall keep the consequences of its responsibility

**Article 11. Independent Contractors**

The **PARTIES** hereto are independent contractors. They shall not be deemed to be agents, employer-employee, partners or joint ventures of the other for any purpose as a result of this Framework agreement and the subsequent Specific Collaboration Agreements or of the transactions contemplated thereby. The **PARTIES** shall not be entitled to act or to make legally binding declarations on behalf of any other **PARTY**. Nothing in this Framework agreement and the subsequent Specific Collaboration Agreements shall be deemed to constitute a joint venture, agency, partnership, interest grouping or any other kind of formal business grouping or entity between the **PARTIES.**

**Article 12. Solving disputes and court**

12.1. The **PARTIES** will consult each other in the event of any difference in interpretation of this Framework agreement and the subsequent Specific Collaboration Agreements, in accordance with the principle of good faith and in a friendly manner. The Coordinating Committee is the principal forum where the **PARTIES** may discuss any difficulties and any unsolved by the Coordinating Committee issues shall be submitted to the Directors of the **PARTIES** for common decision and amicable settlement.

12.2. In case the attempt for amicable settlement between the **PARTIES** fails, the Public Treasury Court of the Capital State of São Paulo is chosen to solve any insurmountable disputes that may have arisen during the performance and interpretation of this Framework agreement

**Article 13- Coordinating the Framework agreement / Contact persons**

13.1. The President of Institut Pasteur, the Dean of USP, and the Chairman of FUSP will designate one (1) person each for monitoring activities related to this Framework agreement.

**Article 14. Effective Date, Duration and Termination**

**14.1.** This Framework a agreement will come into effect on July 1st, 2017 and will remain in force for a period of 5 (five) years.

**14.2.** This Framework agreement shall be terminated automatically and without notice if the premises of the **USP** described in ANNEXE II are not available for proper implementation of the Framework agreement activities, by the 30th of June, 2018.

**14.3.** During the whole term of the Framework agreement, it may be amended upon written consent by all **PARTIES**.

**14.4.** This Framework agreement may be terminated in the event that one **PARTY** commits any breach of its obligations under this Framework agreement and fails to remedy within a period of thirty (30) days after receipt of a notification sent to it by one of the other **PARTIES** by registered letter setting out the breach.
The serving **PARTY** shall then have the right to terminate this Framework agreement without prejudice to any other rights and indemnifications.

The defaulting **PARTY** undertakes to provide immediately after the termination and free of charge the other **PARTY/IES** with all the information required to continue with the implementation of the ongoing activities. Similarly, the defaulting **PARTY** undertakes not to enforce its intellectual property rights against the other **PARTY/IES** for pursuit of the activities and undertakes to grant, without prejudice to third-party rights, a royalty-free license for the use of its Own Knowledge.

The defaulting **PARTY** no longer acquires any right with regard to the Results as from the effective date of termination.

The defaulting **PARTY** shall personally arrange for any repayment of a subsidy or an advance claimed by any funding partner.

The exercising of this termination right shall not discharge the defaulting **PARTY** from complying with its contractual obligations until the effective termination date of the Framework agreement vis—à-vis to it and is subject to settlement of any damage/loss that may be suffered by the other **PARTY/IES** owing to the partial termination of the Framework agreement.

Notwithstanding the previous provisions, the defaulting **PARTY** for this Framework agreement remains responsible for the proper achievement of the activities already started with its participation, notably in the framework of any subsequent Specific Collaboration Agreements.

**14.5.** The end of this Framework agreement (except for the reason explained in article 14.3) does not automatically terminate the ongoing Scientific Collaboration Agreements. Such Scientific Collaboration Agreements shall specify their own reasons for termination.

**Article 15. Document format**

15.1. This Agreement is drawn up in three original copies, in Portuguese, in English and in French, and all versions are authenticated.

15.2. Any eventual discrepancies between versions will be solved in good faith between the **PARTIES**.

São Paulo / Paris

| **São Paulo University - USP** | **Institut Pasteur** | **São Paulo University Support Foundation - FUSP** |
|---|---|---|
| **Marco Antonio Zago** | **Christian Bréchot** | **Antonio Vargas de Oliveira Figueira** |
| Dean | President | Chairman |

Bystander:

**Oswaldo Cruz Foundation**

**Nisia Trindade Lima**
President

**Annex I** – WORK SCHEDULE – An Integrative approach to tackle major communicable and non-communicable diseases of regional or global impact

**Annex II** – PLANS AND DETAILS of the USP premises dedicated to the **PASTEUR-USP SCIENTIFIC PLATFORM**

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**ANNEX I - WORK SCHEDULE**

# An Integrative approach to tackle major communicable and non-communicable diseases of regional or global impact

Brazil is the most prominent of the tropical nations[1]. With 6 ecosystems (Cerrado, Caatinga, Amazon Forest, Atlantic Forest, Pampa and Coastal), Brazil 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 neglected tropical diseases (NTD), such as Dengue, Chagas disease, 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.

Although NTDs severely impact Brazil's public health, more than 80% of the disease burden is due to chronic, non-communicable diseases (NCD), at present the major health priority problem in the country. Brazilian population is aging faster and the figures forecast 32 million people with more than 60 years old by 2025. As ~50% of elderly population in Brazil reports more than one chronic disease (diabetes, hypertension and other chronic respiratory and cardiovascular diseases, as well as neurologic syndromes and neuropsychiatric disordes associated or not to infectious processes). Unfavorable changes of diet and physical activity call for new actions and health policies to control NCD. In addition, there is a growing and urgent need for innovative therapeutic and prophylactic approaches that could help people affected by these illnesses.

The **"USP/FIOCRUZ/PASTEUR"** partnership can provide a real contribution to the advancement of knowledge on both communicable and non-communicable diseases, particularly because of the high scientific impact of its researchers in complementary disciplines. Integrative approaches to different disciplines are a hallmark of high quality science. Furthermore, complex diseases demand studies that are multidisciplinary, and rely in both state-of-the-art and traditional technologies to move the frontier of knowledge forward. Using this mind frame, the overall goals of the scientific cooperation among the Fiocruz Foundation (FIOCRUZ), the University of Sao Paulo (USP) and the Institut Pasteur (PASTEUR) is to contribute to the development of a scientific network in biological, biomedical and biotechnological research, at national, regional and international levels. The consolidation of this network will strengthen the institutional framework within which research and translational research are performed in Brazil and France, as well as other countries where Institut Pasteur is implanted (IPIN Network). Additionally, the proximity of the Amazonian forest as a potential source of emerging pathogens makes Brazil the perfect place to launch an original

collaborative approach to tackle these issues in an integrative framework that takes into consideration both the biodiversity dimension, the microbiome and the associated biotechnology and innovation. In a context of radical and rapid environmental, technological, economic and cultural changes, the Institut Pasteur Brazil (IPB) will have 3 main program priorities (Vector-borne infectious diseases, Neurosciences, and Translational medicine), with 2 transversal methodologies (system biology and population biology). The figure below shows how these approaches will be integrated into the "One Health" concept.


## 1. Infectious Diseases that Greatly Impact Population Health:

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 Chagas, Leishmaniasis, Malaria and several emergent arbovirus diseases (Dengue, Zika, Chikingunya, West Nile, Yellow Fever, Oropouche, Mayaro). Dengue virus alone, which is transmitted by the *Aedes aegypti* 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. 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 the dengue mosquito, which is growing exponentially despite all the efforts made in recent decades to control it by conventional methods. USP, Fiocruz and Butantan Institute 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 under experimental conditions.

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 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 partners - 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 us 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.

## 2. Neurosciences

The new Institut Pasteur Brazil (IPB) will be committed in elaborating advanced projects on neurosciences 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 conditions. Bacteria from the skin and the gut modulate the immune system, and have been described as playing an important role in autoimmune diseases. 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?

Also, a large numbers of unrelated viruses (cytomegalovirus, lymphocytic choriomeningitis virus, Borna, Zika, etc) and parasites (Plasmodium, Trypanosomes, etc) can cause serious abnormalities and brain dysfunctions. The immune response to viruses is complex and deserves interest, but 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: (1) the impact of brain viral infections on major neurological diseases, mental illnesses and lytic effect of brain cells; (2) the breakdown of blood brain barrier by viruses and parasite infections; and (3) the relationship between the immune responses triggered by infectious processes and brain damage.

One of our goals is to contribute to novel and specific diagnostics and treatments for the early development of progressive pathologies, such as Multiple Sclerosis, Parkinson's and Alzheimer's diseases. 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.

The USP has created a "hub" Support for Applied Neurosciences (NAPNA) in 2011 to integrate different research USP laboratories dedicated to the study of brain mechanisms leading to psychiatric and neurological disorders and the development of new therapies. Also, several CEPIDS, (Centers for Research, Innovation and Diffusion of the Sao Paulo state), were created and funded by USP and FAPESP. One of these "USP centers" is on neuromathematics. Important collaborations can be fostered between the Institut Pasteur, USP, Fiocruz and those recent centers, especially in

relation with preventive and diagnostic strategies, contributing to a better understanding of brain functions.

### 3. Translational medicine

The implementation of technological platforms can effectively do a scientific cross talk between complementary disciplines. IPB 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.

One IPB proposal related to translational medicine will count on the development of an automated screening platform of the partnership Institute of Biomedical Sciences/USP and 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 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.

IPB partners want to develop further translational research on emergent and reemergent diseases and can count on high-standing group of Hospitals of the Faculty of Medicine-USP, and particularly the Heart Institute (INCor) facilities [2].

### 4. Systems 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, IPB 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/PASTEUR". The recently created International Network for Data Analysis (INDA) at the Institut Pasteur may boost international cooperation for big data handling with the Brazilian partners. The partnership may count with the Institut Mines Telecom, from the Ministry of Industry, on shared educational systems.

## 5. Population biology

Epidemiology has been defined as 'the science concerned with the study of the factors determining and influencing the frequency and distribution of disease, injury, and other health-related events and their causes in a defined human population (http://medical-dictionary.thefreedictionary.com/epidemiology). In other words, the classical definition of epidemiology emphasizes the causes, frequency and distribution of diseases. Although modern textbooks have already included a new dimension in the definition of epidemiology – time, it is in the field of infectious disease that the time dimension is particularly important. As mentioned in the previous section, infections are complex dynamical phenomena and as such change with time. This time dimension should be emphasized in an alternative definition of infectious diseases epidemiology by including the term 'dynamics'. Hence, epidemiology of infectious diseases would be the science concerned with the study of the causes, frequency, distribution and dynamics of infections in a defined population. Said that, we can attempt a definition of Mathematical Epidemiology: *the study of the causes, frequency, distribution and dynamics of infections in a given population that incorporates concepts from theoretical ecology and evolutionary biology, tools from mathematics, statistics and computational sciences.*

It is imperative to emphasize that this quantitative approach to the dynamics of infectious diseases aims the solution of practical problems related to those diseases. It should, therefore, be seen as an 'engineering' approach in the sense that predicting tools are indispensable because what we call 'solution' of infectious disease problems means control; to control, in turn, we need to understand, describe and predict what will be the temporal course of a given outbreak with and without control measures.

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 is focused on noncommunicable diseases (NCD) and new actions have been settled centered on health diets, physical activity and reduction of alcohol taking and smoking. Regular screening for cervical and breast cancer after 40 years and biennial mammography between 50 and 70 for instance have allowed a prompt adapted treatment after diagnosis. Such legislative and regulatory initiatives may contribute to respond to the challenge represented by chronic diseases. However, a continued increase in mental and behavioral disorders, obesity, cardiovascular and chronic respiratory diseases, cancers and diabetes has shown that those initiatives are not sufficiently strong.

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).

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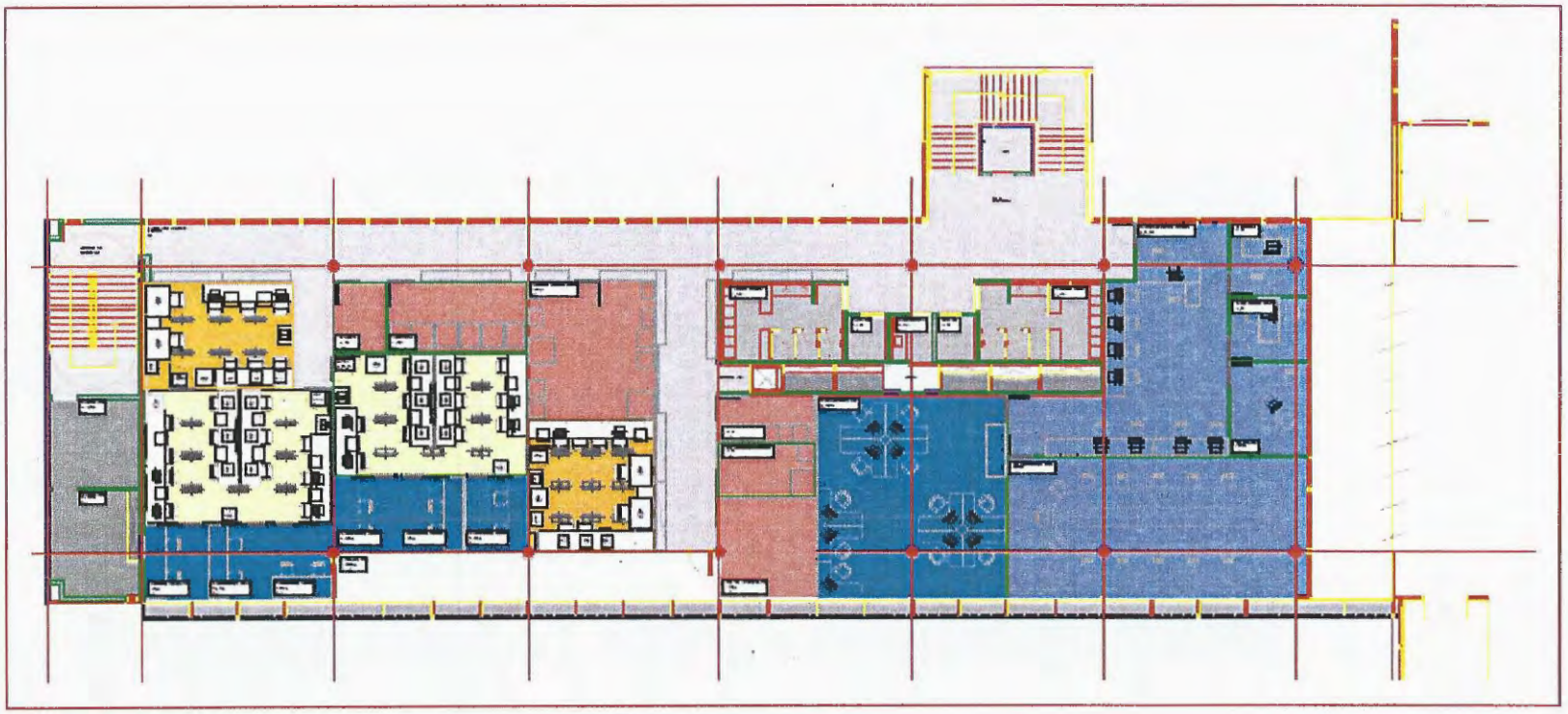

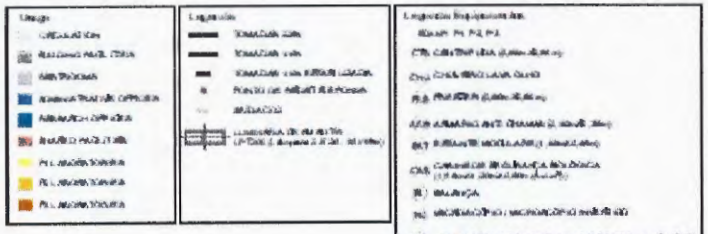

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