Creation of a joint research center on immunology of chronic viral infections and autoimmune diseases

Inserm, Paris-Sud University and CEA have ratified the creation (1st of January, 2015) of a joint research center focusing on the immunology of chronic viral infections and autoimmune diseases: « ImVA ». This center bring together more than 100 scientists working on common scientific challenges relating to innate and adaptive immunity in the context of the onset and regulation of autoimmune disorders, together with viral dissemination, reservoirs and sanctuaries.

ImVA (U1184) is unique in bringing together clinicians with expertise in immunopathology/virology involved in the coordination of large cohorts of patients and therapeutic programs and nonclinical scientists working on experimental models, including non-human primates (NHPs).

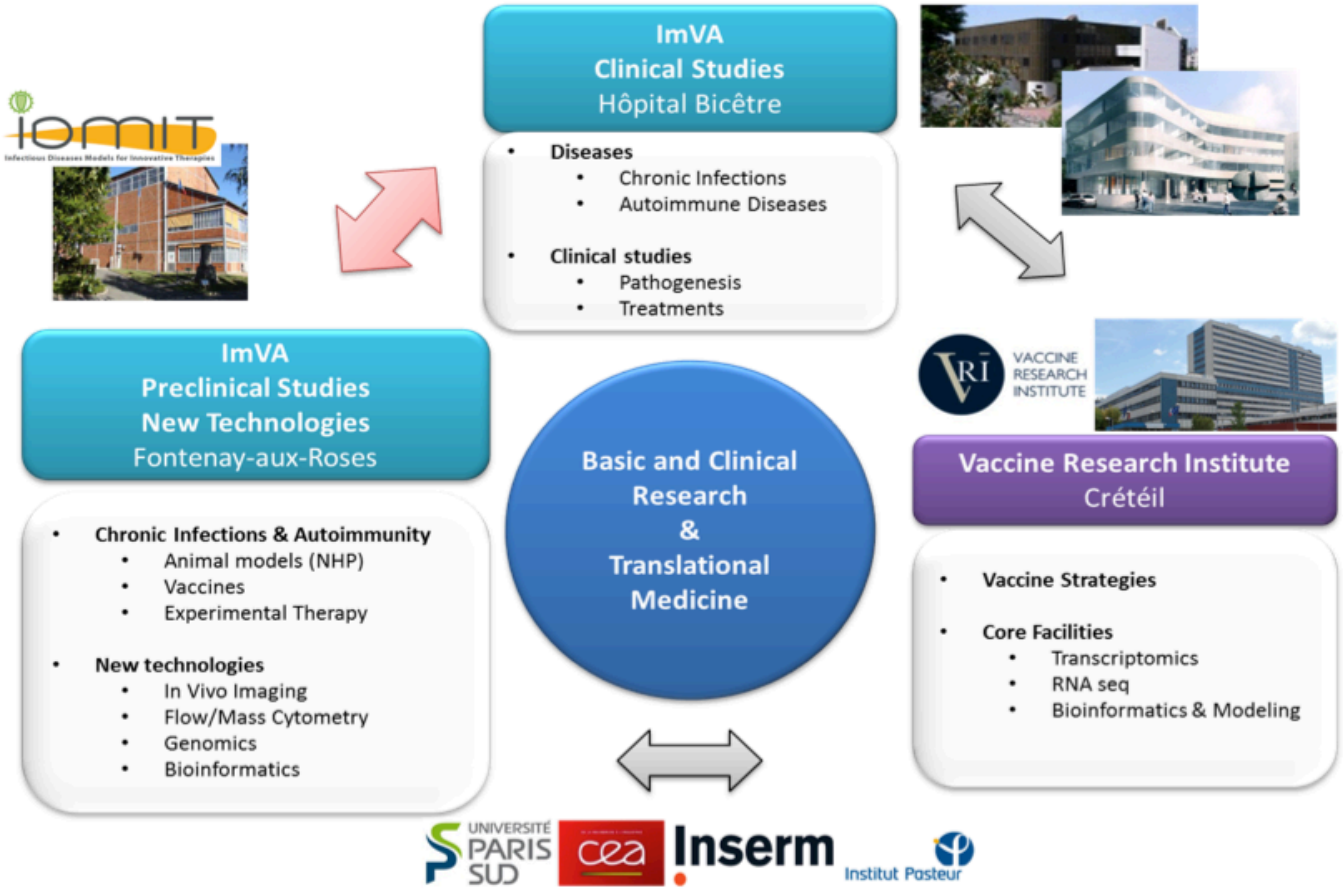
Research programs are supported by outstanding core facilities, advanced technologies for *in vivo* imaging, pharmacology, and the assessment of immune responses and treatments, and by established biobanks from cohorts of patients with chronic viral infections and autoimmune diseases.

ImVA is benefiting from the nearby structures, such as the national infrastructure “IDMIT”, constructed as part of the French “Programme Investissements d’Avenir” and “Grand Emprunt” programs and from already established partnerships.

All facilities are located in close proximity, on the Fontenay-aux-Roses CEA site and at Bicêtre Hospital campus. Our strategy, based on interdisciplinary approaches, should accelerate the transfer of discoveries into clinical practice and should be highly attractive to young investigators and students.

ImVA: environment

The overseeing organizations supporting ImVA, are Paris-Sud University (P-SUD) and two major national research agencies, INSERM (Bicêtre Hospital/Unit 1012) and the CEA-Fontenay-aux-Roses (UMR E1 CEA-P-SUD). The Center benefits of strong partnership with international organizations, in particular with the Institut Pasteur (Paris) and the Vaccine Research Institute (Créteil). Our strategy, based on interdisciplinary and complementary approaches together with new and outstanding core facilities (IDMIT), aims at accelerating the transfer of discoveries into clinical practice.



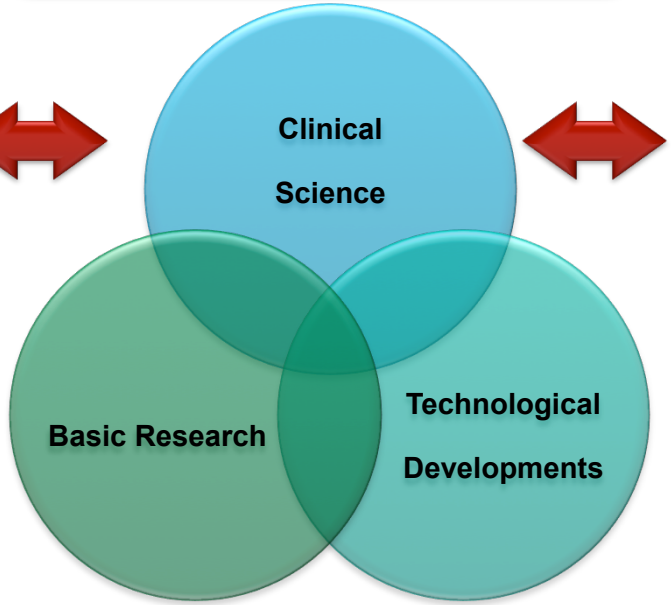
ImVA: integration and complementarity

Research Labs

- **Research Teams**
- **Campus Bicêtre**
  - 800 m2
  - BSL1/BSL2
- **CEA-FAR**
  - 1500 m2
  - BSL2/BSL30

Clinical & Preclinical Research

- **Biobanks**
  - Cohorts of patients
  - Clinical trials
- **Animal models**
  - Non-human primates
  - Mouse



Core Labs

- ***In vivo* imaging**
  NIR-Fluo
  Endo-microscopy
  Two-photon mic.
  PET-CT
- **CyTof**
- **Cytometry**
- **Immuno-virology**
- **Genomics (PCR)**
- **Biological Resource Center**
- **Bioinformatics**

ImVA: a joint preclinical to clinical research center

INSERM Unit 1012
Bicêtre hospital
Pr. Marc Tardieu

- Immunology/virology
  - Primary HIV infection
  - Control of viral replication and reservoirs
- Basic & translational science
- Strong clinical interface
  - Medical science
  - Cohort studies
  - Multicenter clinical trials
  - Epidemiology

- Multidisciplinary technical expertise
  - Molecular & cellular genetics
  - Mouse models

UMR E1 CEA-PSUD
CEA-FAR
Dr. Roger Le Grand

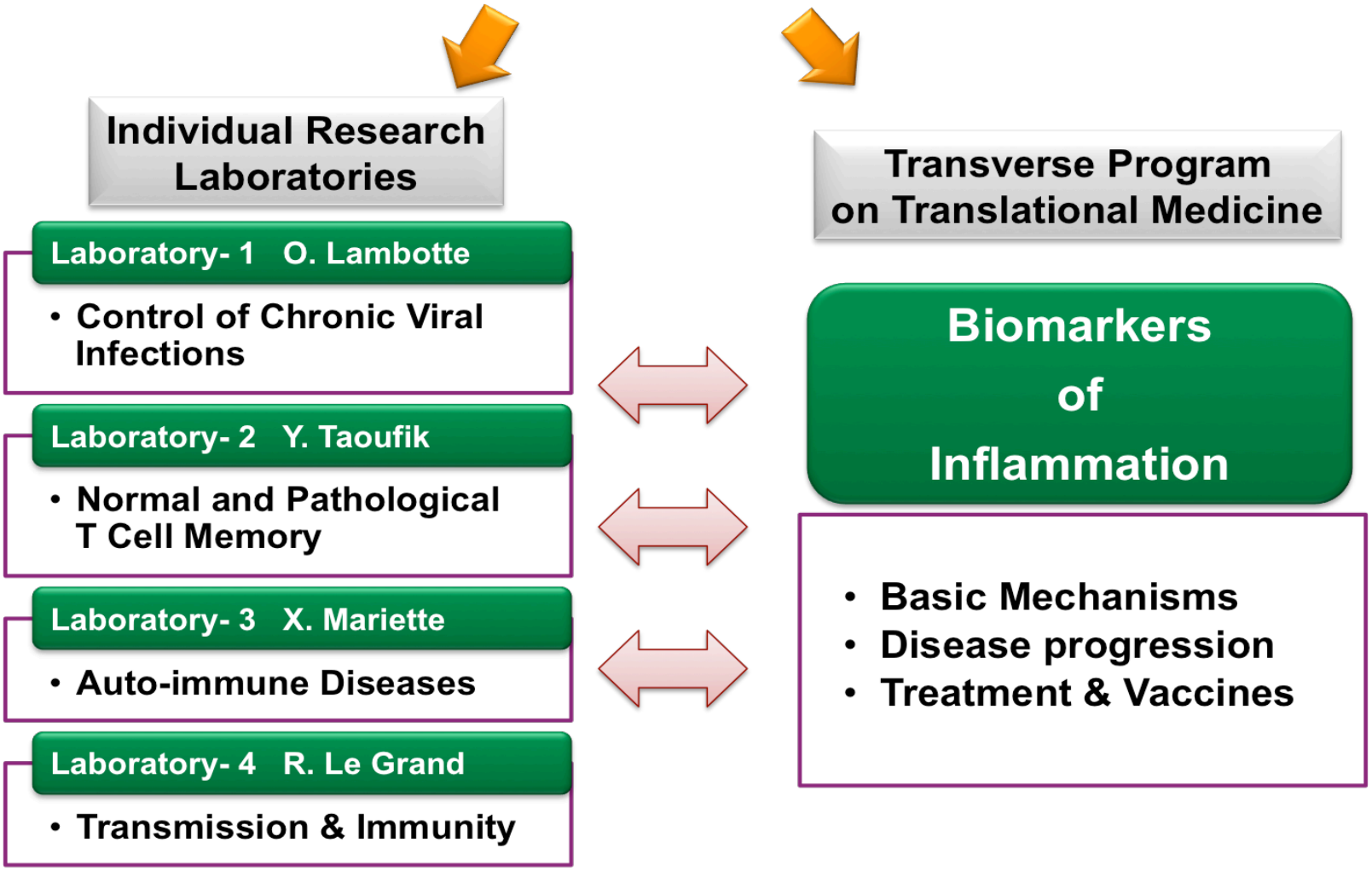
- Immunology/virology
  - Primary HIV infection
  - Control of viral replication and reservoirs
- Basic & translational science
- Strong preclinical expertise
  - Non-human primate modes

- Technological developments
  - Multi-parameter phenotyping (CyTof)
  - In vivo imaging

ImVA: overall strategy

The overall strategy of the ImVA involves two principal approaches:

1) the promotion of highly competitive research programs within four individual teams,
2) the development of a transverse program of research involving the different research teams and core facilities and concerning translational medicine (see below).



ImVA: research laboratories

Laboratory-1: Directed by Pr. Olivier Lambotte, this team focuses on the “Control of chronic viral infections” and the mechanisms involved. Early control of SIV is studied in the macaque model, focusing on the role of innate immunity (dendritic cells and interferons). The team is studying the mechanisms of viral persistence in reservoirs in chronic HIV/SIV infection, focusing on the role of fat tissues as a reservoir, and on the links between the reservoirs and HIV-specific CD8 and CD4 T-cell responses. It studies HIV-1-infected patients in different clinical situations, focusing in particular on HIV controllers and the macaque HIV/AIDS model.

Laboratory-2: Directed by Dr. Yassine Taoufik, this team uses mouse models to study the mechanisms by which CD8 memory precursors are generated and mature into highly functional memory T-cell subsets, including tissue-resident memory cells, together with the long-term maintenance of these subsets. This team is particularly interested in studying the CD4 helper signals sequentially provided by the various CD4 T-cell subsets throughout the process of memory CD8 T-cell differentiation. Studies in mouse models are complemented by translational programs in humans, focusing on the mechanisms underlying defects in the generation and maintenance of CD8 T-cell memory in chronic human viral infections and their relationship to viral persistence (HIV, EBV, JC virus).

Laboratory-3: Directed by Pr. Xavier Mariette, this team studies new mechanisms involved in the pathogenesis of autoimmune diseases, such as primary Sjögren’s syndrome (pSS), rheumatoid arthritis (RA) and autoimmune demyelinating diseases. In particular, they investigate the role of NK cells and B-cell activation in pSS and RA, focusing in particular on genetic and epigenetic regulation. Studies are performed in mouse models, to elucidate the mechanisms of lymphomagenesis in autoimmunity, potentially providing insight into the pathogenesis of individual diseases. Finally, new, highly original NHP models of RA (based on immunization with citrullinated peptides) and of demyelinating diseases are established.

Laboratory-4: Directed by Dr. Roger Le Grand, this team focuses on antiviral immunity, with the specific aim of identifying correlates of protection, which are important for prevention strategies, such as vaccination in particular. Studies on the generation of durable and oriented adaptive responses by vaccination are undertaken, together with studies deciphering transmission events in viral infections. The team aims to identify and to characterize molecular and cellular immune mechanisms at the local level and in the periphery, following exposure to vaccines and in virulent challenge models.

ImVA: transverse program on translational medicine

The general objective is to study and compare inflammation pathways in different immune-pathologic conditions. The ultimate goal is to improve immune-pathological knowledge and to provide new scientific rationales for the prevention and treatment of chronic viral infections and autoimmune diseases. Particular attention is paid to new immune intervention strategies, including vaccines and biological agents (therapeutic antibodies and derived molecules).

Scientific objectives of the translational program

AIM-1: Molecular and cellular mechanisms underlying the generation and regulation of immune memory and tolerance. We hypothesize that innate responses and inflammatory disorders have a significant effect on the induction and regulation of adaptive host responses, particularly through the orientation, amplification and durability of specific immune memory. Exacerbated responses or persistent inflammation in chronic diseases may significantly affect the capacity of the host to fight infections or cancer cells or may impair immune tolerance in autoimmune diseases. An understanding of these mechanisms is critical to the development of a new scientific rationale for innovation in the domain of vaccines and immunotherapy. The experimental approach will be based mostly on the use of *in vitro* models, including primary cells from patients, and on animal studies (mouse model of the generation and regulation of the T-cell response, NHP models of HIV/AIDS or NHP models for experimentally induced arthritis and encephalitis).

ImVA: transverse program on translational medicine

AIM-2: Comparison of the impact of inflammation on immune effectors in chronic viral infections and autoimmune diseases. We further explore the impact of inflammation on memory T-cell responses and on the B-cell and NK-cell subsets, in both chronic infection and autoimmune disorders, through the use of animal models and studies in humans based on the use of biobanks from national and international patient cohorts. The aim is to characterize disease-specific and common inflammatory processes, with a view to identifying new biomarkers for diagnosis and the monitoring of disease progression. In addition to classical assays for immune function assessment, we use advanced “omics” technologies developed by the center and its collaborators (genomics, epigenetics, transcriptomics and single-cell proteomics with CyTof). Data are integrated and analysed, with the use of new bioinformatics (such as the home-developed LIMS “BatLab”) and mathematical approaches for the modelling of interactions between inflammatory/innate responses and immune memory, specific effectors and immune tolerance.

AIM-3: Identifying biomarkers of the safety and efficacy of treatments modulating inflammation in chronic viral infections and autoimmune diseases. Our final aim is to develop new approaches to the fine-tuning of innate and adaptive immune responses and treatment of inflammation-related disorders in chronic diseases. As for AIM-2, we make use of “omics” technologies, data integration and interaction modelling:

(1) in various animal models for immune intervention strategies (anti-inflammatory biological agents, active therapeutic immunization);

(2) in patients suffering from chronic infections or autoimmune diseases, with various treatments based on biological agents (therapeutic antibodies and derived compounds) or therapeutic vaccines.

Data are analysed as a “matrix”, with the cross-comparison of measurements obtained in different therapeutic situations and diseases, so as to differentiate between common and treatment-specific biomarkers. We expect i) to refine therapeutic strategies, improving their safety (limiting the off-target effects of drugs) and efficacy (focusing the drug on the target effects), ii) to identify new targets for therapeutic interventions. The programs developed as part of AIM-1 are essential to link the biomarkers identified with the associated cellular and molecular mechanisms.

ImVA: transverse program on advanced technologies

Translational program on advanced technologies

The objective of this program is to develop new technologies for monitoring infections and immune interventions. Scientists from the center in charge of core facilities will lead programs dedicated to the development of new technologies and tools (instruments, markers, tracers and methods) for:

i) complex cell phenotyping by advanced cytometry approaches, such as mass cytometry (CyTof),
ii) *in vivo* imaging of immune functions and pathogen dissemination (near-infrared fluorescence, two-photon *in vivo* microscopy, PET-CT),
iii) computer science and mathematical methods for data integration and interaction modelling.

Studies in animal models will facilitate these developments, particularly for new probes and tracers for *in vivo* imaging.

ImVA aims to ensure that these new technologies are transferred into the clinic in the short to medium term, for the monitoring of infections and autoimmune disease progression and for assessing treatment efficacy and safety.