Pasteur Institute of shanghai

- ## Founders
  - Chinese Academy of Sciences
  - Shanghai Municipal Government
  - Institute Pasteur
- ## Mission
  - Research into benefits for public health in China and the Asian region.
  - IPS scientists are engaged in **infectious disease research** programs ranging from **viral hepatitis, HIV, respiratory infections to virus-induced cancers**.
  - Goal is develop product candidates in the field of **diagnostics, vaccines and therapeutics** to following challenges:
    - Hand, Foot and Mouth Disease is on the rise in China.
    - HIV/AIDS and related tumors
    - Acute Respiratory Infections (ARI, influenza, SARS)
    - Viral hepatitis
    - Talent Recruitment and Education
    - Domestic and International Cooperation
      - important role Pasteur Institutes in the Asia-Pacific region by participating in network's programs:
        - the research-driven **Response to Acute Respiratory Infections** (RESPARI) program
        - The **Surveillance and Investigation of Epidemic** Situations in Southeast Asia (SISEA) program, which is concerned with **emerging diseases**.
      - IPS-CAS and the Institute Pasteur of Cambodia collaborated to identify the **human Enterovirus 71 (EV71) strain** responsible for an outbreak of hand, foot and mouth disease in Cambodia in 2012.

- ## Board of Directors
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- ## Research focuses
  - **HIV/AIDS and HIV related tumors**
    - Developing an innovative approach to prevent **HIV infection**, including novel immunogen design and membrane bound antibody strategy.
    - Another studies the oncogenesis mediated by **Kaposi's sarcoma** associated herpesvirus

  - **Acute respiratory infections**
    - understand the mechanism of **SARS-Coronavirus** and **avian influenza virus** pathogenesis
    - develop reliable molecular diagnostics, recombinant technology for **vaccines** against avian flu
    - treatments based on immunotherapy or issued form the traditional Chinese medicine

  - **Viral hepatitis**
    - Understand the biology of hepatitis viral infection,
    - virus host interactions
    - **carcinogenesis** at the molecular level
    - To develop **new vaccine and therapeutic** strategies.

  - **Encephalitis**
    - Understand pathogenesis of encephalitis
    - develop second generation of **vaccines**
    - Molecular diagnostics are developed to clarify virus etiology in encephalitis
    - To **monitor West Nile virus** introduction and circulation.

- ## Research units
  - **Anti-infection research** (**Ralf Altmeyer**)
    - Interests on: Virus-host interactions, molecular mechanisms of disease particular focus on pediatric infectious diseases like **EV71 and RSV**.
    - current project:
      - 1- **Anti-EV71 and anti-RSV drug discovery**.
        - Developing inhibitors of EV71 and RSV by screening compound libraries and studying the mode of action of those inhibitors.
      - 2- **Epidemiology of EV71**.

        - Collaboration with Children's Hospital of Fudan University and Institut Pasteur Cambodia, isolating and characterizing enterovirus from clinical samples collected both in Shanghai and Cambodia.

Molecular virology (Bing SUN)

1. Focusing on functions and mechanisms of structural or non-structural **viral proteins** and the anti-viral activity of some key host factors during infection.
2. Use **influenza A virus and HCV as viral models** to study the viral-host interplay
3. Use **coronavirus and EV71 as viral models** to study the viral ion channels and the contribution of channel activity to virus release
4. Viral ion channels and viral polymerase are selected as the **drug targets to screen anti-viral drugs**.

- current project:
    - Part 1 : Host **innate immunity** and virus infection
        - Regulation of inflammasome and inflammation response by viral proteins
        - Host restriction gene in innate immunity to counteract HCV infection
        - Type I IFN signal pathway and DC/macrophage response in infection
    - Part 2 Interplay of **influenza A virus** and the host systems
        - Host and viral SUMOylation in influenza A infection
        - Arrest of host cell cycle by influenza A virus
        - Contribution of polymerase to influenza A pathogenicity and anti-polymerase activity drug screen
        - Development of efficient influenza vaccines
    - Part 3 Study on viral ion-channel proteins
        - Homologous viral ion-channel proteins in coronavirus
        - Viral ion-channel proteins in other important pathogens

Antiviral immunity and genetic therapy (Paul ZHOU)

- Objective 1: Develop membrane-bound antibody-based strategy for anti-viral therapy and prevention
- Objective 2: Develop influenza HA and NA pseudo type-based neutralization assay
- Objective 3: Lentivirus like particle (LVLP)-based immunogens against HIV and HPAI H5N1 viruses

Tumor virology (Ke LAN)

- explore the molecular mechanisms and epidemiology of human **cancers** mediated by **tumor viruses** in China
    - Focuses on **hepatitis viruses and human gamma herpesviruses**.

Viral hepatitis (Jin ZHONG)

- Study biology of **HCV infection** and virus-host interactions at the molecular and cellular levels.

- projects include:
    - Study the functional roles of virus-encoded proteins and host factors in the processes of HCV replication and assembly
    - Study how HCV infection induces and evades host innate immune responses
    - Develop **HCV vaccine**.

Immune regulation (Qibin LENG)

- Understanding both molecular regulation of **T cell response and immunopathogenesis** of viral infections.
- Current research directions:
    - Immune pathogenesis of hand, foot and mouth disease.
    - Antigen recognition of anti-tumor T cells and immunotherapy against cancers.
    - Molecular regulation of CD8 T cell response.

Structural virology (Rong CHEN)

- Particularly Enterovirus 71, respiratory syncytial virus and hepatitis C virus, associated with hand-foot-and-mouth disease, respiratory tract disease and viral hepatitis.
- X-ray **crystallography**, **cryo-electron microscopy** and computer **image processing**, as well as molecular virology and **vaccine** study.
- Research objective is to elucidate the molecular and structural basis of viral pathogenesis and to develop effective therapeutics against these viral diseases.
- research directions:
    - Obtain **three-dimensional models** of macromolecular complexes.
    - Identify **key host factors during EV71 replication**
    - Develop **novel therapeutics** against viral diseases.

Vaccinology and antiviral strategies (Zhong HUANG)

- Developing **vaccines and antiviral drugs** for enterovirus 71 (EV71), coxsackievirus A16 (CVA16), hepatitis C virus (HCV), and HIV.
- Currently **creating virus-like particle (VLP)-based novel recombinant vaccines**.
- research themes:
    - Design, expression, and preclinical testing of chimeric virus-like particles (VLPs) as vaccines and delivery vehicles for therapeutic molecules;
    - Investigation of the mechanisms of VLP uptake, processing and presentation by the immune system;
    - Investigation of **mucosal immunization** and **mucosal adjuvants**;
    - Production of **recombinant vaccines**, **antibodies** and **microbicides** using **plant-based** expression systems.

○ Molecular immunology (Bin LI)

- Elucidate the cellular and molecular mechanisms regulating the immune response in health and disease including infectious diseases, autoimmune diseases and cancer.
    - Understanding the dynamic role of one subpopulation of T cells, (CD4+CD25+FOXP3+ regulatory T cells) (**FOXP3+Tregs**), in major human infectious diseases.
    - Understanding the regulation of FOXP3 and the dynamic ensemble of FOXP3 with enzymatic cofactors in Tregs will provide **therapeutic applications** for major human viral infectious diseases including HIV, hepatitis B and C viruses.
- following projects:
    - To identify the binding partners, upstream regulators and downstream effectors of FOXP3 and analyze their function in modulating Treg activity in infectious diseases;
    - To study signal-dependent spatial and temporal regulation of FOXP3 level, activity and ensemble during infectious processes;
    - To examine activity-dependent post-translational modifications of FOXP3 and the functional consequences in response to various viral infection.

○ Hematopoietic stem cell and transgenic animal model (Yan ZHANG)

- Epigenetic regulation of normal and malignant **hematopoiesis**.
    - Work on Understanding the roles of the other members of Trithorax group protein, in both the normal and malignant hematopoiesis by using transgenic or knockout approaches.
- Epigenetic regulation of lineage commitment and differentiation in the immune system.
    - Exploring the potential roles of histone modifying enzymes in the lineage commitment and differentiation of immune cells, by using gene-targeted mouse models.
- Mouse chromosome engineering for modeling human cancer.
    - Generating model the human cancer diseases in mouse with Cre-LoxP based techniques
- **Humanized Mouse Models** for Studying Human Infectious Diseases and Cancer.
    - Using a combination of nuclease gene-knockout and transgenic approaches to generate immunocompromised mice bearing a mutated IL-2 receptor gamma chain (IL-2rγ) and several human cytokines transgenes.

○ Viral immunology (Jianhua WANG)

- focus on the interactions of HIV-1-host cells and viral pathogenesis:
    - HIV-1 mucosal infections and host cell-mediated viral dissemination
    - Contribution of dendritic cells immunal activation viral pathogenesis during co-infections of HIV-1.
    - To explore the host factors that could restrict HIV-1 replication in monocytes cells.

○ Innate Immunity (Guangxun MENG)

- To understand the function of innate immunity especially **inflammasome** in inflammatory diseases.
    - Regulatory mechanism of inflammasome activation
    - Function of inflammasome in the control of microbial infection
        - Explore the function of NLRP3 inflamamsome in anti-viral and fungal infections.
    - Function of **NLRs in autoimmune diseases and cancer**
    - Pharmacological regulation of inflammasome activity
    - Inflammasome based adjuvant development

Immune Signaling and Regulation (Hui XIAO)

- To uncovering the molecular mechanisms by which TLRs recognize pathogen, initiate inflammation and tailor adaptive immune response, thereby provide novel insights into **development of new vaccines and treatment** of virus-induced chronic inflammation and cancer.
- lines of studies:
    - Decipher the **signaling pathways by which TLRs regulate the expression of proinflammatory genes**, providing new insights into constrain of inflammatory conditions.
    - Identify the mechanisms by which TLRs cross-talk with NLRs and RLRs in pathogen recognition exploring novel **vaccination strategies**.
    - Determine the molecular mechanisms by which **inflammation promotes tumorigenesis**, validating **animal models** for the screening and **test of anti-cancer drugs**.

Anti-infection immunity and vaccine research (Dongming Zhou)

- The goal of our laboratory is to **generate various chimpanzee adenoviruses as vaccine vectors**,
- Set up a platform for **vaccine** development based on **recombinant adenovirus**.
    - develop novel universal vaccine to influenza
    - new HIV vaccine
    - vaccines against foot-and-mouse disease virus and other infectious diseases or cancer,

Respiratory Infection and Histopathology (Xiao Su)

- study how vagus nerve-α7 nAChR pathway regulates the host inflammatory response to bacterial or viral lung infection
- investigate how pathway affects anti-inflammatory memory of macrophages during infection and inflammation,
- Test whether and how activation of this pathway could regulate function of proinflammatory cells and stem cells and determine outcome of acute lung infection and immunity.

Innate Defense and Immune Modulation (Xiaoming Zhang)

- Novel innate regulatory mechanisms in **anti-Mycobacterial** immunity
    - innate immune responses to Mycobacteria and identify IL-10-producing regulatory cells and other potential regulatory cells
    - Try to elucidate the roles of regulatory cells during the course of TB disease and to develop potential intervention strategies.
- Human regulatory B cells and their roles in infectious diseases
- Development of **novel therapeutic vaccines**
    - Develop the strategies to target antigen to specific DC subsets and break the immune tolerance
    - Interested to develop **attenuated Salmonella-based recombinant therapeutic vaccines**.

○ Herpesvirus and molecular virology research (Zhikang Qian)

- Understand the virus-host interactions during **cytomegalovirus (CMV) infection** for identify novel therapeutic targets, and develop effective **vaccine vectors**.
- projects :
    - Elucidate the role of the unfolded protein response in cytomegalovirus infection
    - Define how HCMV inhibits cellular DNA synthesis and regulates cell cycle progression to facilitate viral replication
    - **Develop a high throughput RNAi and small molecule screening** platform for target identification and drug discovery.

○ Viral Disease and vaccine Translational Research unit (Xia Jin)

1. Bioinformatics design and experimental testing of a **subunit HIV vaccine** comprised of multiple T helper cell epitopes;
2. Dissecting **role of each domain of dengue viral envelop** protein at the induction of immune responses.
3. Bioinformatics design and experimental testing of a **single dengue vaccine** capable of eliciting tetravalent neutralization antibodies against multiple dengue virus serotypes;
4. Comprehensive **mapping of T-cell epitopes in HCV infected** patients with/without spontaneous viral clearance.

○ Pathogen-host interaction and Epigenetics (Lubin Jiang)

- Aims to elucidate the molecular mechanisms and biological consequences of epigenetic and genetic factors of pathogen and host interaction in major infectious diseases caused by such as HIV, TB, and Plasmodium falciparum, with the long-term **view toward the design of novel drugs, vaccines and diagnosis.**

- **Virus-associated lymphomagenesis (Xiaozhen Liang)**
  - The main focus in to study **viral pathogenesis in B-cell lymphoma** development
    - By utilizing a **novel viral transformation system** of fetal liver-derived B-cells (FLC) with murine gamma herpesvirus 68 (MHV68) infection,

- **Virus assembly and host dependency (Gang Long)**
  - Major interest is to study the mechanism underlying interactions between **HCV and host Apo lipoproteins**.

- **Pathogenic fungal infection and host immunity (Changbin Chen)**
  - Dissect molecular mechanisms of **virulence and commensalism during C. albicans infection**, and understand how host immune systems act during transitions from being a commensal to being a pathogen.
  - Current research:
    - Role of a unique iron regulatory circuit in C. albicans commensalism and virulence.
    - Functional analyses of determinants important for C. albicans commensalism.
    - Interaction between C. albicans and host immunity.

- **The regulation of Immune cell differentiation unit()**
  - To understand transcriptional regulation in the development and function of Follicular Helper T (TFH) cells and B cells for facilitate new **vaccine development**, meanwhile offering new strategies for the treatment of infectious diseases such as HIV and influenza.

- **Interspecies transmission of arboviruses and Therapeutics research (Dimitri LAVILLETTE)**
  - Project wants to unveil the viral and/or host factors responsible for pathogenicity or resistance to infection.
  - Using different **model alphaviruses and Dengue** virus, to explore
    - the host factors involved in entry, interspecies transmission and host susceptibility
    - The role of cell response in virus replication and the spreading of viruses in vivo in mosquitoes.

- **National Science and Technology Key Projects on "Major Infectious Diseases such as HIV/AIDS, Viral Hepatitis Prevention and Treatment"**

- 1: The Establishment of **Detection Platform for Viral Infection and Immune Response** in the Respiratory System and the Central Nerve System
- 2: Studies of **biology of difficult-to-treat hepatitis C and development of novel strategies for its treatment**

Key Laboratory of Molecular Virology and Immunology

- focuses on:
  - research of virology and immunology against various **outbreaks and emerging infectious** diseases
  - provides original work to contribute to early diagnosis and novel vaccines
  - Endeavor's to establish core technique platform for research translation.
- Main research focuses including
  - research in virology and molecular mechanism of **acute or chronic viral infectious** diseases
  - Understanding of mechanism of immune response to viral infection and the regulation for virus replication caused by antiviral host molecular
  - Cross-disciplines study of virology and immunology, to provide new strategies and foundation for novel vaccine development

International partnership

- **Li Ka-Shing Foundation**
  - The Li Ka Shing Foundation (LKSF) supports IPS in and the Asian-Pacific network of Institute Pasteur for research and training on emerging and re-emerging viral diseases.
    - Collaborating understand the mechanism of **SARS-Coronavirus** and **avian influenza virus** pathogenesis.
    - They develop reliable molecular diagnostics, recombinant technology for vaccines against avian flu, and treatments based on immunotherapy or issued form the Traditional Chinese Medicine.
- **AREVA**Partnership on control of viral emerging infectious diseases. The partnership enables IPS to reinforce its activities in areas such as: High-level scientific training,Supporting young scientists, Personnel information and risk prevention,Basic AIDS research, allowing AREVA to strengthen its commitment to fight the HIV/AIDS pandemic**TOTAL**
  - Partnership aimed at **reinforcing viral hepatitis prevention programs** in China
    - fundamental and applied research, training, and educational activities on viral hepatitis for prevention of the disease in China
- **Air Liquide**
  - Partnership to advance research on the identification and prevention of respiratory infections

- Development of a system for monitoring and preventing epidemics in cooperation with the Chinese public health authorities.

International collaboration projects

RESPARI

- IPS participated in the RESPARI project (www.hku.hk/respari) collaborated by Pasteur Institutes located in Asia-Pacific region.
    - support from international community, French Ministry of Health and Solidarity, French Agency for Development, Li Ka-Shing Foundation

- **SISEA**
    - IPS participates in the SISEA project (Surveillance and Investigation of Epidemic Situations in Southeast Asia), which is funded by the French Agency of Development. IPS is engaged with its partners in Cambodia, Laos and Vietnam in researches and training to reinforce diagnostics. **EU 6th framework**Researchers from IPS participate to two European research projects on avian flu: FLUINNATE (www.fluinnate-project.eu) RIVERS (www.rivers-project.eu).