Hellenic Pasteur Institute (HPI)

Chairman: Antonios Antoniadis, Professor of Microbiology, Aristotle University of Thessaloniki

Establishment in 1920. Prevention and treatment of Diseases through Basic **Research**, **Education** and **Public Health Services**.

- The traditional focus of the Institute has been on Infectious Diseases.
- Currently other diseases such as autoimmune, neurodegenerative, neuromuscular, neuroimmune and cancers are study.

HPI today

Research in Infectiology: hepatitis C virus (HCV), *Leishmania* and *Trypanosoma brucei* (*T. brucei*), gram-negative bacteria such as *enterobacteria*, non-fermentive bacilli, *Neisseria gonorrhea, Helicobacter pylori* and *Chlamydia*.

Studies in Immunology: better understand basic mechanisms of innate and adaptive immunity and of immune-mediated disease pathogenesis.

The **Neuroscience and Neuroimmunology Laboratories**: study of neuromuscular function and neuroimmune interactions, stem cell biology and directed differentiation, the processes of neurodegeneration.

National Reference Centers (NRCs):

- National Influenza Laboratory of Southern Greece
- National Polio-enteroviruses Laboratory
- National Measles and Rubella Reference Laboratory, all three recognized by the WHO
- National Reference Centre for Leishmaniosis
- Reference Centre for Neisseria *gonorrhea*.

Public Health services: well organized Diagnostic Centre specializing in rapid diagnosis of bacterial, viral and parasitic diseases.

Production Unit for Vaccines: provides vaccines for Public Sector and assessment control on vaccines and other biological product.

The Technological Facilities: the transgenic technology and the Microsurgery and Transplantation, Light microscopy Unit and the Flow cytometry unit.

The patent portofolio of the Institute is increasing, several R&D projects are running and some home-made diagnostic products have entered the Diagnostic Services of HPI while others are being negotiated for further development by the industry.

Public Health

- response to detect and isolate pathogens which poses a specific threat to Public Health, by causing outbreaks, epidemics and/or pandemics,
- Assist the Ministry of Health and Social Solidarity policy with the surveillance, prevention and control of infectious diseases.

1- National Reference Laboratories for Infectious Diseases - Director: A.F. Mentis, MD mentis@mail.pasteur.gr

NATIONAL INFLUENZA REFERENCE LABORATORY FOR SOUTHERN GREECE (NILSG)

- The NILSG is part of the WHO worldwide influenza surveillance network.
- Detection, isolation, characterization and typing of influenza viruses from clinical samples.
- The laboratory has participated in the Quality Assurance programs proficiency of the laboratory in detecting, isolating and typing influenza viruses is assessed.

1-1 Entérovirus / Polioviruses (National Poliovirus Laboratoire) -

- Responsible for the virological confirmation of the eradication of poliomyelitis in Greece.
- Participating in the proficiency testing and laboratory accreditation organized annually by WHO.

Services

- Poliovirus isolation and characterization from cases of acute flaccid paralysis.
- Enterovirus isolation and characterization form clinical specimens.
- Enterovirus detection by WHO proposed methodology and by molecular methods.
- Isolation and characterization of enteroviruses from environmental samples.

1-2 Reference Center for Leishmaniosis - Head: Eleni Dotsika, Veterinarian, e.dotsika@mail.pasteur.gr

- Center is the study of visceral leishmaniosis (Kala-Azar).
- Serological examination of patients and dogs suspected for leishmaniosis
- Detection of the parasite in blood or biopsy specimens and classification of species and subspecies
- Keeping record of the incidents, conduction of epidemiological surveys and notification the Mediterranean Zoonosis Control Center
- Mass production and distribution of reagents used in the detection of the parasite.
- Development and implementation of new technology. In particular, development of novel markers/molecules for the amelioration of diagnostic tests in human and animal hosts and the genotypic classification of species and subspecies.

1-3 National Measles and Rubella Laboratory of Greece

- Provide laboratory confirmation of initial measles cases and to isolate and characterize circulating measles viruses during outbreaks.
- It also provides diagnostic support for rubella.
- Measles and rubella serology. Diagnosis of rubella congenital infections in pregnant women. Isolation, genotype characterization and molecular methods for the detection of measles and rubella viruses

2- Vaccines department - Head of the Unit: M. Stratigakis, Chemist.

- The product that is bottled in the Unit is the tetanus vaccine.
- The packaged products include: tuberculin, BCG vaccine, anti-snake venom serum, flu vaccine, DT and tetanus adult vaccine, measles vaccine, rubella vaccine, meningococcal A/C/Y/W-135 vaccine, pneumococcal vaccine, typhus vaccine, cholera vaccine, yellow fever vaccine, polio vaccine, rabies vaccine and tetravac (diphtheria, tetanus, pertussis, poliomyelitis) vaccine

3- Diagnostic service department - Head of the Unit: Dr A. Mentis, MD, PhD, E-mail: mentis@mail.pasteur.gr

- The interest diagnosis of infectious diseases caused by bacteria, viruses or parasites.
- The methods used include serological tests of detection and/or isolation of pathogenic factors.
    - The method of **rapid detection of Herpes** and the **diagnosis of myasthenia gravis**.

Number of services:

1. Quality control of foods and waters for tourist resorts.
2. Controls of anti-microbial action for disinfectant products.
3. Determination of anti-microbial action for new products.
4. Sterility control for industrial products.
5. Quality and anti-microbial control of mobile waste units.

Research

1- Department of medical biochemistry

1-1 Laboratory of Immunology – Head**:** Lymberi Peggy, Research Director E-mail: plymberi@pasteur.gr

- Autoimmunity is the main research field.
  - Study the role of natural autoantibodies of human or animal origin in the homeostasis of the immune system, and relationship with pathology.
  - Investigate the properties and biological role of natural antibodies of IgG class which are able to penetrate into living cells to be used as therapeutic molecules for intracellular intervention.

We aim to:

- develop animal models for Graves' disease
- identify the T-cell epitopes of thyroglobulin and use them for the development of animal models for Hashimoto's thyroiditis
- identify B-cell epitopes of thyroglobulin in order to use for the early diagnosis of thyroid autoimmune diseases
- Development of new immunological products (reagents and immunoassays).
  - Product includes: **anti-isotypic antibodies** and respective **enzyme conjugates**, **immunodiagnostic assays**.

Projects

1- Thyroid Autoimmunity
   - Animal model of Graves' disease
   - B-cell epitopes of Tg and Serology of AITD
   - Effect of non-enzymic glycation on the immunogenicity of Tg and on the development of EAT
   - T-cell epitopes of Tg and Animal model of Hashimoto's thyroiditis

Collaborations**:**

- Dr E. Vlassara (Division of Experimental Diabetes and Aging, Dept. of Geriatrics, Mt Sinai School of Medicine, New York), Prof G. Carayanniotis (Endocrinology Dept., Medical School of St John's University, Newfoundland)

2- Natural autoantibodies able to penetrate into living cells (polyreactive cell penetrating antibodies: **pcPAbs**)
   - Biochemical and immunological properties and cell-penetration characteristics of pcPAbs
   - Therapeutic exploitation of pcPAbs
   - Isolation of pcPAbs from healthy animals and humans

Collaborations**:**

- Dr L. Mouthon (Service de Medicine Interne, Hospital Cochin, Paris) Dr K. Terashima (Pathology Dept., Medical School, University of Tokyo)

1-2 Laboratory of Cellular and Molecular Neurobiology – Head: Rebecca Matsas, PhD-Research Director

Email: rmatsa@pasteur.gr

a) Understanding the genetic, cellular and molecular basis of neuronal birth, migration and differentiation

b) Investigating neuron-glial interactions and myelination

c) Translating our findings into regenerative therapeutic strategies for repair of the injured or diseased nervous system.

- Initiated a study on the derivation of **induced pluripotent stem (iPS) cells** from adult differentiated skin cells.
- Investigate mechanisms of **cell reprogramming and the directed differentiation of iPS** cells towards neuronal populations.

Research programs:

1. Genes inducing cell cycle exit and differentiation of neural stem cells
2. Genetically modified neural stem cells and myelinating cells for the treatment of neurodegenerative diseases and nervous system injury.
3. Generation of a repertoire of stem cell-derived human neurons for **Regenerative Medicine**

1-3 Cellular and Molecular Oncology - Head: Prof. Evangelia Patsavoudi Email: epatsavoudi@teiath.gr

Focused on the biology of molecular chaperones and in particular on the study of the heat shock protein 90 (HSP90).

HSP90 inhibitors cause the destabilization and eventual degradation of HSP90 proteins. Moreover these inhibitors have shown promising **anti-tumor activity** in model systems.

- Produced a monoclonal antibody named **mAb 4C5** which specifically recognizes HSP90.

Research activities are focused:

1. Study and understanding of the mechanisms underlying the function of surface HSP90 using *in vitro* and *in vivo* models of tumor growth

2. Investigation of the possibility of using mAb 4C5 as a therapeutic agent for the treatment of metastatic cancer

3. Study of HSP90 in Cancer Stem Cells and investigation of the possibility to use mAb4C5 as a marker for these cells and ultimately as a therapeutic agent

4. Epitope mapping of mAb4C5 and humanized ch4C5**.**

1-4 Laboratory of Molecular Biology & Immunobiotechnology - Head: Dr. Avgi Mamalaki Email: amamalaki@pasteur.gr

- Goal is exploitation of experimental findings that will be used for development of novel diagnostic and therapeutic approaches.
    - The development of new biotechnological drugs (production of recombinant biomolecules) of known and novel molecular targets,
    - Functional studies of molecular targets and biomolecules for the diagnosis and the therapeutic applications

The main achievements of the laboratory include the:

- Production of rodent recombinant antibody fragments of monoclonal antibodies
- Production of human recombinant antibody fragments
- In vitro affinity maturation of human antibody fragments,
- Production of recombinant proteins or peptides in heterologous expression systems (bacteria, yeast, protozoa)

The current research:

a) New research activity:

1. Cancer Immunotherapy and HER-2/neu. A combined approach of genes, proteins and drugs

2. Immunodiagnosis and Immunotherapy of Metabolic Disease, concerning Hepcidin.

b) On-going research activity:

- Immunotherapy of Autoimmune Diseases – Myasthenia Gravis

1-5 Laboratory of Molecular Neurobiology & Immunology - Head: Prof. Socrates Tzartos, Email: tzartos@upatras.gr

1. Study of the structure and function of nicotinic acetylcholine receptors (AChRs) which implicated in several severe neurological diseases.
2. **Study of myasthenia gravis (MG),** which is usually caused by anti-AChR autoantibodies, and the development of a specific therapy for this disease.
3. Investigation of the pathogenic role MuSK and aquaporin-4, in the autoimmune neurological diseases MG and neuromyelitis optica (NMO).
4. Very sensitive immunochemical diagnosis for three autoimmune neurological diseases (MG, NMO and LEMS).
5. Services to the scientific community and support to the Greek MG Association.

PATENTS

- Production of recombinant fragments of muscle acetylcholine receptor and their use for ex vivo immune adsorption of anti-ACh receptor antibodies from myasthenic patients. Greek and European patent.

2- Department of Microbiology

2-1 Laboratory of Bacteriology - Head: Dr. Eva Tzelepi, tzelepi@pasteur.gr

Analysis of the mechanisms supporting the development and spread of bacterial resistance and also the surveillance of resistance.

1- Bacterial Resistance to Antibiotics
    - Focused mainly on mechanisms of resistance to the newer β-lactam antibiotics in gram-negative bacilli.
        - Biochemical characterization of resistance.
        - Genetic characterization of resistance.
        - Molecular epidemiology for investigating factors affecting dissemination of resistance among nosocomial pathogens.
2- *Neisseria gonorrhea* – Epidemiology and Antibiotic Resistance
    - Epidemiological surveillance of gonorrhea through demographic and disease markers and microbiological markers, such as types and antibiotic resistance profiles of N. gonorrhoeae strains circulating in community.

2-2 Laboratory of Medical Microbiology - Andreas Mentis, Director of Research, mentis@pasteur.gr

Mainly on mechanisms human gastric bacteria *Helicobacter pylori***,** etiologic factor for the development of chronic gastritis and gastric or duodenal ulcer and a major risk factor for the development of gastric adenocarcinoma.

- Study on a cellular and molecular level of mechanisms relating to induction of inflammation and progression to carcinogenesis in the gastric epithelium following chronic infection with *H. pylori.*

Topics under consideration include:

- The correlation *H. pylori* virulence factors to the clinical and histological condition in symptomatic carriers of the infection.
- The pathogenic role of the *H. pylori* CagA virulence factor in the deregulation of intracellular cell signaling.
- Induction of pro-inflammatory chemokine signaling in the early stages of *H. pylori*
- Anti-inflammatory activity of probiotic lactobacilli on H. pylori-induced gastritis
- Maintenance of *H. pylori* Bio bank which includes clinical isolates and the associated biopsies, from symptomatic patients.

Public Health Services:

- Participate in the laboratory surveillance of *H. pylori* antibiotic susceptibility. Our laboratory is the sole National Reference Center for *H. pylori* infections in Greece.

Other research collaborations relating to ***H. pylori***

- Assessment of anti-*H. Pylori* and anti-inflammatory activity of new drugs and natural products utilizing the *in vivo* infection model. Collaboration with pharmaceutical companies (Lavipharm)
- Structural analysis of the lipo-polysaccharide (LPS) of *H. pylori* to develop vaccines based on LPS. Collaboration with the Institute for Biological Sciences, National Research Council, Canada)
- Study of the putative immuno-modulating properties of *H. pylori* in the Experimental Autoimmune Encephalitis mouse model. Collaboration with the Medical School of the Aristotelian University of Thessaloniki.

Other scientific and research collaborations

- *Measles and Rubella*: Determination and phylogenetic analysis of measles during the 2005-6 measles epidemic.
- *Enteroviruses*: Laboratory investigation and phylogenetic analysis of enteroviruses involved in an aseptic meningitis outbreak during the summer of 2007.
- *Respiratory viruses, Influenza:* Laboratory surveillance of altered resistance to oseltamivir and/or antigenic virus specificity of emerging new H1N1 strains during the 2009 pandemic of influenza H1N1.

2-3 Laboratory of Cellular Immunology Head: Dotsika Eleni, PhD, e-mail: e.dotsika@mail.pasteur.gr

Analyses the cellular and molecular immune mechanisms concerning the interplay between host cells and Leishmania spp.

Focus on the:

- Role of CD8+ T cells in experimental L. infantum infection
- Impact of L. infantum infection on macrophage function: role of MAP kinases
- DCs and their role in the induction of protective immunity in L. major infection

2-4 Laboratory of Molecular Genetics - Head: Dr Lesley Probert E-mail: lesley@pasteur.gr

Interested in the interactions between immune system and the central nervous system (CNS) to help maintain brain homeostasis.

- Aim to identify key molecules, mechanisms and cells that are involved in mediating inflammatory neurodegeneration in experimental models for **stroke and MS** with the aim of finding new, more selective therapeutic targets and neuroprotection strategies for the treatment of inflammatory CNS disorders.
- Use **transgenic or conditionally gene-targeted mice** for specific genes and cells of interest in combination with pre-clinical models of CNS inflammation and neurodegeneration, mainly the MS models EAE and cuprizone-induced demyelination.
- Development of **DC-targeted peptide vaccines** for immunotherapy in MS
- Preclinical evaluation of DC-targeted peptide vaccines in a humanized MS model: preparation clinical trials in MS patients
- Study of the role of the cell-specific inactivation of NF-κB in **neuronal function and neurodegenerative** diseases
- Study of the role of the cell-specific inactivation of NF-κB during **inflammation and demyelination of neurodegenerative** diseases using transgenic mice
- Study of phenotypic changes in cortical neuron cultures induced by **mesenchymal stem cells** CM during neuroprotection against glutamate-induced cell death

Collaborations:

- José M Delgado- García- Division of Neurosciences, Pablo de Olavide University, Seville, Spain.
- Hans Lassmann- Centre for Brain Research, Division of Neuroimmunology, Medical University of Vienna, Austria.
- Vijay Kuchroo- Brigham and Women's Hospital Ctr for Neurological Diseases, Boston, MA, USA.
- Xavier Navarro – Institute of Neurosciences, Universitat Autonoma de Barcelona, Bellaterra, Spain.
- Ana M Sebastiao – Institute of Pharmacology & Neurosciences, University of Lisbon, Portugal.
- Hartmut Wekerle- Department of Neuroimmunology, Max Planck Institute of Neurobiology, Martinsried, Germany.

2-5 Laboratory of Molecular Virology - Head: Dr. Penelope Mavromara, Email: penelopm@hol.gr,

- Focuses on the molecular and cellular mechanisms that control pathogenesis of HCV infection.
    - Understanding how viral proteins interact with the host cell machinery to modulate virus replication and/or contribute to pathogenesis of HCV infection.
    - use of viral expression systems based on baculovirus, lentivirus and herpes simplex virus for heterologous gene expression, the development of oncolytic viruses and the production of VLPs.

2-6 Intracellular Parasitism group - Head: Dr Haralabia Boleti, hboleti@pasteur.gr,

Studies aspects of the molecular cell biology of *Leishmania donovani,* and of the parasite interaction with the host cell macrophages.

1. Molecular mechanisms of *Leishmania donovani*, phagocytosis in professional phagocytes and the role of putative parasite virulence factors in the maturation and remodeling of the Leishmaniophorous phagosome
2. Structural and functional characterization of specific *L. donovani* phosphatases.

Studies aim to contribute to the understanding of the initial steps of the infection, after the sand fly bite, and the parasite entry by phagocytosis into the phagocytic cells of the host immune system, as well as to the identification of new potential molecular targets for drug development.

3. Evaluation of the *Leishmania tarentolae* LEXSY system as alternative recombinant protein expression system to express mammalian membrane transporters for structural and functional analysis.

2-7 Laboratory of Molecular Parasitology - Head: **Dr. Ketty Soteriadou**, ksoteriadou@pasteur.gr

The main research activity focuses on the study of the protozoan pathogen Leismania and leishmaniosis.

Focus research on:

- Determination of pathogen factors playing a key role in parasite cell cycle and infectivity/pathogenicity
- Identification and study of putative drug targets in trypanosomatidae like GSK-3 and the determination of new molecules with antiparasitic activity.
- Development of molecular methods for the diagnosis and typing of Leishmania species for usage in epidemiological studies.

Education

Workshops in Research and Technology

organized (2004 & 2005) a series of workshops on Light Microscopy and coordinated the activities of the “Greek Light Microscopy network”.