



# Third international biomedical research meetings

10 June 2011

HÔTEL DE MARIGNY, PARIS

## SUMMARY

*Meetings organised by Aviesan (the French National Alliance for Life Sciences and Health) and ARIIS (Alliance for Research and Innovation in the Health Industries)*



**The third edition of the International Biomedical Research Meetings was held on 10 June 2011 at the Hôtel de Marigny, under the esteemed patronage of the President of the French Republic.** Some fifty academic researchers and as many international R&D directors of human and veterinary drug and diagnostic companies convened together under the aegis of Professor Jean-François Delfraissy, Director of the ITMO "Microbiology and infectious diseases" and Director General of the French National Agency for AIDS and Viral Hepatitis Research (ANRS) to discuss the topic of infectious diseases. These meetings were organised by the French National Alliance for Life Sciences and Health (AVIESAN) and the French Alliance for Research and Innovation in Health Industries (ARIIS).

On this occasion, **French President Nicolas Sarkozy** insisted in his speech on the importance he attached to the field of biomedical research and on the value of these meetings. The results of the first two editions (2009 on neurosciences and 2010 on cardiovascular and metabolic diseases) speak volumes:

- ✓ 28 million euros allocated to signed partnerships
- ✓ 150 constructive exchanges
- ✓ 20 contracts currently at highly advanced stages of negotiation.

The President of the Republic stressed the excellence of academic research in France as well as the need for co-operation between academic researchers and industrialists. He then highlighted all the reforms undertaken in order to make joint research programs more attractive. Funds being allocated to higher learning and research have thus risen by a billion euros each year since 2007. Almost 20 billion euros of the 35 billion euros in the "Investments for the Future" program are to be spent on higher learning and research, with projects being selected by international juries on the basis of excellence. In addition, 2.5 billion euros have been specifically earmarked for biotechnologies and the biomedical sector. **The highest level of future investment concerns the fight against infectious diseases**, particularly through the POLMIT IHU [*University Hospital Institute*] of Marseilles for infectious diseases, awarded 72 million euros, and the IRT (Institute of Technological Research) LyonBiotech for infectious diseases, in which the Institut Pasteur is also involved.

Finally, the President of the Republic underlined his unwavering support for the efforts of researchers and industrialists to create high quality therapies. He expressed his wish for the **establishment of a new foundation for scientific research, bringing together research organisations, universities, university hospitals and companies working in the life sciences** to fuse together the most dynamic elements in place of the countless GIS (Scientific Interest Groups) created over the years. He added that a number of major companies have already shown interest.

"Public action in France is expanding. You are most welcome in our country to work and innovate", concluded the President of the Republic"<sup>1</sup>.

---

<sup>1</sup> Video of the President's speech: <http://www.elysee.fr/president/mediatheque/videos/videotheque.10.html>

## **Infectious diseases: a priority for French academic research**

---

With 17 million deaths worldwide due to infectious diseases, it is clear that these diseases pose serious public health problems in all countries, in both North and the South. The Research Minister stressed the importance accorded to research in this domain, particularly within the context of the “Investments for the Future” programme. A total of over 340 million euros will thus be invested in research into infectious diseases during the initial phase of the programme. The budget devoted to this area has risen 65% in 10 years. Many projects have been selected, including:

- ✓ POLMIT in Marseilles, one of 6 University Hospital Institutes selected in France, which will focus particularly on tropical viruses.
- ✓ Hepsys and Lermite, and the Institute of Vaccines Research: three laboratory centres of excellence for the discovery of new vaccines.
- ✓ LyonBiotech, a technological research institute.
- ✓ FlowCyTech, ImaginEx BioMed, F-Crin, FRISBI and HIDDEN: projects focussing on new tools and technologies for the validation of antiviral strategies and the identification of new viruses.
- ✓ IBEID, the Milieu-Intérieur project, programmes for analysis of data concerning emerging infectious diseases.

Research in the field of infectious diseases is highly active in France, with 12% of investment and 18% of publications in biomedical research being devoted to this area, and 35 existing clinical units. It is concentrated mainly in three large regions of France: Paris (Institut Pasteur, Pitié Salpêtrière, Hôpital Bichat), Lyon (Biopole, IRT LyonBiotech) and Marseilles (Infectiopole Sud, POLMIT IHU).

“The re-emergence of diseases previously thought to have been defeated, emerging viruses, multi-resistant bacteria and the transmission of animal pathogens to humans: these subjects are now of greater significance than ever and require a cross-disciplinary approach in terms of research” stressed Jean-François Delfraissy, organiser of the meeting, Director of the ITMO “Microbiology and infectious diseases” and Director General of the ANRS.

### **Aviesan: structuring life sciences research in France**

Created in April 2009 the Alliance for Life Sciences and Health groups together all the life science research units of French institutes (INSERM, CNRS, Institut Pasteur, IRD, INRA, CIRAD, CEA, and the universities). A key mission for Aviesan is to facilitate relations between academic researchers and manufacturers. At the head of each of its 10 theme-based institutes is a director, who serves as a contact for industrialists wishing to work with a laboratory and develop a project in France. “For example, we have opened an epidemiology portal in France, with a catalogue of 237 databanks, including 130 cohort studies and 76 industrial studies”, offers Aviesan President, André Syrota, by way of illustration. The leitmotif is to identify common strategies for working together.

## Understanding host-pathogen interactions

---

*Many research units are currently working on host-pathogen interactions, which mark the start of infection. A number of novel therapeutic approaches could well emerge from the projects presented during this meeting.*

### **Philippe Sansonetti, Paris - From bugs and men to treatments and vaccines**

Through its immune system, the human body must be able to tolerate the microbiota that has colonised various sites within the intestine, and to recognise and eliminate pathogens. What survival strategy is adopted by pathogens at the epithelial surface? How does it interrupt the ensuing immune response? What signals are transmitted? Philippe Sansonetti's team is seeking to identify the molecules involved in these interactions. A large number of molecules are secreted by the epithelium and diffused throughout the body, thus modifying tissue response in the central nervous system, the blood vessels, adipose tissue, the liver and the lymphatic organs. A number of strategies of pathogens have thus been identified, from the suppression of humeral defence signals to blocking of the dynamics and mobility of T-cells, as well as regulation of Type III effectors. These molecules offer targets for the development of new drugs and vaccines.

### **Guillaume Duménil, Paris - Arterial wall colonization by bacteria: a critical stage before chaos**

During infection, pathogenic microorganisms colonise the blood vessels, whether Gram+ bacteria, Gram- bacteria or fungi. Vascular dysfunction is a key step in the triggering of septicaemia. Guillaume Duménil's team have studied the impact of mechanistic forces at work within the bloodstream, as well as the architecture of tissues, the microcirculation and the specificity of infected species. All of these areas represent key challenges in the study of bacteria. The researchers have worked on a meningococcal model of *Neisseria meningitidis* and have shown that interaction with the endothelium is mediated by pili. These pili allow the bacteria to aggregate and adhere to tissue. This interaction comprises three key stages: determination of the adhesion site and attachment, development of strong bonds between bacteria and host cells and proliferation of the bacteria, and finally, detachment and dissemination throughout the body. These three stages may be targeted in the development of therapeutic strategies. Other pathogens must be investigated to determine whether the model developed by the team may also be applied in these cases.

**Yves Gaudin**, Gif-sur-Yvette - Understanding the rhabdovirus fusion machinery: perspectives opened by dynamic structural biology

In the case of rhabdovirus, glycoprotein G serves as a mediator for viral entry. It is vital for membrane fusion, which is achieved through conformational changes. Using somographic methods, Yves Gaudin has studied the crystalline structure of this protein before and after membrane fusion. In this way, he has determined intermediate conformational structures that constitute novel targets for therapy. Structural virology is an area in which French research can claim expertise, with several research groups at the Institut Pasteur, in Grenoble and Marseilles, adopting different approaches and using cutting-edge techniques.

**Marc Lecuit**, Paris - Studying host-pathogen interactions from a clinical perspective

The study of host-pathogen interactions is of central importance for clinical applications. Marc Lecuit is studying the mechanisms used by microorganisms to induce infectious disease by crossing tissue barriers such as the intestinal, placental and blood-brain barriers. He is primarily interested in *Listeria monocytogenes*, the bacteria responsible for listeriosis. He has organised a prospective study of listeriosis in France - the MONALISA project - which comprises a multi-centre observational analysis of all eligible cases in France since 2010.

His aim is to unravel the secret of the specificity of microbial species as well as host specificity. He is studying the molecular factors behind such specificity through analysis of *in vitro* and *in vivo* models. The future prospects of this work include the development of diagnostic tests, biomarkers, and so forth.

Marc Lecuit is also working on infection with the Chikungunya virus and is studying host response to this virus.

**Didier Raoult**, Marseille - Infectious diseases and microbiology: ignorance, speculative deductions and unconfirmed predictions

There is an enormous gap between the number of existing bacteria and the number of bacteria actually identified and studied. This gap in our knowledge means that all our predictive models are in fact false.

One of the aims of POLMIT IHU in Marseilles (infectious and tropical diseases), under the direction of Didier Raoult, is to complete the library of genes of microorganisms found both in healthy individuals and in diseased patients. These libraries can then be compared in order to identify links between microorganisms and diseases.

Increased knowledge in this area is essential for the development of new diagnostic and therapeutic approaches.

## Targeting resistance mechanisms

---

*Understanding resistance mechanisms in order better to circumvent them is a major area of research at a time when the presence of bacteria displaying multi-resistance to antibiotics is apparent throughout the world. A number of approaches were presented.*

### **Ivo Gomperts Boneca**, Paris - Bacterial infectious diseases: the PG perspective

Peptidoglycan (PG) is a key component in the physiology of bacteria and of resistance to antibiotics. It is involved in cellular division and in host-bacteria interactions. Ivo Gomperts Boneca is seeking to understand the structure and assembly mechanisms of PG. What proteins are required for assembly? Disrupting this complex will result in defective assembly. The team has discovered a peptide - SID - which inhibits assembly and thus opens up possibilities for a new therapeutic strategy. A further area of research is to determine how pathogens use PG to develop resistance.

### **Stéphanie Blandin**, Strasbourg - Mosquito resistance to malaria parasites: Genetic intelligence against disease transmission

Malaria affects 250 million people in the world each year and leads to 860,000 deaths. The disease is transmitted by *Anopheles* mosquitoes infected with the parasite *Plasmodium*. Some mosquitoes have been found to be resistant to this parasite and researchers are seeking to understand why. Stéphanie Blandin has attempted to identify the molecules accounting for such resistance by mapping the mosquito genome. In the genetic loci associated with this resistant character, a certain candidate has been identified: protein TEP 1 (thioester-containing protein 1). Certain polymorphisms of TEP 1 confer resistance to parasites by binding to the parasites and promoting their destruction. Other factors contribute to resistance, such as the virulence of the parasite and the environment. These studies may allow the creation of diagnostic tests to identify resistant mosquitoes, or perhaps to devise a strategy to eradicate mosquitoes that are not resistant to the parasite.

### **Eric Oswald**, Toulouse – *Escherichia coli*: the enemy within

*E. coli* is a commensal bacterium that by and large lives without incident in our gastrointestinal tract. However, certain strains are pathogenic and can cause diarrhoea, urinary infections, food poisoning, septicaemia, and so on. This organism is also responsible for 10 to 50% of nosocomial infections. The huge diversity of *E. coli* pathotypes is due to the plasticity of the genome. Only 40% of the bacterial genome is highly conserved between the various strains. The genome of some strains contains a genomic islet containing all of the genes necessary for biosynthesis of a toxin known as colibactin. This toxin causes breakages within the double-stranded DNA of host cells and disrupts the cell cycle. It is a factor for virulence and a promising target for the development of new anti-infective agents.

This factor is also involved in the onset of cancers and induces instability within the genome of host cells, thus promoting the emergence of cancerous cells. A link has been established between colorectal cancer and the presence of colibactin-producing *E. coli*.

**Marie-Cécile Ploy**, Limoges, and **Patrice Nordmann**, Bicêtre - Resistance to antibiotics: emerging threats and new molecular targets

The mechanisms responsible for the acquisition of resistance genes involve genetic structures known as integrons naturally present in bacteria. These organisms, which are particularly mobile, can move from one bacterium to another, causing the spread of resistance genes. If a bacteria is subjected to stress (confrontation with antibiotics), it triggers the SOS system that involves dissemination of resistance genes. One of the key elements in integron mobility is the integrase enzyme, expression of which is repressed by the LexA protein. However, this protein is destroyed during the SOS response and the transfer of resistance genes by integrons is promoted. One way of combating resistance phenomena could involve interfering with the SOS system and avoiding the destruction of LexA protein.

A number of resistance genes have been identified, including NDM-1 (New Delhi metallo-beta-lactamase 1), which is integrated into several types of bacteria. It enables the synthesis of an enzyme that inactivates the majority of antibiotics currently commercially available. The reservoir for this organism is the Indian subcontinent of Pakistan, India and Bangladesh. Several dozen cases have been detected in the UK, due to the privileged ties of the population there with India. In all, a dozen or so NDM-1 hotspots have so far been identified throughout the world. It is necessary to develop new antibiotic molecules to combat these forms of resistance.

**Jean-Michel Pawlotsky**, Paris - Hepatitis C virus: towards eradication of an oncogenic viral agent

Some 130 million individuals throughout the world are infected with the hepatitis C virus and 300,000 die each year. Current treatment is based on the combined use of pegylated interferon-alpha (IFN- $\alpha$ ) and ribavirin.

In order to understand the mechanisms of resistance to treatments, Jean-Michel Pawlotsky's team extracted the virus from the serum of 586 patients included in clinical trials between 2005 and 2010. The viral genome was studied and sequenced (RT-PCR, mPCR and pyrosequencing). The researchers developed software to process and analyse all of the resulting data, enabling the viral population to be studied throughout the different stages of treatment. The results showed the emergence of certain mutations in the viral genome conferring resistance to treatment.

In 20% of cases, infection with the hepatitis C virus (HCV) progresses towards severe complications (cirrhosis and hepatocellular carcinoma). Models are needed for the study of HCV-induced hepatocellular carcinoma. What viral proteins are involved and what is the cascade of events resulting in damage to cellular DNA? This genomic instability favours the onset of cancer.

The team is also attempting to select inhibitors of cyclophilin, a human protein that binds with viral protein NS5A to modulate viral replication. Three compounds have currently demonstrated activity in this regard.

## Acting on immune system response

---

*The immune system obviously lies at the core of strategies to combat pathogens. Which weaknesses within this system do pathogens exploit to survive and proliferate? What vaccinal strategies are available?*

**Jean-Laurent Casanova**, Paris - Lethal infectious diseases of childhood: single-gene inborn errors of immunity?

Only a fraction of infected individuals go on to actually develop disease. What are the causes of this individual variability? Is part of the immune system missing in susceptible subjects? The genetic and molecular mechanisms of several immune deficiencies predisposing to infection have been identified in recent years. Jean-Laurent Casanova and his team have focused on herpes simplex encephalitis (HSE). This rare infection affects only a very small number of individuals infected with herpes simplex virus type 1 (HSV-1), a very widespread virus responsible in particular for cold sores. Two children with the disease were seen to produce insufficient levels of interferon-alpha and -beta (IFN- $\alpha$ , IFN- $\beta$ ) in response to viruses, and were carriers of homozygous mutations of a gene necessary for interferon production. As a result, high levels of viral replication caused cell death in a large number of neurons. These discoveries provide information on the genetic and immunological basis for control of HSV-1 infections and open up new therapeutic horizons in HSE.

**Monsef Benkirane**, Montpellier - HIV1 - Identification of the specific restriction factor SAMHD1

Dendritic cells act as sentinels of the immune system. They are found in the skin, mucous membranes and lymphatic tissues, where they detect the presence of microbes and trigger co-ordinated immune response. However, in the case of HIV1 infection, their action is defective. If the virus is successfully captured by dendritic cells, it infects them only incompletely, thereby probably reducing optimal innate and specific immune response directed against the virus. The dendritic cells are thus refractory to HIV1 infection. The question is whether the virus manages to escape recognition by the immune system through failure of the dendritic cells to recognise it. Monsef Benkirane has identified a specific restriction factor named SAMHD1 which limits the ability of HIV1 to infect dendritic cells. It inhibits the very first stages of the viral cycle, thereby preventing viral replication. This discovery opens up new perspectives for the creation of a therapeutic and preventive vaccine targeting dendritic cells. Reducing levels of SAMHD1 could allow better infection of dendritic cells by HIV1, thus rendering it more readily recognisable by the immune system.

## **Béhazine Combadière, Paris - Skin targeting for vaccine efficacy**

Béhazine Combadière has chosen to focus on the skin in order to increase vaccinal efficacy. She has developed a needle-free vaccination method around hair follicles, which house cells essential to the immune system: the Langerhans cells. These hair follicles are opened, the hair removed, and a few drops of the vaccine applied, from where they penetrate into the skin. These Langerhans cells then carry viral proteins and stimulate the T-cells, enabling them to recognise and kill infected cells.

Different particles may be applied in this way: nanoparticles, fragmented viral particles, etc. Proof of concept of this approach was provided in a phase I clinical trial of influenza virus, in which Béhazine Combadière's team showed that follicular Langerhans cells coming in contact with the virus enhanced CD8 and CD4 T-cell response. Five clinical trials are planned within the European CUT HIVAC project.

## North-South partnerships: what is at stake

---

*It is difficult to envisage a meeting on infectious diseases without discussing the public health problems facing the countries of the South. In these countries, infections are responsible for two-thirds of all deaths among children under the age of 5 years, through pneumonia, diarrhoea, etc. Reducing this mortality is one of the major health challenges of the 21<sup>st</sup> century, and research partnerships are one of the ways in which this can be achieved.*

**François Dabis**, Bordeaux - Tackling infectious diseases: French-based international research networks

French researchers are particularly active in the fight against infectious diseases afflicting the countries of the South, via four complementary networks having international branches: the networks of the Institut Pasteur, IRD, ANRS, and Cirad. In Southern Asia, 9 institutes associated with the Institut Pasteur are working on the main infections such as malaria, dengue, hepatitis and respiratory infections. They have developed many tools like cultures of microorganisms, biobanks, patient cohorts, etc.

One example of the success of these networks is the study concerning the decreased risk of mother-to-child transmission of HIV. A research project conducted by ANRS in this domain in the Ivory Coast showed that levels could be reduced. Following on from this work, the WHO last year issued guidelines to promote such prevention, and the UNICEF has set itself the goal of eliminating paediatric HIV by 2015.

A private and public investment is essential to enable the transition from fundamental research to translational research.

**Eric Leroy**, Franceville, Gabon - Ebola: research at the heart of the African tropical forest

The Ebola virus is an emerging pathogen discovered in 1976. Eric Leroy's team has analysed the historical development of the virus with its sequences, by means of cohort studies, animal studies and research projects by laboratories within the BSL-4 laboratory, which is unique in South Africa. The only defence against the virus is avoidance of all contact with patients. However, certain individuals infected by the same virus as deceased patients are in fact asymptomatic; in these subjects, extremely early inhibition of viral replication is seen, conferring specific immunity.

A global surveillance network and an excellent local research platform constitute undeniable advantages for this type of research project.

## **Selected quotes from convinced participants!**

---

**Eric Vivier, Director of the Marseille-Luminy Immunology Centre**

“The notion of industrial partnerships is a source of inspiration for our research.”

**Philippe Tcheng, Vice-President for Public and Government Affairs in France, Sanofi**

“Knowing and understanding one another between the academic world and the pharmaceutical sector is essential. There should be more of these meetings.”

**Scott Brun, VP Infectious Disease Research, Abbott**

“These meetings are extremely valuable since they provide us, in a single day, with a very broad panorama of the research projects on infectious diseases being conducted in France.”

**Stéphanie Blandin, Researcher, Strasbourg**

“My research is in fact fundamental research with no immediate applications. However, these meetings allow me to identify manufacturers potentially interested in my research. This is a very positive step.”

**Mike Seeley, President of BMS France**

“These meetings clearly demonstrate the excellence of French research and encourage industrialists to invest in partnerships.”

**Jean-François Delfraissy, ITMO infectious diseases**

“Quite simply, public-private partnerships enable us to move faster.”

## **Alliance for Research and Innovation in the Health Industries (ARIIS)**

A non-profit association founded by professional organisations, members of the French Health Industries Federation (FEFIS), and in particular the LEEM (Association of the French Pharmaceutical Industry), SIMV (Association of Veterinary Medicine Industry), SFRL (Association of In Vitro Diagnostics Industry) and SNITEM (Association of Medical Technology Diagnostics Industry). AVIESAN is also represented on the ARIIS board.

Among other things, ARIIS, an offshoot of the CSIS (French Strategic Healthcare Council), acts as the spokesperson for AVIESAN, which groups together the principal academic research bodies, and its main aims are:

- ✓ to form a broad federation of the health industries and, consequently, to reflect the diversity of the health sector in terms of the diversity of the various actors (SMEs, international groups, biotech firms, start-ups, etc.) and of the different areas of research (upstream and translational, clinical, epidemiological, industrial, etc.);
- ✓ to develop public/private partnerships. Innovation in healthcare is largely dependent on collaboration between industrialists and research laboratories, both public and private. Through its scientific board with equal representation, ARIIS strives to promote opportunities for exchange between these various actors and to multiply partnerships;
- ✓ to offer greater transparency for its partners.

[www.ariis.fr](http://www.ariis.fr)

## **French National Alliance for Life Sciences and Health (AVIESAN)**

The French National Alliance for Life Sciences and Health (**AVIESAN**), made up of the CEA (French Atomic Energy Commission), the CNRS (French National Scientific Research Centre), the INRA (French National Institute for Agronomic Research), the INRIA (French National Institute for Research on Informatics and Automation), INSERM (French National Institution of Health and Medical Research), the Institut Pasteur, the IRD (Institute of Research for Development), the CPU (Conference of University Presidents), and the Conference of Directors General of Regional and University Hospitals. AVIESAN's aim is to foster a continuum at the highest level between all areas of life science and health research, from fundamental research to ultimate applications. AVIESAN comprises ten multi-organism theme-based institutes (ITMO), which constitute the functional bodies responsible for co-ordinating research, and which in particular are responsible for providing an up-to-date overview of French research classified by major themes.

[www.aviesan.fr](http://www.aviesan.fr)