ACTIVITY REPORT

2008 2010

finovi

Innovations in Infectiologious Diseases

THE FINOVI FOUNDATION AT A GLANCE

The FINOVI Foundation (Innovations in Infectious Diseases) was established by a decree dated 21 March 2007 by nine major players in local and national research: the CNRS (National Centre for Scientific Research), École Normale Supérieure, INRA (Public Scientific Institute for Agricultural Research), INRIA (National Institute for Research in Computer Science and Control), INSERM (National Institute for Health and Medical Research), Institut Pasteur, the Lyonbiopole Competitive Cluster, Claude Bernard University (Lyon) and Joseph Fourier University (Grenoble). The Hospices Civils of Lyon have been partners of the Foundation since 2009. The FINOVI Foundation was created with the aim of structuring and developing a themed network of academic research focusing on infectious diseases. In all, 28 research units representing approximately 1,700 researchers form this themed network.

When it was founded, the FINOVI Foundation received a government grant of 13,000,000 euros, and the founding members in the first five years undertook to add 3,150,000 euros, bringing the Foundation's total initial budget to 16,150,000 euros.

The FINOVI Foundation supports research on infectious diseases, and more specifically viral hepatitis, respiratory infections and nosocomial infections. Its goal is to contribute to the development of new therapeutic and preventive solutions against infectious diseases. Its objective is to expand the network of local research teams on the theme of infectious diseases.

GOVERNANCE

The Board of Trustees is chaired by Mr. Charles Kleiber. It meets twice a year. The Scientific Board has been chaired since June 2010 by Mr. Pierre Meulien, CEO of Génome Canada, replacing Mrs. Geneviève Chêne, PU-PH Inserm U897/ University of Bordeaux. The Scientific Board is called upon by the management team several times a year, both on scientific strategy and on the scientific quality of proposals under evaluation. It meets once a year.

Since July 2009, Christelle Bidaud, Secretary General and Mrs. Jacqueline Marvel, Senior Scientist, have been in charge of it.
The Executive Board monitors the evaluation of calls for proposals and provides scientific guidance.

TOOLS

The FINOVI Foundation awards subsidies through calls for proposals created with the aim of:
- Attracting future leaders to the field of infectious diseases (creation of young teams),
- Supporting local research (financing postdoctoral fellows and supporting the start-up of innovative research programmes).

In addition to these calls for proposals, the FINOVI Foundation strives to:
- Unite and lead the scientific communities of Lyon and Grenoble around infectious diseases with the aim of developing new projects,
- Associate fundamental research with clinical research on public health issues,
- Participate in and organise scientific events.

RESEARCH UNITS CAN TAKE ADVANTAGE OF THE FOUNDATION'S TOOLS.

The FINOVI Foundation is committed to supporting research units that have contributed to the creation of its research network. Only these units may benefit from the financial support offered by the Foundation. Over these four years of existence, the composition of the network has evolved. Since the initial network was put in place, three teams have joined the viral hepatitis and nosocomial infection themes. The network now features 25 research units and three teams.
A distinction can be drawn between the core units (whose research activities in the life sciences are directly linked to infectious diseases) and the partner units (which contribute know-how and knowledge so that upstream, multidisciplinary projects can be developed).

Most of these research units were evaluated by AÉRES in 2010. The results of this evaluation show that almost all the units associated with the Foundation received scores of A or A+.

summary

2007/2008

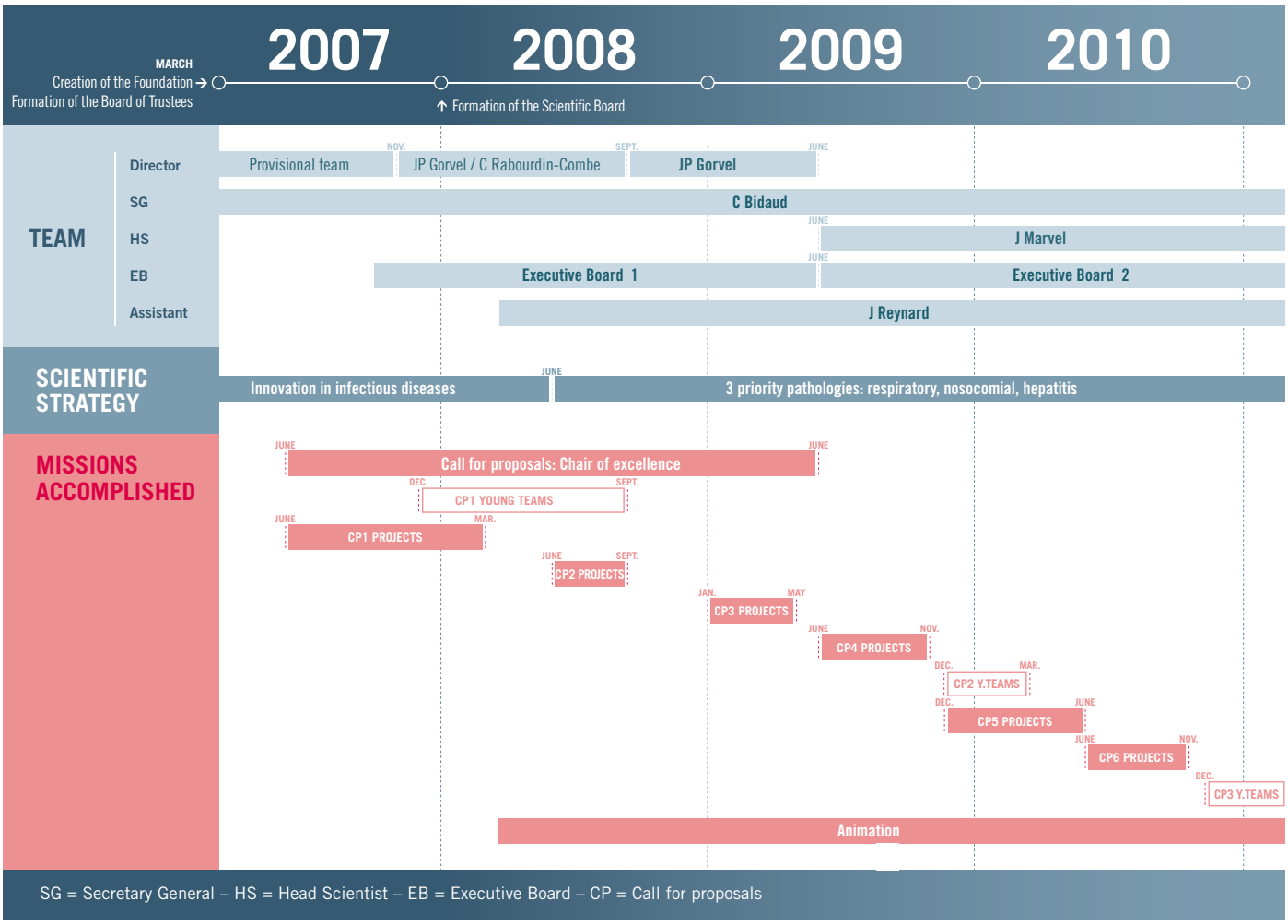
- Creation of the Foundation
- Determination of the 3 priority research areas and of the scientific strategy
- Determination and organisation of tools and missions

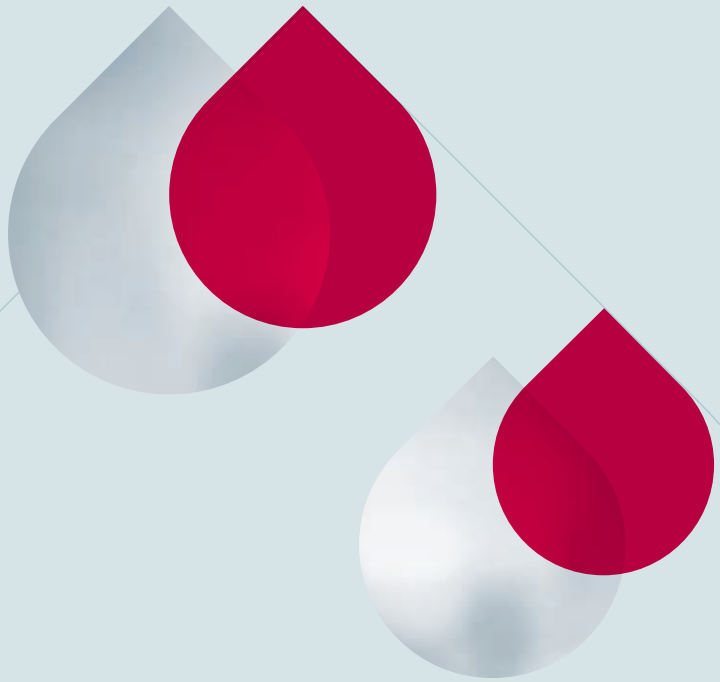
2009/2010

- Strengthening and developing the 3 priority focus areas thanks to the calls for proposals and leadership and networking efforts

→ **2 teams created** (total envelope of 2,500,000 euros, including the creation of 8 jobs

→ **33 research projects financially supported** (total envelope of 3,423,000 euros, including the creation of 27 postdoctoral fellowships)





01 OPERATIONAL REPORT

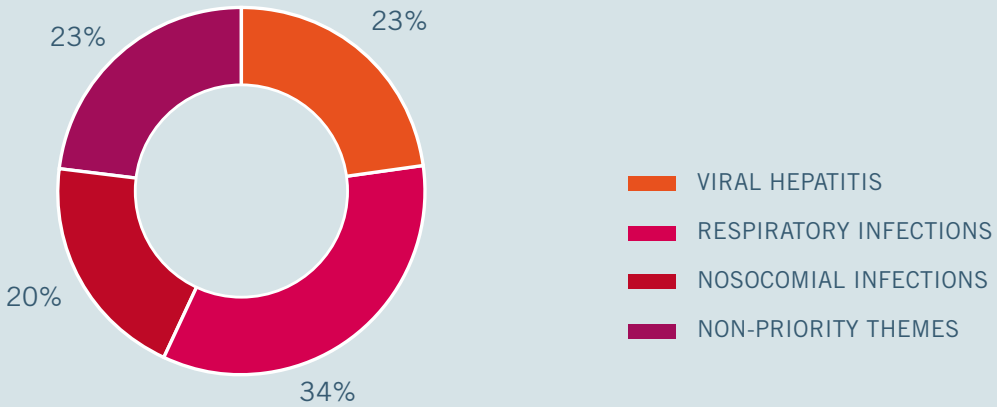
2008 2010

FUNDING OF PROJECTS SINCE 2007

The financed projects all aim to strengthen the innovation potential of research units and develop inter-team and multidisciplinary projects. Although priority themes have been determined, about ¼ of the financing is awarded to projects outside of the priority areas of focus, due to their innovative nature for research in infectious diseases.
The project initiators are required to regularly submit an activity report for the period during which the financing applies. The Executive Board monitors these reports and projects.

CALL FOR PROPOSALS FOR PROJECT FUNDING

DISTRIBUTION OF AMOUNTS BY THEME



CALLS FOR PROPOSALS FOR PROJECT FUNDING

SINCE 2007, SIX CALLS FOR PROPOSALS HAVE BEEN ISSUED: THREE ON AN OPEN THEME ASSOCIATED WITH INFECTIOUS DISEASES, AND THREE OTHERS ON PRIORITY THEMES.
AT THE END OF THE EVALUATION PROCESS FOR ALL OF THESE CALLS FOR PROPOSALS, THE FOLLOWING PROJECTS HAVE OBTAINED FINANCING SINCE THE CREATION OF THE FINOVI FOUNDATION:

⬢ multidisciplinary projects – ✖ projects initiated thanks to the strategy and work of the Finovi network

VIRAL HEPATITIS PROJECTS

• **New antiviral molecules targeting the human HIV, HBV and HCV viruses (2008)**
Jean-Luc Darlix - Human Virology Unit, U758 INSERM/ENS

• **Role of plasmacytoid dendritic cells in the immunological escape of the HCV virus (2009)** ✖
Dominique Kaiserlian – Immunity, Infection and Vaccination Unit, U851 INSERM/UCBL/HCL

• **Role of the hepatic microenvironment in the infection of hepatocytes by the Hepatitis C virus: an integrated microscopy approach (2009)**
Eve-Isabelle Pecheur and Florence Ruggiero - Institute of Biology and Chemistry of Proteins, UMR5086 CNRS/UCB

• **Rational design of vaccine candidates against the hepatitis C virus based on the results of studies on its cellular entry and neutralisation (2009)**
Dimitri Lavillette – Human Virology Unit, U758 INSERM/ENS

• **Is the hepatitis B virus really silent? Demonstration of the innate response of the hepatocyte to infection by hepatitis B. (2009)**
Fabien Zoulim - Unit of molecular physiopathology and new treatments for viral hepatitis, U871 INSERM/UCB

• **Hepatitis C and carbohydrate and fat metabolism (2009)**
Patrice Andre - Immunity, Infection and Vaccination Unit U851 INSERM - UCBL - HCL

• **Cou®tesy: a system against viral resistance (2009)** ⬢
Christophe Combet – Institute of Biology and Chemistry of Proteins, UMR5086 CNRS/UCB

RESPIRATORY INFECTION PROJECTS

• **Mutations of *Influenza* polymerase: How the bird flu virus becomes pathogens that are highly infectious for humans (2008)**
Darren Hart - Unit of the Structural Biology of Interactions between Viruses and Host Cells UMI3265 CNRS - UJF - EMBL

• **Study of two new carriers of *Streptococcus Pneumoniae*: towards a link between multiple-drug resistance and virulence (2008)**
Jean-Michel Jault - Institute of Structural Biology – CEA – CNRS - UJF UMR5075

• **Identification of molecular host/pathogen interactions, dependent on IL-17A and TNF-alpha, in the myeloid core of mycobacterial granuloma (2008)**
Christine Delprat - Unit of Molecular Cell Biology UMR5239 CNRS -ENS Lyon-INRA

• **Investigation of the Molecular Basis for Paramyxovirus Replication (2009)**
Martin Blackledge - Institute of Structural Biology – CEA – CNRS - UJF UMR5075

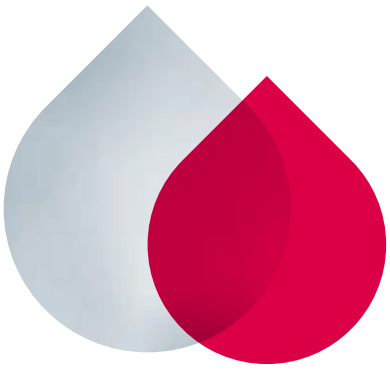
• **Towards complementarity between experimental evolution and digital evolution: the PEACE project (2009)** ⬢ ✖
Dominique Schneider - Unit of adaptation and pathogenesis of microorganisms - UMR5163 CNRS - UJF

• **Identification of the virulence factors of *Legionella Pneumophila* required to fight autophagia (2010)** ✖
Mathias Faure - Immunity, Infection and Vaccination Unit U851 INSERM - UCBL - HCL

• **Innate immune response to *Streptococcus Pneumoniae*: role of the lectin pathway in the human complement system (2010)**
Nicole Thielens - Institute of Structural Biology (IBS) UMR5075 CEA-CNRS-UJF

• **Multi-Scale Modelling of the Immune Response CD8 (2010)** ⬢ ✖
Fabien Crauste – Institute of Complex Systems CNRS - INRIA - ENS - UCB - UJF

• **Structural and functional characterisation of the signal peptide of Panton-Valentine leukocidin involved in the adhesion of *S. Aureus* to heparan sulphates (2009)** ⬢ ✖
Anne Tristan and François Vandenesch - Immunity, Infection and Vaccination Unit - U851 INSERM - UCBL – HCL



	2008	2009	2010	TOTAL
NUMBER OF PROJECTS RECEIVED	59	38	46	143
NUMBER OF PROJECTS FINANCED	8	11	14	33
SUCCESS RATE	14%	29%	30%	23%
AMOUNTS AWARDED IN K€	1 193	1 030	1 200	3 423

NOSOCOMIAL INFECTION PROJECTS

• **Correction of lymphocyte anergy as an innovative therapy in the treatment of septic states and in the prevention of nosocomial infections (2009**)
Guillaume Monneret - Immunity, Infection and Vaccination Unit U851 INSERM - UCBL – HCL

• **Signalling and detection of the signal in the virulence of Pseudomonas aeruginosa (2010)**
Ina Attrée – Bacterial pathogenesis and cell response - Unit of Cancer and Infection Biology

• **Effect of Staphylococcus aureus on the resorption of osteoclasts in vitro and in a model of nosocomial infection in joint prostheses (2010)** ⬢
Pierre Jurdic - Institute of Functional Genomics de Lyon - UMR5242 CNRS - UCBL1 - ENS - INRA

• **Strategies of glycochemistry against nosocomial infections by Aspergillus fumigatus and other filamentous fungi (2010)** ⬢ ✖
Anne Imberty – Immunology of chronic pathologies team - Institute Albert Bonniot U823 INSERM - UJF - CHU - EFS - CNRS

• **Targeting antigen-based vaccines on the thymus-independent arm of the humoral response: a new vaccine strategy against nosocomial infections. (2010)** ✖
Thierry De France - Immunity, Infection and Vaccination Unit U851 INSERM - UCBL – HCL

• **Measures of inter-individual contacts and transmission of infectious diseases in hospitals (2010)** ⬢ ✖
Nicolas Voirin - Unit of Biometrics and Evolutionary Biology UMR 5558 CNRS - INRIA - UCBL1

• **Individual-oriented experimentation of models of resistance and dissemination (2010)** ⬢
Eric Fleury – Unit of Parallel Computing UMR 5668 CNRS - INRIA

PROJECTS ON INFECTIOUS DISEASES NOT ASSOCIATED WITH A PRIORITY AREA OF FOCUS

• **New biophotonic fluorescent imaging probes for the study of viral traffic (2009)** ⬢
Marie-Thérèse Charreyre - Joliot Curie Laboratory USR3010 - CNRS – ENS

• **Diversity and interactions of the microbial community of ticks in France with the vectorized pathogens, and case of *Coxiella Endosymbiont* and *Coxiella Burnetii* (2010)** ⬢
Lionel Zenner - Unit of Biometrics and Evolutionary Biology UMR 5558 CNRS - INRIA - UCBL1

• **Exosomes: shuttles for the transmission and dissemination of infectious prions (2010)**
Pascal Leblanc - Unit of Human Virology U758 INSERM-ENS Lyon

• **Exploration of the role of the viral protein BARF1 in infection by the Epstein-Barr virus (2010)**
Wim Burmeister – Unit of the Structural Biology of Interactions between Viruses and Host Cells UMI3265 CNRS - UJF - EMBL

• **Structural and functional characterisation of the minimal machinery of membrane fission recruited by HIV (2010)**
Win Weissenhorn - Unit of the Structural Biology of Interactions between Viruses and Host Cells UMI3265 CNRS - UJF - EMBL

• **Cellular and population analysis of the endogenization of retroviruses in fruit flies. Christophe Terzian - Retrovirus and Compared Pathology Unit (2008)**
UMR754 INRA-ENVL-UCBL

• **The role of variants for high-risk HPV types in the development of cervical cancer worldwide (2008)**
Gary Clifford - CIRC

• **Study of the response to damage to the centrometric chromatine caused by the ICP0 protein of the herpes simplex virus 1 (2008)**
Patrick Lomonte - Centre for Molecular and Cellular Genetics UMR 5534 CNRS/UCBL1

• **Manipulation of programmed cell death by intracellular bacteria in insects (2008)**
Fabrice Vavre - Unit of Biometrics and Evolutionary Biology UMR 5558 CNRS - INRIA - UCBL1

HOSTING YOUNG TEAMS

IN 2009, THE **FINOVI FOUNDATION** HOSTED THE TWO YOUNG RESEARCHERS SELECTED IN 2008 TO CREATE THEIR RESEARCH TEAM: T**HOMAS HENRY** AND **THIERRY WALZER**. THEY BOTH BENEFITED FROM A BUDGET ALLOWANCE ENABLING THEM, FOR A PERIOD OF FOUR YEARS, TO MANAGE A TEAM OF FOUR PERSONS. THEY ARE CURRENTLY ASSOCIATED WITH THE IMMUNITY, INFECTION AND VACCINATION RESEARCH UNIT (U851 INSERM-UCBL-HCL) RUN BY DR JACQUELINE MARVEL, AND PLAN TO JOIN THE CIRI (INTERNATIONAL CENTRE FOR RESEARCH ON INFECTIOUS DISEASES) AS SOON AS IT IS CREATED.

THE RESEARCH PROJECTS INITIATED BY THOMAS HENRY AND THIERRY WALZER HAVE ALSO SERVED AS CONCRETE EXAMPLES OF THE FINOVI FOUNDATION'S AMBITION. THEIR ARRIVAL CONTRIBUTES TO THE ENHANCEMENT OF LOCAL RESEARCH SKILLS, AS PART OF THE PRIORITY THEMES OF THE FINOVI FOUNDATION. IN THE LONG RUN, THEIR WORK WILL CONTRIBUTE TO A DEEPER UNDERSTANDING OF INFECTIOUS DISEASES.

THOMAS HENRY, working since July 2009 in a laboratory leased by the FINOVI Foundation at the Lyonbiopole Centre for Infectious Diseases, is exploring the mechanisms of innate immunity during bacterial infections. He received his PhD from the Centre of Immunology of Marseille-Luminy (CIML), and in 2005 he went to the San Francisco Bay Area (California, United States), where he conducted research for four years at Stanford University.
In Lyon, Thomas Henry is working on a project on the activation of inflammasome during bacterial infections. This project is studied primarily within the context of infections with *Francisella Tularensis* (agent of *Tularemia*), *Legionnella Pneumophila* (agent of Legionnaire's disease) and *Staphylococcus Aureus*.
His research will contribute to a higher level of understanding of the factors of bacterial virulence and of the natural mechanisms of immunity to bacteria. Furthermore, his team is currently testing the efficacy of a drug that could be used for the treatment of a fatal type of pneumonia caused by *Staphylococcus Aureus*.
Thomas Henry obtained a position with CR1 Inserm in 2010. He is involved in six collaborative projects at national and international levels. His team received three national and European grants (European Marie Curie Reintegration Grant, ANRS grant, a grant from the Foundation for Medical Research for 2 years of post-doc).
T. Henry contributed three publications in 2010 (*The Journal of Immunology*, PNAS, PLoS Pathogens).

THIERRY WALZER works in the premises of U851, located on the Gerland campus.
He is an expert on the cytotoxic lymphocytes NK and CD8. He uses systems biology approaches to identify the specific markers of NK cells. Thierry Walzer received his PhD from the Ecole Normale Supérieure of Lyon, and after a post-doctorate in the US in the biotech firm Amgen, he joined the CIML in Marseille and in 2004 obtained a research fellow position at the INSERM.
In Lyon, Thierry Walzer is working on a project concerning cytotoxic lymphocytes and their roles in antiviral responses in mice and humans (Lyon-Sud Hospital). His objective is to identify new genes participating in the function of these cells, in the context of infectious diseases. The research work of Thierry Walzer will make it possible to better understand the mechanisms of protection against viruses, and could, in the long term, result in new therapeutic options based on the manipulation of the identified genes.
Since his arrival in Lyon, in 2010 Thierry Walzer obtained the ANR Award for Young Researchers, as well as the Arloing-Courmont Prize from Institut Pasteur, Lyon. He is also supported by the University of Lyon, the Regional League Against Cancer and by the pharmaceutical company Celgen. This year he applied for financing in the form of an ERC Starting Grant. His project was selected for the second evaluation phase. Since his arrival, he has published eight original articles or reviews in high-impact journals (Blood, Science Signalling, Trends in Immunology etc).

THE PROGRESS MADE BY THESE TWO RESEARCHERS SINCE THEIR ARRIVAL, BOTH IN TERMS OF THEIR INTEGRATION INTO THE LOCAL SCIENTIFIC COMMUNITY AND IN TERMS OF FINANCING AND RECOGNITION OBTAINED, VALIDATES THE CHOICE OF FINOVI.

CALL FOR PROPOSALS FOR THE CREATION OF YOUNG TEAMS

2,500,000 EUROS
investment

8 POSITIONS CREATED

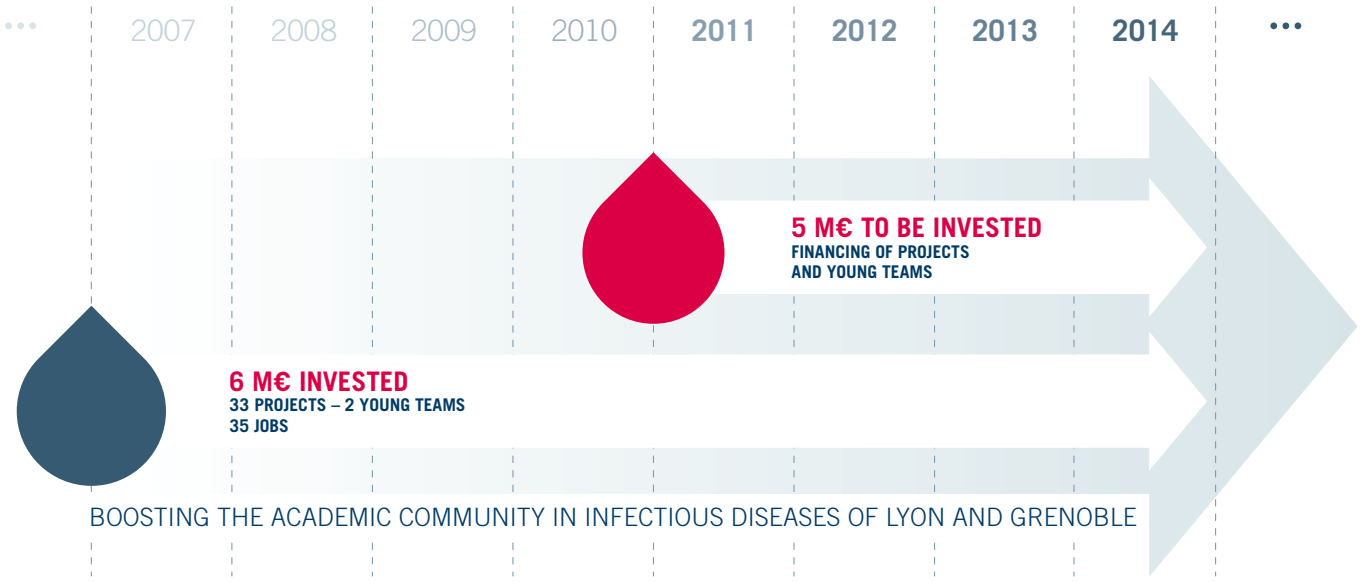
465 K€ OBTAINED
by the two teams, from other sources of financing

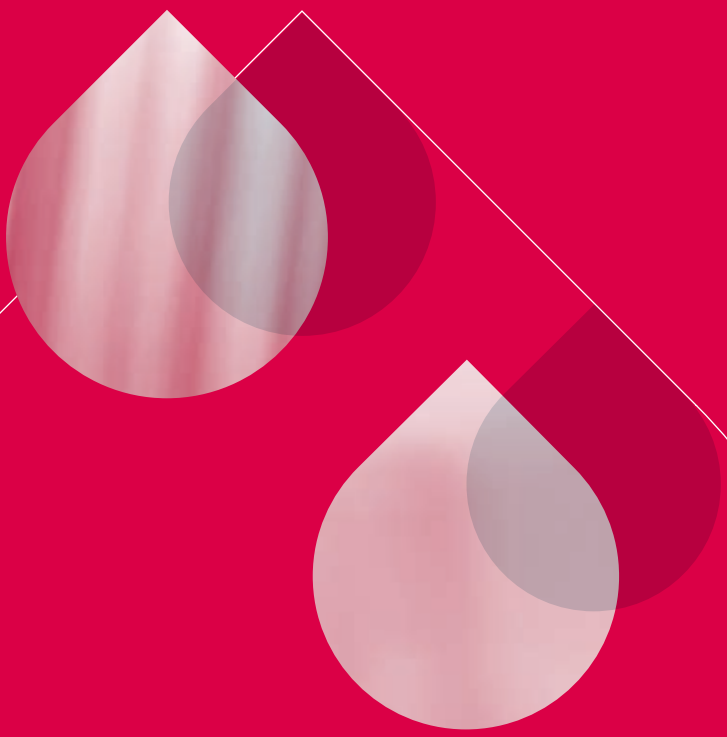
DEVELOPING RESEARCH OF EXCELLENCE AND CREATING A NETWORK IN THE FIELD OF INFECTIOUS DISEASES

THANKS TO THE LEADERSHIP OF THE OPERATIONAL TEAM AND ITS KNOWLEDGE OF THE FIELD, THE **FINOVI FOUNDATION** HAS BUILT A RESEARCH NETWORK THAT HAS BECOME DENSER OVER THE PAST THREE YEARS. IN CONCRETE TERMS, THIS MEANS THAT LINKS AND PROJECTS HAVE BEEN CREATED BETWEEN PEOPLE AND TEAMS WHO DID NOT KNOW EACH OTHER BEFORE OR WHO DID NOT USUALLY WORK TOGETHER.

AMONGST THE 33 PROJECTS FINANCED, 12 ARE NEW PROJECTS that have increased the research potential of the academic community in infectious diseases, thanks to the leadership and networking of the Foundation.
Amongst these projects, it is also important to consider the multidisciplinary character of certain projects, the creation of projects at the boundary between clinical and fundamental research and the fact that new teams have been drawn to the priority themes.
Finally, it is important to remember that the FINOVI Foundation has made it possible to significantly develop the relationships between Lyon and Grenoble, on the basis of the skills of these two communities and their complementary nature.

These leadership and networking efforts have produced the following outcomes for the operational team:
- A precise knowledge of the forces to be reckoned with and of the issues and a comprehension of the future challenges to research in these areas
- The emergence of collaborative projects and of new avenues of investigation





02 REPORT ON SCIENTIFIC ASPECTS

IMPACT OF THE FOUNDATION ON THE LOCAL SCIENTIFIC COMMUNITY

The actions of the FINOVI Foundation have influenced the activity of the network's research units. Starting in 2012, the research projects supported by the FINOVI Foundation will be sufficiently advanced for indicators, such as publications, patents filed, the number of collaborative projects initiated and the number of ANR grants obtained for projects initiated by the Foundation, to be accurate gauges to measure the impact the FINOVI Foundation has had on the research carried out by the network of teams associated with the Foundation.

VIRAL HEPATITIS

VARIOUS VIRUSES FROM DIFFERENT FAMILIES ARE CAPABLE OF INFECTING THE LIVER AND CAUSING ITS INFLAMMATION, RESULTING IN HEPATITIS. THESE LIVER INFECTIONS CAN BE, DEPENDING ON THE VIRUS AND THE PATIENT, TRANSIENT (ACUTE) OR CHRONIC (POTENTIALLY LEADING TO MORE SERIOUS PATHOLOGIES). THE HBV VIRUS (HEPATITIS B VIRUS) AND HCV (HEPATITIS C VIRUS) ARE RESPONSIBLE FOR CHRONIC INFECTIONS, IN 20% AND 80% OF CASES RESPECTIVELY, AND ARE THE LEADING CAUSES OF CHRONIC HEPATITIS, WHICH MAY LEAD TO LIVER CIRRHOSIS AND LIVER CANCER (= HEPATOCELLULAR CARCINOMA, HCC). HEPATOCELLULAR CARCINOMA (HCC) IS THE FIFTH MOST COMMON CANCER WORLDWIDE, MOST CASES BEING ATTRIBUTABLE TO THE HBV AND HCV VIRUSES.

About a third of the world's population has serological signs of a past or present HBV infection. Although there is an effective vaccine against this virus, there are still 350 million carriers who are exposed to the complications of the disease (cirrhosis and HCC). Chronic hepatitis associated with HBV and leading to liver cirrhosis or liver cancer are responsible for over 1 million deaths a year, currently representing 5% to 10% of liver transplants. In France, there are 300,000 chronic carriers of HBV, and the complications associated with this infection are estimated to be the cause of 1,500 deaths a year.
Unlike HBV, there is no vaccine against HCV, and 175 million people worldwide (600,000 in France) are chronically infected with this virus. These chronic infections are also responsible for cirrhosis and liver cancer.

Current treatments for chronic hepatitis B and C are not yet satisfactory. The antiviral treatment with nucleoside analogues for chronic hepatitis B is a suppressive treatment, but it is lifelong, which exposes patients to the emergence of resistant viruses. The antiviral therapies currently used against HCV (ribavirin associated with PEG-IFN-α), in spite of spectacular advances, still cause many unwanted side effects and mixed results, essentially dependent upon the viral genotypes.
On average, the treatment is effective in 60% of cases, and the non-respondents are exposed to the risks of progression of the liver disease. Clinical trials are underway for the development of specific inhibitors of HCV to increase the cure rate. The current failures point to the importance and urgency of developing new, more effective and more specific agents against the hepatitis viruses.

The viruses of other forms of hepatitis, i.e. HAV and HEV, are eliminated spontaneously and cause acute diseases, principally in developing countries.
The hepatitis delta virus (HDV) is a satellite virus of HBV, causing a worsening of the disease caused by HBV in case of secondary infection. There is no active fundamental research in the Rhône-Alpes Region on these viruses.

Parties involved in 2007

A large number of teams from units associated with the FINOVI Foundation with international expertise in projects concerning hepatitis were identified when the Foundation was created.

The research covers a broad range of disciplines. Certain areas of focus were fundamental, such as studies on the entry process of HCV (U758 INSERM-ENS, IBCP UMR5086 CNRS-UCBL), the assembly and viral morphogenesis process of HCV (U851 INSERM-UCBL-HCL, IBCP UMR5086 CNRS-UCBL, U871 INSERM-HCL), the role of lipids in the viral cycle of HCV (U758 INSERM-ENS, U851 INSERM-UCBL-HCL, IBCP UMR5086 CNRS-UCBL), general host/virus interactions of HCV (Project I-MAP, U851 INSERM-UCBL-HCL), the translation mechanism (UMI3265 CNRS - UJF – EMBL U758 INSERM) and the development of hepatocellular carcinoma (U871 INSERM-HCL). Other research topics were more translational, such as the development of vaccines against HCV (U758 INSERM-ENS), or more clinical, such as studies on HBV resistance to antivirals and the mechanisms of viral persistence (U871 INSERM-HCL). A European database (viral sequences / prediction of structure) was also developed (euhcvdb.ibcp.fr, IBCP UMR5086 CNRS-UCBL).

As the "hepatitis" community was already large and well structured in 2007, the objectives of the Foundation were:
- to improve the synergies between the relevant teams,
- to support the development of new areas of research in association with other disciplines,
- to boost translational, clinical and industrial research.

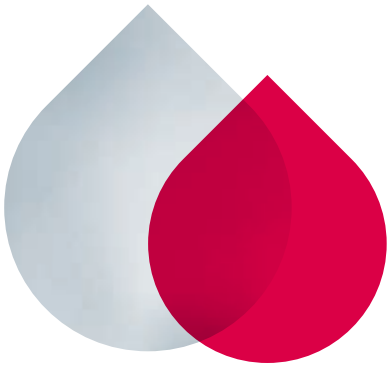
Actions carried out by the FINOVI Foundation

A call for proposals targeting the viruses responsible for hepatitis was issued in September 2009. A leaders' meeting had been held prior to this call for proposals to stimulate the community and bring about synergies. Thanks to this call for proposals and to the open calls for proposals, seven new projects were financed, making it possible to attract new teams and skills to this theme (immunology, cellular biology etc.). Another characteristic of the projects supported is that they are collaborative and all involve at least two teams from the FINOVI network. Therefore, these projects also made it possible to increase the synergies between researchers in Rhône-Alpes working in the field of hepatitis. Some of this research has already led to joint publications.

The project initiated by Jean-Luc Darlix (U758 INSERM - ENS) aims to identify the NC/core equivalent in HBV and characterise the molecular interactions involving the NC of HIV and the core of HCV. Based on the laboratory's knowledge of the replication of VIH-1, HBV and HCV, one objective is to evaluate these interactions as possible therapeutic targets by screening chemical compound banks.

A new research theme concerning the innate, adaptive response to the hepatitis viruses will be able to be developed thanks to the support of FINOVI. The project, initiated by Dominique Kaiserlian (U851 INSERM – UCBL - HCL), aims to evaluate the role of plasmacytoid cells (pDC) in the pathology of HCV, the initiation of the inflammatory response and the induction of immune tolerance of HCV-specific T cells in the liver.

- The project initiated by Fabien Zoulim (U871 INSERM - UCB) aims to identify and characterise the innate cellular signalling pathways involved in the recognition of HBV and in the activation of the Interferon pathway.



- The project initiated by Eve-Isabelle Pecheur (UMR5086 CNRS - UCB) aims to improve knowledge of the early phases of HCV entry by analysing the involvement of the glycoaminoglycans, proteoglycans and other molecules of the cellular micro-environment of the hepatocytes. Time-lapse microscope and electron microscope technologies will be used to analyse the internalisation dynamics and the role of different cell surface molecules. This project also received support from FINOVI for technical platform development, for the purchase of a GATAN UltraScan camera.

The interaction between the HCV virus and the metabolism of lipids is a key element in the biology of this virus. Two projects on this important theme have been supported.

- The project initiated by Dimitri Lavillette (U758 INSERM - ENS) aims to understand how the association of HCV with lipoproteins during the assembly process modulates, on the one hand, the entry process of HCV into hepatocytes, and on the other hand, the accessibility of the HCV proteins to the neutralising antibodies. The characterisation of the influence of lipoproteins will make it possible to improve the quality of the immunogens tested as vaccine candidates, and should enable the development of neutralising antibodies that can be used in immunotherapy.

- The project initiated by Patrice Andre (U851 INSERM - UCBL – HCL) aims to understand the cellular mechanisms of the metabolism of the lipids and of the glucose diverted by HCV for its replication. The question of the generalisation of the metabolic pathways diverted for the production of the virus will be raised for other viruses based on the results of the two-hybrid screening already carried out by this team.

- The project initiated by Christophe Combet (Institute of Protein Biology and Chemistry, UMR5086 CNRS - UCB) and Fabien Zoulim (U871 INSERM - UCB) aims to develop a database of treatment resistance of HCV and HBV variants. This database, the algorithms developed and the knowledge generated will be useful for implementing treatment methodologies and software to improve the use of drugs while limiting their capacity to select resistant mutants. This database and these conclusions will be at the service of the worldwide scientific community working on the hepatitis viruses.

As the call for proposals was issued in 2009, the first employment contracts started in 2010. This is why the total number of publications remains limited. There should be more publications in the coming months. The two-year FINOVI grants have made it possible to recruit six researchers from France and from other countries, which increases the attractiveness of the Rhône-Alpes Region.

In brief, thanks to the calls for proposals, Finovi has boosted the research dynamic in the field of hepatitis. Teams launched new research themes. In parallel, groups were integrated into the FINOVI Foundation (Team of P. Marche, Albert Bonniot Institute INSERM/UJF U823) as they had a research theme associated with hepatitis (immune response against HCV and in particular the intra-hepatitis immune response). Furthermore, collaborations between Grenoble and Lyon were developed (collaboration between IBS UMR5075 CEA-CNRS-UJF and U758 INSERM) to screen oligosaccharide banks to inhibit the fixation of the HCV virus within the context of a programme supported by the DGE (Carbinfect).

RESPIRATORY INFECTIONS

RESPIRATORY INFECTIONS REPRESENT A MAJOR PUBLIC HEALTH PROBLEM IN LARGE CITIES AND IN DEVELOPING COUNTRIES. THE PRINCIPAL PATHOGENS INVOLVED IN THESE PATHOLOGIES ARE THE FOLLOWING:

- BACTERIA: *Mycobacterium Tuberculosis* WHICH CAUSES TUBERCULOSIS, *Streptococcus Pneumoniae* WHICH CAUSES INFECTION IN INFANTS, *Legionella* WHICH CAUSES LEGIONNAIRE'S DISEASE,
- VIRUSES: *Influenza* WHICH CAUSES THE FLU, AND HUMAN RESPIRATORY SYNCYTIAL VIRUS.

The FINOVI Foundation has mainly supported the development of research in three of these respiratory pathogens: *Mycobacterium Tuberculosis*, *Influenza* and *Streptococcus Pneumoniae*.
The number and diversity of research projects underway in 2007 in these three pathogens was quite varied. This is why different objectives were set for each of them. For each pathogen, the inventory of the parties involved in 2007 is given, and the principal actions conducted by FINOVI between 2007 and 2010 in order to promote research and innovation in these areas are summarised.

TUBERCULOSIS

Tuberculosis is a major public health problem, with 8 to 9 million new cases every year and a latently infected population estimated at 2 billion.

Parties involved in 2007

Two units with projects concerning Mycobacterium tuberculosis were identified:

- Unit of Biometrics and Evolutionary Biology (LBBE UMR 5558 CNRS - INRIA - UCBL1) associated with the Regional Tuberculosis Surveillance Centre
- Institute of Protein Biology and Chemistry (IBCP UMR5086 CNRS-UCBL)

The research projects concerning the evolution of mycobacteria and protein kinases in bacteria.
The objectives of FINOVI were to promote the development of research projects on this pathogen.

Actions conducted by the FINOVI Foundation

The FINOVI Foundation recruited Professor Jacques Banchereau (Director, Baylor Institute for Immunology Research, INSERM U899) as a consultant to coordinate the development of tuberculosis research.
The objective was to promote the study of the host response and to develop tools for diagnosing the disease.
For 2 years, Jacques Banchereau's work, conducted in collaboration with the Executive Board of FINOVI, has enabled the development of an international collaborative project associating the team of Anne O'Garra (MRC, London), with researchers and clinicians in Lyon. This project started up in the spring of 2010. It is now financed by Mérieux Alliance Research Grants and the Hospices Civils of Lyon and has the objective of determining the gene expression signature associated with mycobacterial infection. Local research teams involved in the project are in charge of forming a first set of patient groups with tuberculosis and a selection of confounding pathologies that could be the basis for a broader study. Technology and know-how will also be transferred between the teams in Lyon and their counterparts in other countries.

As part of a call for proposals for the financing of research projects, the FINOVI Foundation financially supports a new research project run by Christine Delprat on the interaction between Mycobacterium and infected myeloid cells (Unit for Molecular Cell Biology UMR5239 CNRS-ENS Lyon-INRA).

INFLUENZA

The flu pandemic in 2009 reminded us that old or emerging viruses can infect the world's population at speeds that can easily outpace international prevention plans. What this pandemic also demonstrated is that the production of a new strain-specific vaccine to protect people requires several months. In order to be able to adapt more quickly to other pandemics, it is therefore crucial for antiviral drugs or new multipurpose vaccines to be developed for this pathology.

Parties involved in 2007

Many teams, belonging to the network of the FINOVI Foundation, are involved in studying the Influenza virus, and the research covers a broad spectrum of disciplines.
The structuralists of the Unit of the Structural Biology of Interactions between Viruses and Host Cells (UMI3265 CNRS - UJF – EMBL) are studying the structure and function of the virus' proteins.
The research team of Bruno Lina and the National Reference Centre (CNR) that he runs is studying the pathogenic mechanisms associated with the various strains of influenza.
A systems biology approach with the aim of defining the network of interactions between viral proteins and host cell proteins started up in the "Immunity, Infection and Vaccination" Unit (U851 INSERM-UCBL–HCL) in 2007.
Projects aiming to improve flu vaccination are being developed in the Unit of Human Virology (U758 INSERM-ENS) and in the "Immunity, Infection and Vaccination" Unit (U851 INSERM-UCBL–HCL).

The objectives of FINOVI were to support innovation, multidisciplinary research and inter-regional collaborations, by financing projects.

Projects supported by the FINOVI Foundation

As part of these calls for proposals for the financing of projects, the FINOVI Foundation is supporting 5 projects on influenza.

Three innovative projects supported by the FINOVI Foundation could lead to the development of new drugs:

- Collaboration between the teams of Cusack-Ruigrok and Darren Hart (Unit of the Structural Biology of Interactions between Viruses and Host Cells UMI3265 CNRS - UJF - EMBL): determining the crystallographic structure of polymerase and more specifically characterising the regions involved in the adaptation to humans of viruses of animal origin. Specific inhibitors of these regions are under development with the financial support of the EMBL and the European Union.
  This project is part of a collective effort to determine the structure of the proteins involved in the adaptation of viruses to humans.
- Collaboration between Lyon and Grenoble (B.Lina CNRS FRE 3011 and the Partnership for Structural Biology): characterising through electron cryo-microscopy the mechanisms controlling the pairing of viral RNA, a process involved in the generation of "new" flu viruses. This project was initiated thanks to the science theme days.
- Project of Martin Blackledge (Institute of Structural Biology (IBS) UMR5075 CEA-CNRS-UJF), collaboration between the European High Field NMR Centre of Lyon and Grenoble: determining by NMR the structure of the nucleocapside of the measles virus.
  This methodological approach will also make it possible to study and characterise flexible non-structured segments of viral proteins in many viral proteins, including the flu virus.

Two multidisciplinary projects are also receiving support:

- Collaboration between the mathematicians (IXXI: Institute of Complex Systems CNRS - INRIA - ENS - UCB - UJF) and the immunologists of U851: a project for the multi-scale modelling of the CD8 response with the aim of modelling the cell immune response to the flu virus. This type of model could lead to the development of tools enabling improved prediction of the quality of the vaccine response.
- Collaboration between physicians from the Physics Unit UMR 5672 CNRS – ENS and clinicians from the Unit of Biometrics and Evolutionary Biology UMR 5558 CNRS - INRIA - UCBL1: project on measuring the propagation of the flu in a hospital setting. The modelling of the nosocomial flu should lead to improved knowledge and thus to improved control of the propagation of this type of infection in hospitals.

STREPTOCOCCUS PNEUMONIAE

Streptococcus Pneumoniae (Pneumococcus) causes the death of more than one million persons every year (1.6 million, WHO figure 2002). Those at highest risk are infants, the elderly and patients with reduced immunity. Antibiotic treatment remains effective, although an increase in the resistance to ß-lactams has been observed. This pathology can be prevented through vaccination. However, the current polysaccharide vaccine is ineffective in very young infants and rare serotypes not covered by the vaccine are starting to emerge. In this context, it is important to develop new vaccines protecting against all serotypes (universal vaccines) or capable of protecting infants under the age of two.

Parties involved in 2007

The teams of the IBS* are studying the protein structure of the cell wall of the pneumococcus involved in host/pathogen interactions or in resistance to beta-lactam.
The U851 is developing projects aiming to identify adjuvants capable of eliciting a response to bacterial polysaccharides in infants. **The objectives of FINOVI were to support projects on the biology of the pathogen or the host response.**

Projects supported by FINOVI

Two IBS* projects were supported:

- The project of Nicole Thielens aims to better understand the role of complement lectins in the innate response to *Streptococcus Pneumoniae*.
- The project of Jean-Michel Jault aims to study the structure of two new carriers involved in the drug resistance and virulence of *Streptococcus Pneumoniae*.

* Institut de Biologie structurale de Grenoble

NOSOCOMIAL INFECTIONS

NOSOCOMIAL INFECTIONS (NI) REPRESENT A SERIOUS PUBLIC HEALTH PROBLEM THAT TRANSLATES, AMONGST OTHER THINGS, INTO:

- A HOSPITAL MORTALITY RATE OF 10% TO 30%
- AN EXTENSION OF HOSPITAL STAYS
- EXCESSIVE CONSUMPTION OF ANTIBIOTICS

These infections develop in high-risk patients, of whom the most exposed are patients hospitalised in intensive care, surgical patients and immunosuppressed patients. Due, on the one hand, to an increase in the average age of hospitalised patients and on the other hand to an increase in therapeutic and diagnostic techniques that carry a risk of infection (endoscopy, interventional radiology, prostheses, transplantations, etc.) the incidence of these infections may rise in the coming years. Furthermore, the widespread and sometimes inappropriate use of antibiotics causes the emergence of resistant bacteria.
The importance of these infections in terms of public health and the existence of recognised expertise in this field in the Rhône-Alpes Region (in particular with the presence in Lyon of the *Staphylocoque Aureus* CNR - National Reference Centre) have led the FINOVI Foundation to develop specific actions on this theme.

Parties involved in 2007
Several research teams and hospital department teams (CHU of Grenoble and Hôpitaux de Lyon) are involved in this theme at regional level, but very often, the "gateway" to the theme of nosocomial infections is integrated into broader research areas concerning certain germs (*i.e. S. Aureus*) or types of disease (i.e. intensive care or haematology departments). It has thus become essential to clearly identify the theme of nosocomial infections as an investigative field in its own right, requiring a specific approach due to the multiple factors involved in the emergence of these infections. This area of focus should integrate microbiological, environmental, epidemiological and clinical components.

The avenues explored have led to the preferential sequencing of two germs for which high-quality, recognised research is being conducted in Rhône-Alpes: *Staphylocoque Aureus* and *Pseudomonas Aeruginosa*. The detection of these two infectious agents, very involved in the development of nosocomial infections, facilitated the identification of clinical and biological teams with an interest for studying these germs and united these teams around project proposals. An initial observation made it possible to identify teams in Grenoble and Lyon that either had few exchanges in terms of collaboration or teams for whom collaboration could be more formal and effective.

Actions developed by the FINOVI Foundation
The FINOVI Foundation supported this theme on several scores

- Creating a network of researchers and uniting them around joint projects
- Increasing added scientific value by integrating new teams
- Organising regional science days
- Financing projects in the framework of calls for proposals

• *Creation of a network of researchers*
A review of the state of affairs was conducted in order to identify biology teams in the broad sense (microbiology, immunology, fundamental sciences, etc.) and clinical and epidemiological teams likely to build this network. The existence of an epidemiological surveillance network of these infections between Grenoble and Lyon facilitated this process. This network essentially relies on the intensive care units of the two university medical centres. Several meetings were held in order, on the one hand, to structure collaborative functioning, and on the other hand, to identify shared research themes without neglecting the themes specific to each team.

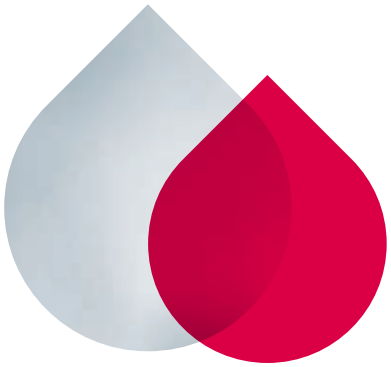
The teams of the FINOVI network comprising the core of this focus area in 2007 belonged to the following units:

- Unit of Biometrics and Evolutionary Biology
  UMR 5558 CNRS-INRIA-UCBL1
- Immunity, Infection and Vaccination Unit
  U851 INSERM-UCBL–HCL
- Microbial Ecology Unit
  UMR 5557 CNRS-INRA–UCB
- Unit for the Adaptation and Pathogenesis of Microorganisms
  UMR5163 CNRS–UJF, IBS UMR5075 UJF-CNRS

The working group set up between the teams in Grenoble and Lyon made it possible to:

- Organise two collaborative projects between the teams in Grenoble and Lyon
- Organise a national multi-centre cohort project studying the risk of infection from artificial hip joints (initiated by: Professors Chiddiac and P Vanhems, coordination: Finovi) which was submitted to the call for proposals on cohorts in the framework of the "Grand Emprunt" public loan. This project, submitted in collaboration with LyonBiopole, was not selected. Nevertheless, it made it possible to intensify collaboration between the teams, and it may serve as the foundation for a future project, for future funding requests
- Collaborate with LyonBiopole since 2010, especially on the theme of sepsis. Although sepsis can be community-acquired or nosocomial, this initiative is one of the priorities of FINOVI, and it is important from the point of view of this pathology's impact on public health, for which the mortality rate can be 30% and sometimes more

Research activities concerning nosocomial infections should also be brought into perspective with another priority area of FINOVI: respiratory infections. Indeed, in the long term it would be useful, for example, to consider projects on pulmonary nosocomial infections acquired in intensive care.
Finally, it is important to note that nosocomial infections were selected as research themes in the development of the IRT of Lyon. Members of the Executive Board of FINOVI participated in several meetings required fro the development of this project.



• *Integration of new teams*
Two teams of researchers whose areas of research have enriched the nosocomial theme have joined the FINOVI network. It was the team directed by I. Attrée (Pathogenesis of bacteria and cell response ERL5261-UMR 1036-CEA-UJF) and the team directed by A. Imberty (Molecular Glycobiology - CERMAV UPR5301-CNRS-UJF). These fundamental research teams could contribute to the study of pathogenic phenomena facilitating the development of nosocomial infections in both of the two selected target germs. The dearth of nosocomial-infection studies in the fundamental sciences is stressed on a regular basis (in editorials, conventions, reports, etc).

• *Regional science days*
Twice, FINOVI took the initiative of organising science days on the theme of nosocomial infections in 2009 and 2010 (programme in Appendix). Speakers internationally renowned in the presented themes were invited to complement presentations by local researchers. In 2010, this event was co-organised with LyonBiopole, which made it possible to broaden the audience to a larger number of industrial players. The quality of the presentations was unanimously acclaimed, and this event will be repeated in 2011. In addition to the presentations, exchanges that took place between the participants and the Executive Board of FINOVI also made it possible to identify the areas of research that may represent new avenues of investigation, such as nosocomial infections in the elderly.

• *Projects financed as part of the calls for proposals*
Thanks to the calls for proposals, the FINOVI Foundation has been able to support a certain number of innovative projects often proposed by teams whose area of expertise is not directly part of the theme of nosocomial infections. The major themes supported by FINOVI are given below.

Two of the financed projects combine modelling, physics and epidemiology. These multidisciplinary projects, initiated by N. Voirin and E. Fleury, study the propagation of viral and bacterial infections in hospitals. (Nicolas Voirin - Unit of Biometrics and Evolutionary Biology UMR 5558 CNRS-INRIA-UCBL1, Eric Fleury, Unit of Parallel Computing UMR 5668 CNRS–INRIA).

A new approach of vaccination against *Staphylococus Aureus* is going to be tested by the team of Dr T De France. (Thierry De France - Immunity, Infection and Vaccination Unit - U851 INSERM-UCBL–HCL).

Three of the projects study the molecular mechanisms of the interaction between "nosocomial" pathogens (*Staphylococus Aureus, Pseudomonas Aeruginosa, Aspergillus Fumigatus*) **and their host** (Ina Attrée – Team on Bacterial Pathogenesis and Cell Response - Unit of Cancer and Infection Biology, Anne Imberty – Molecular Glycobiology Team - Centre for Research on Plant Macromolecules (CERMAV) UPR5301-CNRS-UJF, Anne Tristan and François Vandenesch - Immunity, Infection and Vaccination Unit U851 INSERM-UCBL–HCL).

The interaction between *Staphylococus Aureus* and the cells that cause bone homeostasis (osteoclasts, osteoblasts) will be studied in order to identify the mechanisms that may be responsible for osteolysis, associated with prosthesis infections. The project was initiated by the team of Pierre Jurdic, specialising in the study of bone cells. (Pierre Jurdic - Institute of Functional Genomics of Lyon UMR5242 CNRS-UCBL1-ENS–INRA).

A clinical research programme initiated by G. Monneret aims to better understand the deregulations of the immune system associated with sepsis (Guillaume Monneret - Immunity, Infection and Vaccination Unit U851 INSERM-UCBL–HCL).

Conclusions: The networking and promotional efforts made by the FINOVI Foundation have brought about innovative new projects, focusing on the issues of nosocomial infections and combining a wide variety of skills (from epidemiology to cell biology, together with structural biology and microbiology). The issues addressed by the projects fit into the theme of nosocomial infections, financed by the Foundation, perfectly illustrating the transdisciplinary research strategy that is required for the emergence of innovative projects applied to these pathologies.

Research units attached to the FINOVI Foundation

Core units

Unité de Virologie Humaine
U758 INSERM-ENS Lyon

Centre de Génétique Moléculaire et Cellulaire
UMR 5534 CNRS/UCBL1

Unité de Biologie Structurale des Interactions entre virus et cellule -hôte
UMI3265 CNRS - UJF – EMBL

IBCP (Institut de Biologie et Chimie des Protéines)
UMR5086 CNRS-UCBL

Unité d'Immunité, Infection et Vaccination
U851 INSERM - UCBL –HCL

Unité Rétrovirus et Pathologie Comparée
UMR754 INRA-ENVL-UCBL

Unité de Biométrie et Biologie Évolutive
UMR 5558 CNRS - INRIA - UCBL1

Institut de Biologie Structurale (IBS)
UMR5075 CEA-CNRS-UJF

Institut de Génomique Fonctionnelle de Lyon
UMR5242 CNRS - UCBL1 - ENS – INRA

Unité de Biologie Moléculaire de la Cellule
UMR5239 CNRS-ENS Lyon-INRA

Unité de Biologie des Infections Virales Émergentes
UBIVE Institut Pasteur

Unité de Physiopathologie Moléculaire et Nouveaux Traitements des Hépatites Virales
U871 INSERM – UCB

Équipe Pathogénèse des Bactéries et Réponse Cellulaire ERL5261 - Unité de Biologie du Cancer et de l'Infectieux
UMR1036 INSERM - CEA – UJF

Équipe de Glycobiologie Moléculaire - Centre de Recherches sur les Macromolécules Végétales (CERMAV)
UPR5301 - CNRS – UJF

Équipe Immunologie des Pathologies Chroniques - Institut Albert Bonniot
U823 INSERM - UJF - CHU - EFS – CNRS

Partner units

Unité d'Écologie Microbienne
UMR 5557 CNRS - INRA – UCB

Unité de Génétique Moléculaire, Signalisation et Cancer
UMR 5201 CNRS

Laboratoire Joliot Curie
USR3010 - CNRS – ENS

Unité Adaptation et Pathogénie des Micro-organismes
UMR5163 CNRS – UJF

Unité de Physique
UMR 5672 CNRS – ENS

Unité de l'Informatique du Parallélisme
UMR 5668 CNRS – INRIA

Unité de Mathématiques Pures et Appliquées
UMR 5669 CNRS – ENS

Institut des Systèmes Complexes
CNRS - INRIA - ENS - UCB – UJF

Unité de Sciences de la Terre
UMR 5570 CNRS - ENS – UCB

Unité de Chimie
UMR 5182 CNRS

Unité de Reproduction et Développement des Plantes
UMR 5667 CNRS – INRA

Unité de Recherche INRIA Rhône-Alpes

Centre International de Recherche contre le Cancer

GLOSSARY

CIRI : Centre International de Recherche en Infectiologie

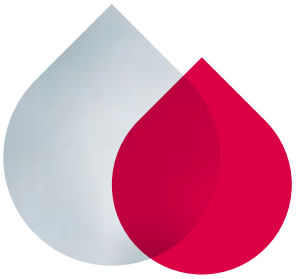
IBS : Institut de Biologie Structurale

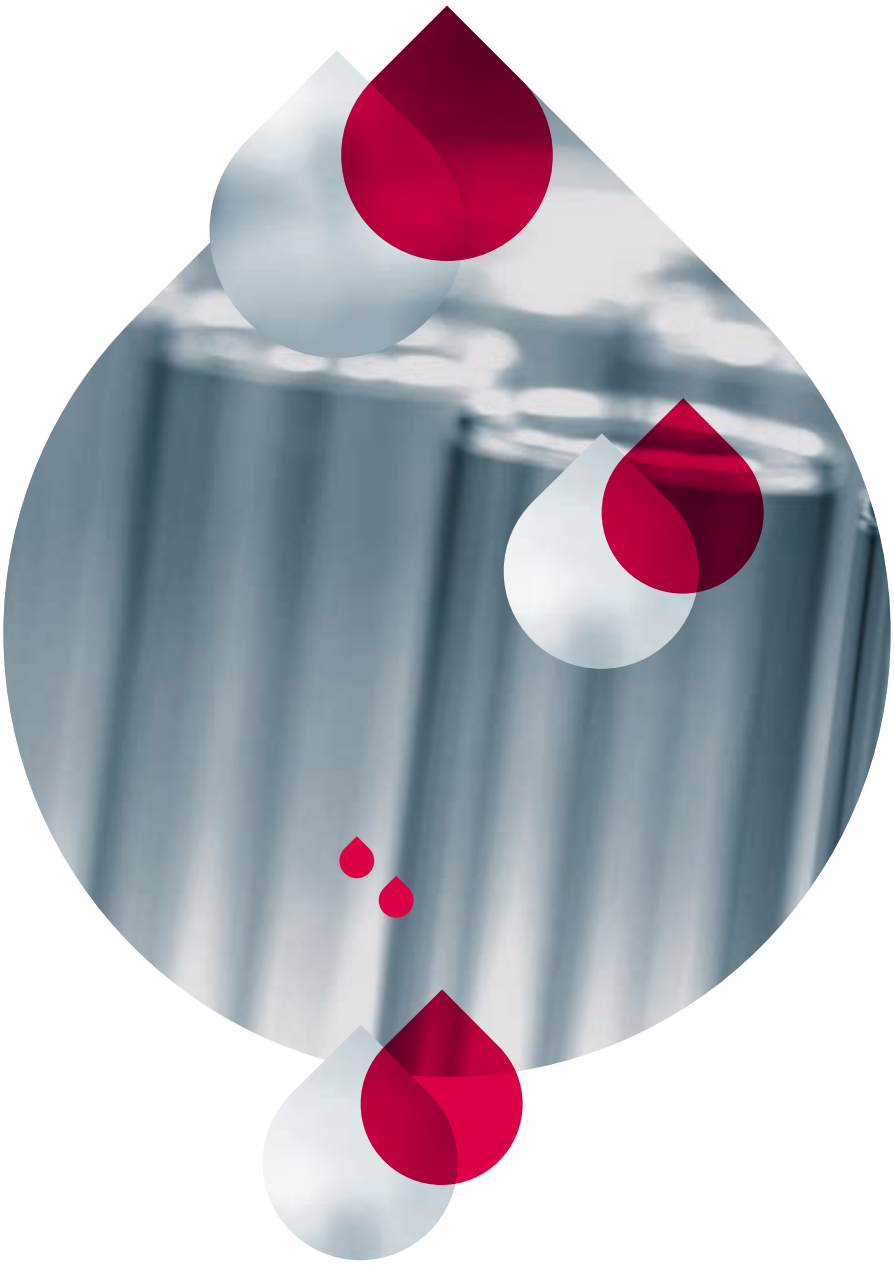
IBCP : Institut de Biologie et Chimie des Protéines

AERES : Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur

CHU : Centre Hospitalier Universitaire

IN : Infections nosocomiales





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Innovations in Infectiologious Diseases

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