Département **H**ospitalo-**U**niversitaire

TORINO

THORAX INNOVATION

COORDINATOR: MARC HUMBERT, MD, PhD

UNIVERSITE PARIS-SUD
AP-HP, IGR, CCML
Inserm

SCIENTIFIC PROJECT

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TORINO project

Coordinator: Marc Humbert

UNIVERSITY/HOSPITALS DEPARTMENTS
(DHU)
Ile-de-France Region

The relevant local committee for health and biomedical research has been notified of the proposal

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Proposal Coordinator: **Pr Marc HUMBERT**

Le Kremlin Bicêtre, 18th October 2011

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Le Kremlin Bicêtre, 18th October 2011

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Le Kremlin Bicêtre, 18th October 2011

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Le Kremlin Bicêtre, 18th October 2011

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SELECTED ABBREVIATIONS

1. AP-HP: *Assistance Publique – Hôpitaux de Paris*
2. CCML: *Centre Chirurgical Marie Lannelongue*
3. DHU: *Département Hospitalo-Universitaire*
4. ED: *Ecole Doctorale*
5. IGR: *Institut Gustave Roussy*
6. Inserm: *Institut national de la santé et de la recherche médicale*
7. LERMIT: Laboratory of Excellence on Research in Medication and Innovative Therapeutics

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SUMMARY

The *Departement Hospitalo-Universitaire* (DHU) TORINO (Acronym for "THORAX INNOVATION") is a multidisciplinary consortium composed of high-profile physicians and surgeons, educators, biologists, physiologists, epidemiologists, pharmacologists, and other healthcare providers joining forces to collectively improve care, education and research of major thoracic disorders and explore novel medical and surgical therapeutic avenues thereof.

Our joint goal is to improve healthcare, education and research - and ultimately cure - three major groups of thoracic diseases that represent a significant threat to society: chronic pulmonary vascular diseases and their associated cardiac consequences; thoracic cancer; and asthma. To achieve this goal, our strategy is to:

1. build and reinforce strong clinical networks and patient registries;
2. improve our understanding of these diseases based on multidisciplinary approaches, from research of environmental disease determinants through epidemiology, to the molecular mechanisms causing these diseases through basic science;
3. discover new therapeutic targets and companion biomarkers/diagnostic tools in order to provide diagnostic solutions for patient subgroups;
4. design and develop new approaches to treat - or stop the progression of - these diseases in a personalized medicine perspective; and
5. support educational programs for MD, PhD and post-doctoral fellows in the TORINO environment.

The various partners will offer the highest standard of modern medical and surgical healthcare in the TORINO fields. In this unique environment, graduate students, young post-doctoral fellows and all TORINO members will be exposed to cutting-edge developments in thoracic disease understanding, modeling of disease, drug discovery, medical and surgical therapeutic innovation, epidemiology and pharmacovigilance, through unique interdisciplinary networking and training courses. Besides maintaining the highest standards of academic research, TORINO will generate intellectual property.

To this aim, TORINO will capitalize on a unique combination of expertise present within the *Université Paris-Sud*. This University is unique in the *Ile de France/Paris* region in that it hosts a Faculty of Medicine, a Faculty of Pharmacy, a Cancer Institute and a Thoracic Surgical Centre. It is a true international leader in the three main clinical aspects of TORINO.

First, our University has a recognized Thoracic Division at the *Hôpitaux Universitaires Paris-Sud, Assistance Publique Hôpitaux de Paris,* hosting the French Referral Centre for Severe Pulmonary Hypertension, and a strong clinical research unit in the field of severe pulmonary hypertension.
Second, the Institut Gustave Roussy, a leading academic cancer institute in Europe, has a pivotal role in thoracic cancer care, education and research.
Third, the Centre Chirurgical Marie Lannelongue is a world-renowned thoracic surgical centre hosting a unique combination of expert surgeons, a tissue bank, an experimental surgery laboratory and a research unit devoted to pulmonary hypertension pathophysiology and clinical research in partnership with Inserm, *Assistance Publique Hôpitaux de Paris and Université Paris-Sud.*

In addition, our epidemiology division consists of renowned pulmonary epidemiology teams dedicated to the study of several large cohorts of major interests, with a particular emphasis on asthma research. Last, three doctoral schools allow doctoral and post-doctoral research in the fields of epidemiology, oncology and therapeutic innovation.

Our ambition is to promote thoracic innovations in our University. TORINO thus represents a driving force behind the university/hospital dynamics, creating a new synergism and helping to innovate and revolutionize site policy. TORINO represents a major opportunity for the Hospitals, the University and Inserm to gain visibility over the three dimensions of quality of care, teaching and research, thus strengthening the appeal of the university/hospital sites. In addition, TORINO will promote stronger links between *Assistance Publique Hôpitaux de Paris* and major hospitals in the South Paris area, allowing cross-talk to consolidate a unique European partner in the field.

FOREWORD

Since 2011, the *Université Paris-Sud* (http://www.u-psud.fr/en/index.html) is the leading French University in the academic rankings of world universities (rank 40, http://www.shanghairanking.com/ARWU2011.html) and it is one of the three French Universities in the top 100 of academic rankings of world universities in Clinical Medicine and Pharmacy (rank 75-100, http://www.shanghairanking.com/FieldMED2011.html). This University hosts 30,000 students and has a strong interest in all aspects of science, with several campuses in the southern suburbs of Paris. This University is unique in the *Ile de France/Paris* region in that it hosts a Faculty of Medicine with strong historical links with the *Assistance Publique Hôpitaux de Paris* (AP-HP, the largest hospital in Europe with 90,000 employees in 37 hospitals and 12 hospital groups), a Faculty of Pharmacy, a Cancer Institute and a Thoracic Surgical Centre. In the 2010-2014 strategic plan of the *Assistance Publique Hôpitaux de Paris* (http://www.aphp.fr/site/connaitre/plan-strategique.html), a priority for the *Hôpitaux Universitaires Paris-Sud* was the promotion of an *Institut du Thorax,* corresponding to the present application.

Our proposed *Département Hospitalo-Universitaire* TORINO (Acronym for "THORAX INNOVATION") is an alliance of leading hospital departments, Inserm mixed research units (most of them with a top A+/A AERES evaluation) and doctoral schools (*Ecoles doctorales,* ED) all within the *Université Paris-Sud* area:

- TORINO includes 12 healthcare departments (hosting 3 rare disease referral centres) in hospitals from the *Assistance Publique Hôpitaux de Paris (Hôpitaux Universitaires Paris-Sud),* the *Institut Gustave Roussy* (IGR, Cancer Institute) and the *Centre Chirurgical Marie Lannelongue* (CCML, Thoracic Surgical Centre).

- TORINO has a strong research and teaching capacity with 14 Inserm teams in 9 Inserm research units as well as a strong partnership with the Laboratory of Excellence on Research in Medication and Innovative Therapeutics (LERMIT, coordinator Rodolphe Fischmeister, a core partner of our current proposal).

- TORINO contributes to 3 doctoral schools (ED418, oncology, ED420, public health, and ED425, therapeutic innovation) that have a large number of staff members and students and are all within the *Université Paris-Sud.*

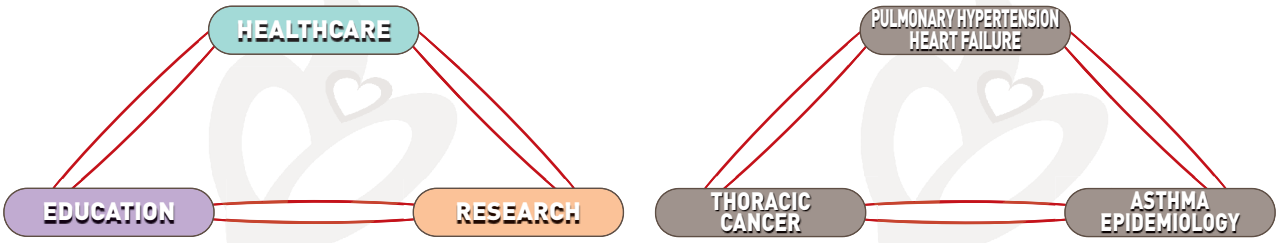
- In the last 10 years, TORINO partners have produced more than 1,500 original articles in leading international journals (including N Engl J Med, Lancet, Nat Med, Ann Int Med, Circulation, J Clin Oncol, J Clin Invest, J Exp Med, Am J Respir Crit Care Med...). TORINO members have been principal investigators in more than 100 randomized controlled trials in partnership with the industry. They have raised more than 25 M € thanks to a large number of clinical, basic and translational grants at the French, European and international level (LabEx Investissements d'Avenir, PHRC, EU FP5, FP6, FP7, IMI, NIH, Leducq, INCa...). TORINO partners host some of the largest biobanks, tissue banks and DNA banks in their fields, and they have patented original discoveries (more than 10 patents obtained or in progress). In parallel, they have strong teaching commitment and they have built professional and friendly links with national and international patients associations in their field of interest.

Of note, the Laboratory of Excellence LERMIT has boosted our current proposal. Indeed, LERMIT is a multidisciplinary laboratory of the *Université Paris-Sud* composed of 15 partners with expertise in medical biology, biological chemistry, medical chemistry, physico-chemistry and pharmaceutical sciences joining forces to collectively explore new therapeutic avenues. One of the major TORINO objectives will be to act as a translational research structure that allows LERMIT discoveries to be tested at the bedside in the thoracic arena. This will allow high quality healthcare, education and research in 3 groups of thoracic conditions that have clear unmet clinical needs:

- Chronic pulmonary vascular diseases and their consequences on the right heart
- Thoracic cancer
- Asthma, respiratory epidemiology and environment

SCIENTIFIC FOCUS AND OBJECTIVES

TORINO'S CONCEPT



Over the last 30 years, the *Université Paris-Sud* has been able to build and support world-leading centres in pulmonary vascular medicine, thoracic cancer, thoracic surgery and respiratory epidemiology, together with the Inserm, the *Hôpitaux Universitaires Paris-Sud* of the AP-HP, the CCML Thoracic Surgical Centre and the IGR Cancer Institute. However, these sites have historically developed their own strategies independently or have adopted only limited partnerships with one another. There is thus room for a major alliance in order to promote a global program for thoracic healthcare, education and research in the *Ile de France/Paris* Region.

In order to meet its ambitious objectives, the TORINO proposal corresponds to a strong multi-disciplinary consortium composed of high-profile physicians and surgeons, educators, biologists, physiologists, epidemiologists, pharmacologists, and healthcare providers joining forces to collectively improve care, education and research of major thoracic disorders and explore novel medical and surgical therapeutic avenues. TORINO will thus represent a driving force behind the university/hospital dynamics, creating new synergism and helping to innovate and revolutionize site policy. TORINO represents a major opportunity for the Hospitals, the University and Inserm to gain visibility over the three dimensions of quality of care, teaching and research, thus reinforcing the appeal of the university/hospital sites. In addition, TORINO will promote stronger links between AP-HP and major hospitals in the South Paris area, allowing cross-talk to consolidate a unique European partner in the field.

Pulmonary hypertension and right-heart failure, thoracic cancer and asthma are three major burdens to mankind that lead to chronic disability and often premature death, and have enormous direct and indirect economic consequences for our healthcare system. TORINO's first goal is to facilitate in-depth interactions of 3 highly competitive communities from the same geographic region into a single hospital/university partnership in order to create a world leader in the respiratory/thoracic field. The ultimate objective is to create a consortium that builds on current successes to enable future development in the fields of pulmonary vascular medicine and its cardiac consequences, thoracic cancer and its management, asthma and respiratory epidemiology, as well as developing innovative therapies in these 3 major areas, including innovative surgical techniques when appropriate. A core aim of TORINO is the reduction of the burden of these major thoracic conditions by improvement of patients' management and outcomes. TORINO will also facilitate the education of clinicians and researchers, as well as medical and paramedical professionals with respect to these conditions in order to improve awareness, screening, prevention, management and research. In addition, TORINO partners have included patients' associations in their priorities. For example, academic and friendly links have been established with patients' associations in the field of thoracic conditions, including *Asthme et Allergies, HTAP France,* Pulmonary Hypertension Association Europe and Pulmonary Hypertension Association US.

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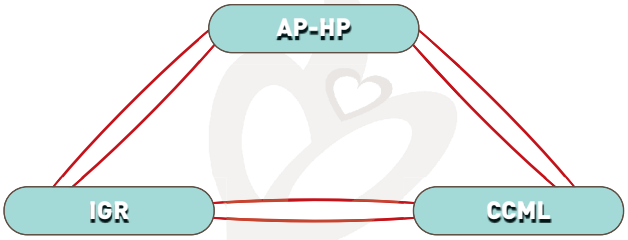
PARTNERS

TORINO brings together a large number of healthcare departments from our major University hospitals and Inserm mixed research units contributing to three doctoral schools. TORINO will gather a critical mass of hospital staff, educators, and lecturers/researchers in the thoracic medicine arena.
In the following section, we will briefly describe the hospital healthcare departments as well as education and research facilities that will be partnered in the field of respiratory/thoracic medicine. This document will focus primarily on how the group will transform and structure the field in the *Université Paris-Sud* with AP-HP, IGR, CCML and Inserm.

HOSPITAL PARTNERS



THE HEALTHCARE SECTION OF TORINO

- AP-HP: Pôle Thorax des Hôpitaux Universitaires Paris-Sud (National Referral Centre for Severe Pulmonary Hypertension)
- AP-HP: Medical intensive care department
- AP-HP: Surgical intensive care department
- AP-HP: Pharmacy of the Hôpital Antoine-Béclère
- AP-HP: Laboratory of Hematology (National Referral Centre for von Willebrand disease and National Referral Centre for Thrombotic Microangiopathies)
- CCML: Departement of thoracic surgery
- CCML: Department of congenital heart diseases
- CCML: Department of pathology
- IGR: Department of medical oncology
- IGR: Service d'Innovation Thérapeutique et Essais Précoces
- IGR: Department of radiation therapy
- IGR: Department of medical imaging

The healthcare section of TORINO is built around three core centres at the forefront of their respective fields in Europe and belonging to each of the three major hospitals of the *Université Paris-Sud.* These three hospitals play a major role in patient management and have complementary expertise in thoracic medicine. The DHU call offers our community a unique opportunity to demonstrate its ability to transform and structure the thoracic field and build a European leader in our area.

- AP-HP: the *Pôle Thorax des Hôpitaux Universitaires Paris-Sud* is one the world leaders in the field of pulmonary hypertension care, education and research. This structure includes some of the most renowned leaders in the field and has long been a driving force in clinical research and drug development. Its clinical research facilities have allowed the group to contribute to major clinical studies of medical therapies in pulmonary arterial hypertension (PAH) and chronic thrombo-embolic pulmonary hypertension (CTEPH). This department is the French Referral Centre for Severe Pulmonary Hypertension and has structured a network of 26 centres throughout the country (including overseas departments) with a shared web-based registry (with an Inserm label), a unique tissue bank (that processes explanted lungs at the time of lung transplantation), a biobank and the largest DNA bank in the world.

- IGR: this Institute gathers an impressive number of health care providers, educators and researchers in the field of cancer. The impact of the thoracic cancer teams is outstanding. The Medical and Radiation therapy departments and the *Service d'Innovation Thérapeutique et Essais Précoces* are leaders in thoracic cancer care, education and research, with a strong emphasis on early phase drug development. The department of medical oncology with its leading phase I unit plays a key role in the early assessment of novel strategies.

The contribution of this partner to thoracic oncology is outstanding and has become even stronger in recent years with the development of a well-structured personalized cancer medicine program, a major commitment of this centre, together with a competitive research program on biomarkers. In addition, new imaging and radiation therapy equipments have allowed development of innovative stereotactic radiotherapy techniques in order to enhance anti-tumor efficacy with minimal toxicities at the thoracic level. These up-to-date methodologies in the setting of a larger partnership will reinforce the leadership role of this group.

- CCML: the *Département de Chirurgie Thoracique* is a recognized leader in thoracic surgery for pulmonary hypertension and has considerable expertise in lung transplantation, as well as tracheal and lung cancer surgery. This centre has always emphasized that preclinical and experimental surgical research is a prerequisite to develop truly innovative surgery. Thanks to this, translational research from bench to bedside has been developed at this centre for severe thoracic malignant and nonmalignant conditions. The *Laboratoire de Chirurgie Expérimentale,* a platform of Inserm UMR_S 999, is a key component of this success. In recent years, this Centre has established successful links with services in the IGR and AP-HP. Thus, a stronger and closer "three partners relationship" with AP-HP together with IGR services through an academic department such as TORINO would be a major step forward.

Linked to these three core members, a network of important contributors will include:

AP-HP

- The *medical intensive care* and *surgical intensive care departments* have a recognized expertise in hemodynamic assessment and management of acute hemodynamic and cardio-pulmonary dysfunction. These two departments have expertise in hemodynamic physiology but are in need of direct collaboration with local research laboratories and doctoral schools in order to grow and establish novel collaborations. Within the *Pôle Thorax des Hôpitaux Universitaires Paris-Sud,* the *Department of Physiology* has a definite expertise in hemodynamics and exercise physiology. Currently, there is a clear need for this group of distinguished clinicians, educators and researchers to broaden its horizon in the setting of a larger facility such as the TORINO proposal.
- The *Hematology Laboratory* features the National Referral Centre for von Willebrand disease and is also the laboratory of the National Referral Centre for Thrombotic Microangiopathies. This laboratory plays a critically important role in the management of pulmonary vascular diseases and has been a partner for many years; the TORINO proposal will allow a new collaborative boost.
- The *pharmacy of the Hôpital Antoine-Béclère* is extremely dynamic in therapeutic education programs, and has been recognized by the Regional Health Agency for several conditions, including asthma and pulmonary hypertension; this partner will benefit from the large TORINO care, education and research facilities.
- The *outpatient clinic* of the *Pôle Thorax des Hôpitaux Universitaires Paris-Sud* has a strong interest for severe refractory asthma clinical research. It has been able to act as primary investigator in the pivotal trial of the only biologic approved for severe asthma in the world (omalizumab), as well as the first tyrosine kinase inhibitor phase II trial (masitinib), and the first anti-IL-5 monoclonal antibody phase II trial (mepolizumab). These biologics and tyrosine kinase inhibitors have helped our group to identify severe asthma as another focus in the strong clinical trial facility built in *Pôle Thorax des Hôpitaux Universitaires Paris-Sud.* This clinical expertise will benefit greatly from more interaction with the innovative therapy doctoral school and from the immunology and epidemiology research programs of TORINO.

IGR

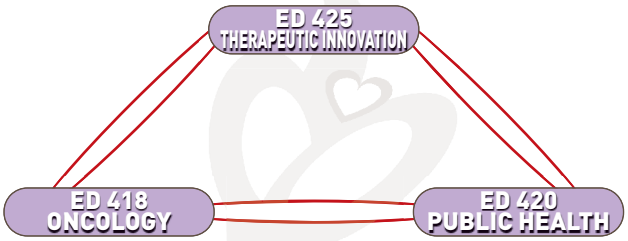
- The *department of medical imaging* with its unique platform of image-guided diagnosis and therapy is dedicated to minimally invasive treatment of cancer via image-guided percutaneous ablation of lung tumors using various techniques such as radiofrequency, microwaves or irreversible electroporation.
- *The department of radiation therapy* has a longstanding interest in the thoracic effects of irradiation on both healthy (heart and lung) and tumoral tissue.

CCML

• The *department of congenital heart diseases,* an international leader in the medical and surgical management of these conditions, will play an active role in this program and will benefit from the academic dynamics in the thoracic field.

• The *department of pathology* has been able to build two outstanding tissue banks for thoracic cancers and pulmonary vascular diseases, and has an established relationship with partners in AP-HP, IGR and Inserm in the *Université Paris-Sud;* TORINO will give a new boost to this department in the University with its diverse partners.

DOCTORAL SCHOOLS



THE DOCTORAL SCHOOLS OF THE TRAINING PROGRAM OF TORINO

- ED418: " Oncology: Biology, Medicine, Health"
- ED420: "Public Health"
- ED425: "Therapeutic innovation: from basic to advanced technologies"

The training program of TORINO is organized through three doctoral schools from the *Université Paris-Sud,* allowing high quality education in innovative therapies, medical oncology, cardio-oncology, and epidemiology.

• **ED418:** The PhD program "Oncology: Biology, Medicine, Health" is a thematic network mainly supported by IGR and Institut Curie and composed of about 80 research teams developing researches in the various fields of oncology. The school is at present composed of 200 PhD students with an average of 35 PhD thesis defended every year. The PhD program includes research project and teaching courses in the fields of biology of cancers, pharmacology and therapeutics as well as radiobiology. In the context of TORINO, ED418 will offer research programs in the aforementioned scientific and medical fields and training courses organized either by the research master in oncology or the doctoral school itself. Two new training courses will be organized, one dealing with the targeted therapy and the other one with the personalized medicine in oncology. These courses will be organized in connection with clinical services of IGR. The teaching program will therefore offer teaching units either close to fundamental research or close to clinical practice and will provide to students coming from various origins the access to an integrated formation in both molecular and clinical oncology.

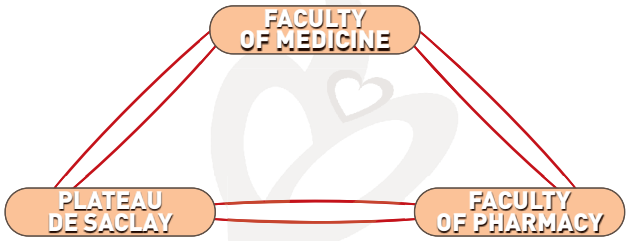
• **ED420:** The PhD program *"Public Health"* will offer high profile support in respiratory public health, pharmacovigilance and statistical genomics through unique interdisciplinary training courses. Two intensive courses, focusing on statistical genomics and pharmacovigilance will be organized. A seminar on new developments in the epidemiology of respiratory disease will also be proposed. The "statistical genomics" course will present recent biostatistical innovations for modeling next-generation sequencing data applied to human diseases and developing specific data integration approaches for association, classification and prediction purposes. The challenge in integrating statistical genomic concepts to lung diseases will be examined. The "pharmacovigilance" course will present the context of drug evaluation with recent methodological developments for surveillance and risk quantitative analysis. These courses will be designed for PhD students and postdoctoral fellows who are seeking training in state-of-the-art research approaches in statistical genomics and pharmacovigilance that are needed to pursue studies in lung diseases. These courses are also intended to foster new collaborative and interdisciplinary projects.

• **ED425:** The PhD program *"Therapeutic innovation: from basic to advanced technologies"* is currently composed of 280 PhD students and an average of 50 PhD theses are defended each year. This PhD program offers a variety of teaching programs in the field of therapeutic innovation. In the context of TORINO, the ED425 will offer cutting-edge research developments in drug discovery and therapeutic innovation through unique interdisciplinary training courses in translational medicine. The ED425 will develop two training courses offered to PhD students in the first year of the DHU: one in experimental surgery applied to therapeutic innovation and one covering the area of new molecular targets in cardiovascular and lung diseases. These training courses will be of one week's duration and will provide a unique access for PhD students to

clinicians that are leaders in their field. The training courses will be open to all PhD students that are either already working in the clinical setting or coming from laboratories engaged in fundamental research, thereby allowing the possibility for interdisciplinary exchanges.

Linked with these three core doctoral schools, a network of other educational tools will contribute substantially to TORINO and, most importantly, the *Pôle Thoracique des études de santé* at the *Faculty of Medicine of the Université Paris-Sud.*

RESEARCH TEAMS



THE MIXED RESEARCH UNITS OF TORINO

- Inserm UMR_S 669 (1 team): Integrative epidemiological genetics and multifactorial human diseases
- Inserm UMR_S 753 (1 team): Tumoral antigens and cytotoxic T cell reactivity
- Inserm UMR_S 769 (3 teams): Signalling and cardiac pathophysiology
- Inserm UMR_S 770 (2 teams): Hemostasis and vascular biology
- UMR_S 935 (1 team): Malignant and therapeutic stem cells
- Inserm UMR_S 981 (1 team): Biomarkers and novel molecular strategies in cancer therapy
- Inserm UMR_S 999 (2 teams): Pulmonary hypertension: pathophysiology and novel therapies
- Inserm UMR_S 1018, CESP (2 teams): Respiratory and environmental epidemiology; Biostatistics
- Inserm UMR_S 1030 (1 team) : Molecular radiotherapy

The research section of this DHU is led by groups and teams from major laboratories (the majority of which boast the highest ratings, i.e. AERES A+ or A) and their associated partners. Together, these form a network of sufficient critical mass to allow the research section to become established as a true world leader in the field. All are mixed research units or UMR (Unités Mixtes de Recherche), indicating that support is provided by the *Université Paris-Sud* and the Inserm.

Pulmonary Hypertension and (right) heart failure:

• Inserm UMR_S 999 is a core member of the DHU TORINO. The "Pulmonary hypertension: pathophysiology and innovative therapies" unit has two teams, one within AP-HP *Hôpitaux Universitaires Paris-Sud* (Antoine-Béclère and Bicêtre sites), and the other within CCML. This research unit aims to translate novel information produced by its own basic and clinical research units into advances for patient care. This group includes the leading French teams in pulmonary hypertension research, education and care, working jointly to improve the understanding and treatment of pulmonary hypertension, a severe condition with a largely underestimated burden and significant unmet needs. This research group promotes synergies between basic scientists and clinicians with a shared access to a large clinical registry, tissue bank and related biobanks in a fast-moving and competitive area of medical research.
A priority of the immunopathology group of Inserm UMR_S 999 is to better describe the immune characteristics of PAH, which frequently arises as a complication of autoimmune or infectious conditions such as systemic sclerosis or HIV infection. This group of Inserm UMR_S 999 will develop strong relationships with team 2 of Inserm UMR_S 996, which has a strong research emphasis on cytokines, chemokines and pulmonary inflammation and will allow a better understanding of the immunopathology of (auto-) immune mechanisms that lead to chronic remodeling of the small pulmonary arteries. Of note, pulmonary vascular remodeling is also a consequence of chronic aeroallergen exposure in sensitized individuals. This phenomenon will be further explored through our novel partnership, as will methods of inducing tolerance in chronic pulmonary immune conditions such as asthma and auto-immune PAH.
• The three teams of Inserm UMR_S 769 are core members of TORINO. Inserm UMR_S 769 is located on the campus of the Faculty of Pharmacy. The unit is conducting basic science research in cardiac pathophysiology and is deeply involved in education and training of pharmacy students at undergraduate and graduate levels. Inserm UMR_S 769 is a founding member of the Laboratory of Excellence LERMIT. Cardiovascular diseases remain the leading cause of death in developed countries, and chronic heart failure in particular is a major cause of morbidity and

mortality. Heart failure is the only cardiovascular disease that is increasing in prevalence in Europe and the USA. Heart failure is generally defined as inability of the heart to supply sufficient blood flow to meet the body's needs and most cases are caused by diseases of heart muscle that result in pathologic hypertrophy ("remodeling" at the ventricular chamber level) and contractile dysfunction. The work of UMR_S 769 is based on the study of signaling pathways in adult cardiomyocytes, and of their modifications during cardiac hypertrophy and failure. The Unit is composed of three teams that work synergistically on complementary aspects, sharing similar animal and cellular models. Importantly, the TORINO exercise will facilitate a strong collaboration with other TORINO partners on (1) right-heart failure and pulmonary hypertension, a topic currently regarded as a priority among unmet thoracic needs and (2) cardiac complications of cancer treatment (radiotherapy and chemotherapy), which represents a major burden to cancer patients. TORINO aims to revolutionize links between partners in cardiology, pulmonology, oncology and related educators and researchers.

• The AP-HP *Hôpitaux Universitaires Paris-Sud* (Paul Brousse)-based UMR_S 935 and its related stem cell platform will strongly support the inclusion of stem cell research in the setting of our thoracic program. Of note, Inserm UMR-S 999, together with our experimental surgery laboratory, is designing a pig model of right heart failure secondary to congenital heart disease (tetralogy of Fallot pathophysiology) and has already obtained support to assess the potential for stem cell-based therapy to restore right ventricular function in that model, as assessed by invasive, non invasive and structural approach measurements. This novel alliance within the South Paris University will transform and structure the landscape of thoracic translational research, involving the Faculty of Medicine and Pharmacy, hospitals and research laboratories.

Thoracic cancer:

• The IGR-based Inserm UMR_S 981 has built an outstanding program on biomarkers and novel molecular strategies for cancer therapy. This laboratory is a major partner of the *Service d'Innovation Thérapeutique et Essais Précoces,* promoting transfer to and from the laboratory in the setting of personalized medicine. This laboratory has a particular focus on thoracic cancers and has played a key role in the discovery of molecular biomarkers (circulating cancer cells and DNA). It has also built a platform to analyze kinase activity in tumors. This latter component of the program is of particular relevance in our collaborative efforts, since kinase inhibitors are now also being examined as therapeutic adjuncts in nonmalignant diseases such as PAH and refractory asthma. Given the extensive knowledge of and experience with this class of agent (including potential effects in thoracic cancers and nonmalignant conditions, as well as associated cardiac and pulmonary toxicities), the TORINO alliance will allow us to become a genuine world leader in the field of kinase inhibitor therapeutics. One of the top priorities of the TORINO consortium will be to focus on the "double-edge sword" effects of kinase inhibitors in thoracic cancers and nonmalignant pulmonary diseases. An improved understanding of the mechanisms of action of this class of agent will allow clinicians to better predict, prevent and manage cardio-pulmonary side effects of these and other drugs used in oncology, in particular unexpected cardiac and pulmonary vascular side effects. This will be accomplished by enabling a collaboration between all of the TORINO research partners in order to describe, understand, prevent and manage life-limiting side effects, including imatinib-induced heart failure and dasatinib-induced PAH.

• The IGR-based Inserm UMR_S 1030 team has an original and combined focus on both tumor radiation sensitivity and mechanisms that lead to damage of normal tissue. Emphasis is placed on tumor-microenvironement cross-talk, both in terms of tumor and normal tissue responses to treatments. The focus on cardio-pulmonary effects of radiation is of utmost importance and will allow interactions between TORINO clinicians and researchers with the ultimate goal of designing drugs and strategies to prevent/reverse these side effects.

Public Health and Biostatistics:

• The AP-HP *Hôpitaux Universitaires Paris-Sud* (Paul Brousse) hosts the Inserm team *"Respiratory and environmental epidemiology"* of the *"Centre for Research in Epidemiology and Population Health"* (CESP, Inserm UMR_S 1018). This team has a leading position in the field

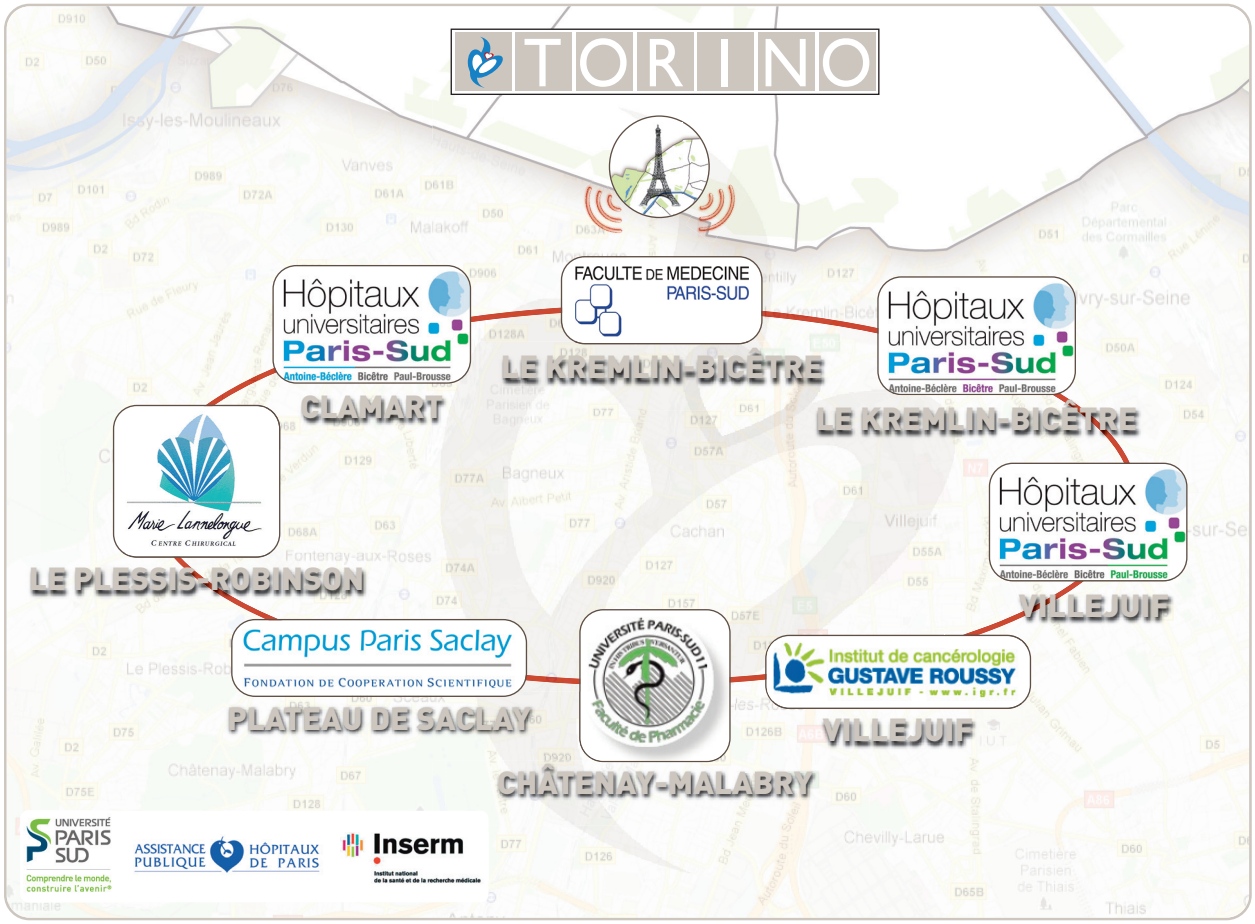
of respiratory epidemiology education and research, with a clear emphasis on asthma. Specific areas of research concern the improvement of asthma phenotyping over the lifecourse, the study of environmental and lifestyle determinants (air pollution, occupation, diet, smoking) and their interactions with genetic determinants. TORINO will boost the respiratory epidemiology studies in our University area with novel clinical and epidemiological collaborations. Deciphering asthma phenotypes will be a priority with the clinical and biological expertise of our partners. In addition, the population-based approach of this team will permit novel interactions with partners in the field of pulmonary vascular diseases, allowing a better use of the resources of the French Pulmonary Hypertension Registry supported by Inserm.

The preliminary observations suggesting the implication of the Nrf-2 pathway in the interaction between smoking and asthma based on pathway approach analyses from GWAS data in the Epidemiological study on the Genetics and Environment of Asthma may allow further insight into the pathogenetic role played by different occupational exposures, which represents a major burden in respiratory diseases worldwide. New interdiscipline collaborations are also currently being set up in the context of TORINO in order to better decipher different asthma phenotypes. This is a topic of considerable international interest that we intend to explore by developing greater collaborations between respiratory epidemiologists and respiratory physicians. They will also facilitate the incorporation of research in environmental determinants (in particular air pollution, and possibly occupational exposures) in the expression of the various diseases of interest for the TORINO collaborative, while providing basic clinical training to epidemiologists with a statistical background. Co-direction of doctoral students is already underway, and more co-supervision of students will be developed at the pre-doctoral level to foster multidisciplinary collaborations. In addition, Team 2 of Inserm UMR_S 996 will develop two major research projects related to lung diseases in the TORINO program, testing the role of glucocorticoid-induced leucine zipper (GILZ) in immune tolerance in allergic asthma and the role of Nrf-2 in respiratory chemical allergy. These two projects will address key questions on the role of the epithelium environment in governing the fate of the adaptive immune response, allowing novel scientific interactions with the epidemiology team of TORINO.

• The AP-HP *Hôpitaux Universitaires Paris-Sud* (Paul Brousse) hosts the Inserm team Biostatistics (CESP, Inserm UMR_S 1018), which has a strong focus on pharmacovigilance issues. This platform has enabled a scientific approach to the handling of major outbreaks of drug-induced PAH identified by the French Network of Pulmonary Hypertension in recent years, leading to international alerts on fenfluramine-, dexfenfluramine-, benfluorex-, and dasatinib-induced PAH.
A specific program will be established to implement pharmacovigilance systems in the TORINO clinical centres and networks.
• The AP-HP *Hôpitaux Universitaires Paris-Sud* (Paul Brousse) hosts a team dedicated to Statistical Genomics and Genetics (Inserm UMR_S 669). This group develops innovative statistical models and methods devoted to genomic-oriented (microarray and next generation sequencing) data analyses with subsequent transfer of results into clinical research. It is primarily interested in the fields of class comparison, class prediction and class discovery, with a particular focus on two important issues: the first relates to clinical cancer research and the investigation of the prognostic relevance of combining and integrating information from the genome, transcriptome and proteome in order to predict clinical outcome; the second relates to genomic diversity in solid tumors and the investigation of tumoral genomic heterogeneity in different human populations. Results from these investigations have important implications for translational research. These projects are conducted in close collaboration with national and international groups and focus in particular on thoracic tumors (adenocarcinomas, sarcomas, thymomas). TORINO will allow novel interaction between this team and all TORINO partners.

Linked with these core members, partner laboratories will provide expertise in the fields of immunology, physiology, and hematology in order to better cover the whole spectrum of TORINO-related targets with an emphasis on ambitious translational programs. These include research sites that will play an active role in the next TORINO programs, such as Inserm UMR_S 753 cancer immunology team and the Inserm UMR_S 770 teams dedicated to research on hemostasis and vascular biology.

GEOGRAPHIC IMPLANTATION, RESOURCES AND SYNERGIES



All partners are part of the *Université Paris-Sud* in the suburban Southern Paris, a highly populated area with a strong network of healthcare, teaching, and research facilities. The hospital, education and research sites are located in Clamart, Le Plessis Robinson, Villejuif, Le Kremlin Bicêtre, and Chatenay-Malabry/Plateau de Saclay. These hospitals and universities have already a successful history of collaboration, thanks to the Faculties of Medicine and Pharmacy of the *Université Paris-Sud.* Indeed, each of the sites has a recognized leadership role in healthcare, education and research.

The current proposal gathers together sites and partners with the express purpose of developing firmer links in order to tackle the current challenges of respiratory/thoracic international competition. All partners have obtained international support in the last 10 years (European Union FP5, FP6, FP7, Leducq Foundation and NIH/NHLBI programs) and also have regular support from the *Agence Nationale de la Recherche* (ANR), the *Institut National du Cancer* (INCa), the *Fondation pour la Recherche Médicale* (FRM), and the *Projets Hospitaliers de Recherche Clinique* (PHRC) clinical programs, as well as other major sources of support such as the recently awarded programs *Investissements d'Avenir*. In addition to dedicated programs for novel thoracic surgical approaches, the TORINO partners are leaders in proof-of-concept and pivotal randomized trials of novel medications in the fields of pulmonary hypertension, thoracic cancer and severe asthma. In the last years, TORINO partners have been principal investigators in a number of industry-sponsored studies leading to several high-impact publications in top

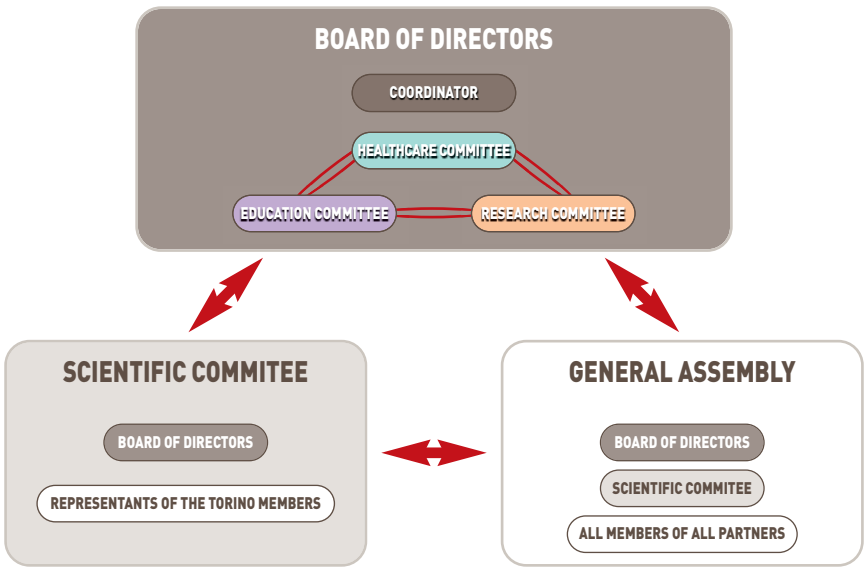
medical journals (N Engl J Med, Lancet, Ann Int Med, J Clin Oncol, Circulation, Am J Resp Crit Care Med...). This also contributed to generate resources and regular funding for our research programs. We are convinced that we will demonstrate that novel synergies between our groups will amplify our current successes and allow TORINO to take a truly leading role on the European academic stage.
Of course, some partnerships between our groups have already become extremely successful in recent years. Indeed, a convention was signed in the 1990's between the AP-HP *(Hôpitaux Universitaires Paris-Sud)* and CCML surgical centre for the medical and surgical management of patients with severe pulmonary hypertension. Similarly, the A+ Inserm UMR_S 999 was launched in 2010 on two sites (AP-HP *Hôpitaux Universitaires Paris-Sud* and CCML). In addition, an ambitious thoracic oncology program has led to the *Institut d'Oncologie Thoracique* that links not only the IGR and CCML, but also associated Inserm laboratories. Thus a broader partnership between IGR, CCML and the *Hôpitaux Universitaires Paris-Sud* should be a logical consequence of the TORINO proposal with active exchanges between the partners. This will certainly allow ambitious healthcare, education and research collaborations in order to have a stronger thoracic impact thanks to the TORINO synergistic programs. A major strength of our proposal is the leadership of the core partners in their own field and their wish to improve and explore original areas through novel partnerships. Indeed, novel developments have now been identified, including:

- Implementation of expert epidemiology techniques in thoracic medicine within TORINO (pulmonary hypertension registry, thoracic cancer programs, asthma and environment programs...)
- Implementation of structured pharmacovigilance tools in the TORINO clinical sites
- Utilization of accumulated knowledge relating to left heart failure in order to better understand right-sided heart failure that is characteristic of chronic pulmonary hypertension
- Description of beneficial and deleterious cardiopulmonary effects of cancer therapies (radiotherapy and chemotherapy) and identification of novel preventative/ curative approaches
- Reinforcement of our experimental surgery program, including image-guided therapy with the TORINO partners
- Proof of concept of stem cell therapy in chronic pulmonary vascular disease and right-heart failure
- Development and testing of tyrosine kinase inhibitors in both preclinical models of pulmonary hypertension and in patients with PAH.

Besides maintaining the highest standards of academic research, TORINO will generate intellectual property with the support of the Hospital, University and Inserm offices. Discoveries from TORINO partners will be tested in the clinical setting thanks to the outstanding clinical networking of the TORINO clinical sites in their major fields of interest. The TORINO partners have also built links and mutual respect with industrial partners in the field of respiratory medicine, cardiology, and oncology and are key partners in international phase I, II and III clinical trials.

6

GOVERNANCE



The TORINO program coordinator will be Marc Humbert, MD, PhD, 48 yo, professor of respiratory medicine at the *Université Paris-Sud,* vice dean of the Faculty of Medicine, president of the Research Committee of the AP-HP, and director of Inserm UMR_S 999 located at AP-HP and CCML.
These positions place him at the crossroads of the TORINO players and priorities.
The Board of Directors will have 10 members, in addition to the TORINO coordinator, including:

A healthcare committee, with colleagues involved in thoracic medicine and surgery from the three hospital partners

- G. Simonneau, chair, respiratory medicine, AP-HP
- P. Dartevelle, thoracic surgery, CCML
- JC. Soria, thoracic oncology, IGR

An education committee, including colleagues involved in thoracic education from the three doctoral schools

- M. Pallardy, chair, ED425 (Therapeutic Innovation)
- C. Auclair, ED 418 (Oncology)
- P. Broët, ED 420 (Epidemiology)

A research committee, including colleagues with a background in Physiology, Pharmacology, and Epidemiology

- R. Fischmeister, Faculty of Pharmacy, Inserm, Therapeutic Innovation, LabEx LERMIT, chair
- E. Deutsch, Faculty of Medicine, Cancer, IGR
- A. Griscelli-Bennaceur, Faculty of Medicine, Stem Cell, AP-HP
- F. Kauffmann, Faculty of Medicine, Epidemiology, Inserm

The Board of Directors will meet at least twice a year, and more often if necessary. The Board will identify the priorities in the 3 dimensions of TORINO: Healthcare, Education, and Research.

A Scientific committee will meet once a year.
The members of the Scientific Committee will include the Board of Directors and representatives of the TORINO members. By alphabetical order (with the main affiliation and interest):
V. Algalarondo (AP-HP, thoracic medicine), F. André (Inserm, oncology), T. de Baere (IGR, radiology), B. Besse (IGR, thoracic oncology), S. Bobin (AP-HP, dean of the Faculty of Medicine), J. Bousquet (Inserm, respiratory epidemiology), D. Chemla (AP-HP, thoracic physiology), F. Chouaid (Inserm, immunology), S. Cohen-Kaminsky (Inserm, immunology), C. Denis (Inserm, hematology and hemostasis), P. Dorfmüller (CCML, thoracic pathology), J. Duranteau (AP-HP, medicine), S. Eddahibi (Inserm, thoracic pathophysiology), E. Fadel (CCML, thoracic surgery), V. Godot (Inserm, immunology), C. Guignabert (Inserm, thoracic pathophysiology), D. Hémon (Inserm, epidemiology), T. Le Chevalier (IGR, thoracic oncology), D. Montani (AP-HP, thoracic medicine), F. Parent (AP-HP, thoracic medicine), F. Perros (CCML, immunology), X. Monnet (AP-HP, medicine), K. Olausen (Inserm, oncology), L. Parmantier (Inserm, administration), M. Raphaël (AP-HP, hematology), JF Renaud de la Faverie (Inserm, thoracic pathophysiology), O. Sitbon (AP-HP, thoracic medicine), JC. Soria (IGR, thoracic oncology), JL. Teboul (AP-HP, medicine), P. Tubert (Inserm, pharmacovigilance), A. Turhan (AP-HP, hematology), G. Vandecasteele (Inserm, pathophysiology), A. Veyradier (AP-HP, hematology), MC. Vozenin (Inserm, oncology)

A General Assembly will also take place once a year, gathering all members of the TORINO partnership.

WORKPACKAGES

WP-1: Thoracic innovative therapy

- Deliverable 1: Novel tyrosine kinase use in PAH: efficacy and cardio-pulmonary safety in preclinical models and clinical trials
- Deliverable 2: Heart and lung side effects of radiotherapy: novel therapeutic approaches
- Deliverable 3: Phosphodiesterase remodeling in heart failure due to chronic precapillary pulmonary hypertension
- Deliverable 4: NMDA receptors as novel target in PAH
- Deliverable 5: Personalized thoracic cancer medical therapy
- Deliverable 6: Innovative and experimental thoracic surgery
- Deliverable 7: Innovative immunotherapy in thoracic diseases
- Deliverable 8: Thoracic stem cell therapy
- Deliverable 9: Companion biomarkers for PAH therapy
- Deliverable 10: Biomarkers in thoracic oncology
- Deliverable 11: Innovative strategies in cardio-oncology: management of cardio-pulmonary toxicity induced by anti-cancer therapy

WP-2: Thoracic epidemiology, statistic genetic and genomic

- Deliverable 1: Pulmonary hypertension registries
- Deliverable 2: Thoracic pharmacovigilance
- Deliverable 3: Asthma studies
- Deliverable 4: Clinical genomic epidemiology applied to rare thoracic malignant and nonmalignant diseases

WP-3: Thoracic education

- Deliverable 1: Thoracic innovative therapies MD / PhD program
- Deliverable 2: Thoracic oncology MD / PhD program
- Deliverable 3: Thoracic epidemiology MD / PhD program
- Deliverable 4: New challenges in thoracic and cardio-oncology: from efficacy to toxicity

MILESTONES (5-YEAR OBJECTIVES)

WP-1: Thoracic innovative therapy

• Deliverable 1: Novel tyrosine kinase use in PAH: efficacy and cardio-pulmonary safety in preclinical models and clinical trials
- M12 = Efficacy/safety clinical trial of imatinib, masitinib and nilotinib in preclinical models of pulmonary hypertension
- M24 = Efficacy/safety study of imatinib in human PAH
- M36 = FGFR2 targeting in experimental PAH
- M60 = Gene expression and targeted phospho/proteomic analysis of PAH patients whole lung versus laser capture microdissected-derived vessel tissue and explanted endothelial and smooth muscle cell populations

• Deliverable 2: Heart and lung response to radiotherapy: novel therapeutic approaches
- M12 = Development of accurate diagnosis tools (imaging)
- M24 = Definition of biomarkers of tumors/normal response to radiotherapy+/- chemotherapy +/- smart drugs
- M36 = Optimization of radiotherapy delivery using multi-modal imaging, stereotactic and adaptive radiotherapy to increase efficacy and decrease toxicity
- M48 = Investigation of signaling pathways activated in tumor and stroma following irradiation to identify therapeutic targets: modulation of tyrosine kinase pathways (BIBF1120), modulation of cell migration and chemoattraction (SDF-1/CXCR4 axis), alteration of cytoskeleton (actin, Rho/ROCK).
- M60 = Clinical proof of concept: Phase I/II trials with Rho/ROCK modulators

• Deliverable 3: Phosphodiesterase remodeling in heart failure due to chronic precapillary pulmonary hypertension
- M12 = Expression pattern of cAMP-PDE isoforms in the right ventricle and pulmonary arteries from human and experimental models of precapillary pulmonary hypertension
- M24 = Modulation of local cAMP signaling by cAMP-PDEs in the right ventricle and pulmonary arteries and their modification in experimental models of precapillary pulmonary hypertension
- M48 = Use of knock-out mice for PDE4 isoforms to assess the role of PDE4 subtypes in experimental models of precapillary pulmonary hypertension
- M60 = Clinical proof of concept: trials with novel PDE inhibitors in human precapillary pulmonary hypertension (PAH and inoperable CTEPH)

• Deliverable 4: NMDA receptors as a novel target in PAH
- M12 = Search for dysfunction of NMDAR signaling and glutamate sources in explanted lungs from PAH patients and identify biomarkers of NMDAR dysfunction in PAH patients
- M18 = Provide proof of concept of NMDAR involvement in the pathophysiology of PAH and understand how NMDARs are involved in PAH using available NMDAR antagonists
- M24 = Design and synthesis of novel compounds targeting the peripheral NMDAR (that do not cross the blood-brain barrier) and that target inflammatory sites (characterized by a low pH)
- M36 = Structural modeling and molecular dynamics of the interaction between a molecular model of NMDAR and novel compounds
- M48 = Perform preclinical studies in animal models of precapillary pulmonary hypertension, and determine the mechanism of action of these novel NMDAR antagonists *in vitro* and *in vivo*
- M60 = Select the best compounds to be tested in phase I and II studies in human PAH, through escalation dose studies, toxic dose studies, and benefit/risk assessment in animal models of precapillary pulmonary hypertension

• Deliverable 5: Personalized thoracic cancer medical therapy
  - M6 = Methodological validation of a functional kinome test in the form of a microarray by using specific drugs in vitro that target different kinases (erlotinib, vatalanib, everolimus, volociximab, sorafenib, CPT11, sunitinib, temsirolimus, among others)
  - M12 = Determination of cell lines with respective molecules that show synergies among each other or in association with conventional drugs (cisplatin, paclitaxel, gemcitabine, pemetrexed) or radiotherapy
  - M18 = Associate gene expression with kinase inactivations (or activations) using the preselected drugs
  - M24 = Testing of the feasibility of kinase-directed decisions on mouse models and on selected clinical samples (the main strategy is to determine how tumor samples react to drugs in vitro and/or how the profiles could predict clinical response to different drugs)
  - M36 = Kinase profiling to enrich patients with molecular anomalies for Phasel/II clinical trials of drug combinations showing highest synergy profiles
  - M60 = Start a clinical trial using kinome-directed decisions based on the kinome profile of the tumor
• Deliverable 6: Innovative and experimental thoracic surgery
  - M6 = Develop a large animal model of CTEPH (pig model of recurrent embolism)
  - M12 = Develop an experimental model of right ventricular failure secondary to chronic overload that mimics congenital heart failure (pig model of tetralogy of Fallot) (same as M12 of Deliverable 8)
  - M24 = Tracheal transplantation preclinical and clinical program
  - M36 = Evaluate bronchial and tracheal healing after single-lung, double-lung or heart-lung transplantation in animals chronically exposed to tyrosine kinase inhibitors blocking PDGF, VEGF, FGFR2, and c-kit
  - M60 = Long-term medical vasodilator therapy in a pig model of CTEPH
• Deliverable 7: Innovative immunotherapy in thoracic diseases
  - M12 = Study up-regulation of GILZ expression in dendritic cells following oral corticotherapy using a transgenic mouse model (overexpressing GILZ in DCs; CD11c-GILZ mice) in terms of frequency of circulating allergen-specific Tregs and protection of mice against allergic asthma
  - M24 = Evaluate whether up-regulation of GILZ expression in dendritic cells following oral corticotherapy in allergic patients contributes to the increased frequency of circulating allergen-specific Tregs
  - M36 = Demonstrate that in allergic asthma bronchial epithelium contributes to the inappropriate activation of allergen-presenting dendritic cells by down-regulating GILZ expression
  - M60 = Address the role of Nrf-2 in occupational asthma induced by chemicals and the potential role of the epithelium environment in this process
• Deliverable 8: Thoracic stem cell therapy
  - M12 = Develop an experimental model of right ventricular failure secondary to chronic overload that mimics congenital heart failure (pig model of tetralogy of Fallot) (same as M12 of Deliverable 6)
  - M24 = Non invasive right-heart hemodynamic characterization of the model
  - M60 = Application of cell-based therapy to restore right ventricular functional disorder in this model
• Deliverable 9: Companion biomarkers for PAH therapy
  - M12 = Identification of biomarkers of NMDAR dysfunction in PAH patients (search of autoantibodies to NMDAR, titration of circulating glutamate levels)
  - M 24 = Identification of biomarkers linked to BMPR-II pathway to delineate PAH patient subgroups
  - M36 = Immune signature in the lung

of PAH patients and validation as a non invasive circulating biomarker of disease subgroups
- M60 = Olfactory signature in exhaled breath of PAH patients. Setting up of an "electronic nose" dedicated to PAH

• Deliverable 10 : Biomarkers in thoracic oncology
- M6 = Implementation of a test that allows to follow in a quantitative manner the number of DNA-based cisplatin adducts. Monitoring of these adducts either on tumor biopsies, pleural effusions or circulating tumor cells isolated by the ISET technique
- M12 = Detection / quantification of protein pathways of DNA repair in biopsies and in CTC (molecular characterization that will also include CGH arrays to detect genomic instability and mutations arrays to correlate the status of EGFR mutations and MAPK pathway activation of the tumor)
- M18 = In vitro modulation of the expression of DNA repair proteins (ERCC1, MSH2, BRCA1, PARP1, p53) that sensitize cells to cisplatin, using either targeting of DNA repair proteins such as ERCC1 (p38 inhibitors) or synthetic lethality (for instance PARP inhibition in BRCA1-deficient tumors)
- M24 = Validation of the molecular profiling and DNA repair modulation in vivo (mouse xenografts)
- M36 = Clinical assay using DNA repair based strategies (in CTCs or biopsies) to enrich phase I/II study populations and/or to predict response to therapy
- M48 = Evaluation of circulating glutamate as a biomarker of cancers and radiotherapy toxicity
- M60 = Mesurement of Divpenia® (i.e decreased T and B cell repertoire diversity) for quantification and qualification of the immune repertoire as a predictive marker of successful cancer therapy (http://divpenie.com/). Stratification of cancer patients for successful therapy on the basis of their immune competence before therapy

• Deliverable 11: Innovative strategies in cardio-oncology: management of cardio-pulmonary toxicity induced by anti-cancer therapy
- M12-24 = Identification of predictive biomarkers of cardiac disease using national patients' cohorts (CANTO, COHORT, EURO2K, BREAST)
- M36 = Development of up-to-date experimental models (multi-modality radiotherapy +/- systemic chemotherapy +/- targeted drugs)
- M48 = Characterization of signaling pathways involved in cardiopulmonary toxicities, with particular focus on fibrosis, hypertrophy and heart failure (small G proteins, Epac and Ca2+ homeostasis)
- M60 = Identification of metabolic and mitochondrial anti-cancer therapy-induced cardiac toxicity

WP-2: Thoracic epidemiology, statistical genetics and genomics

• Deliverable 1: PAH registry research
- M6 = describe the 2006-2009 French PAH cohort: baseline characteristics and comparison with the 2002-2003 cohort at baseline
- M12 = comparison of the French and US REVEAL Registry, 3-year survival
- M24 = French survival equation and REVEAL score cross-validation
- M36 = Early detection of PAH in pre-symptomatic *BMPR2* mutation carriers (baseline characteristics of the DELPHI-2 PHRC program)
- M60 = Early detection of PAH in pre-symptomatic *BMPR2* mutation carriers (2-year follow-up of the DELPHI-2 PHRC program)

• Deliverable 2: Thoracic pharmacovigilance
- M12 = Benfluorex-induced PAH population characteristics and outcomes
- M24 = Dasatinib-induced PAH population characteristics and outcomes
- M36 = Full report of drug exposure in the French PAH Registry
- M60 = Time-to-onset of drug induced PAH

• Deliverable 3: Asthma studies
  - M12 = Improved phenotyping of asthma in the Epidemiological Study on the Genetics and Environmental of Asthma (EGEA) and in the case control study on asthma nested in the large E3N cohort conducted in women affiliated to the Mutuelle Générale de l'Education Nationale
  - M24 = Role of the Nrf-2 pathway in asthma-related phenotypes, taking into account environmental determinants
  - M36 = Characterization of gene-environment (smoking, occupation) interactions in asthma through various methodologies
  - M60 = Determination of the role of environmental determinants in epidemiological studies with improved asthma phenotypes (including temporal phenotyping in E3N and biological phenotyping in EGEA)
• Deliverable 4: Clinical genomic epidemiology applied to rare thoracic malignant and nonmalignant diseases
  - M12 = Pilot project focusing on a series of epithelial thymic tumors. Identification and characterization of exclusively deleted or amplified genomic areas from high-resolution aCGH
  - M24 = Integrative analysis using genomic and transcriptomic data. Development of novel analytical tools.
  - M36 = Whole genome sequencing on targeted samples. Validation of analytical tools
  - M60 = Transfer of applicable statistical tools to other rare thoracic diseases, including PAH

WP-3: Thoracic education

• Deliverable 1: Thoracic innovative therapies MD / PhD program
  - M12 = Training courses offered to PhD students: experimental surgery applied to therapeutic innovation
  - M12 = Training courses offered to PhD students: new targets in cardiovascular and lung diseases
  - M36 = First wave of ED425's TORINO MD / PhD defenses
  - M48 = Second wave of ED425's TORINO MD / PhD defenses
  - M60 = Third wave of ED425's TORINO MD / PhD defenses
• Deliverable 2: Thoracic oncology MD / PhD program
  - M12 = Training courses offered to PhD students: targeted therapies in thoracic oncology
  - M12 = Training courses offered to PhD students: personalized medicine in thoracic oncology
  - M36 = First wave of ED418's TORINO MD / PhD defenses
  - M48 = Second wave of ED418's TORINO MD / PhD defenses
  - M60 = Third wave of ED418's TORINO MD / PhD defenses
• Deliverable 3: Thoracic epidemiology MD / PhD program
  - M12 = Training courses offered to MD / PhD students: Statistical Genomics
  - M12 = Training courses offered to MD / PhD students: Pharmacovigilance
  - M36 = First wave of ED420's TORINO MD / PhD defenses
  - M48 = Second wave of ED420's TORINO MD / PhD defenses
  - M60 = Third wave of ED420's TORINO MD / PhD defenses
• Deliverable 4: New challenges in thoracic and cardio-oncology: from efficacy to toxicity
  - M12 = short training courses offered to year 1 and 2 Master students to present major topics in thoracic oncology
  - M24 = Specific training courses incorporated into pre-existing PhD program
  - M12-60 = Dedicated training program (Cardio-oncology University Diploma) offered to MD, PharmD and PhD students.

9

CONCLUSION AND PERSPECTIVES

Our ambition is to establish and develop TORINO, a Centre of Excellence for thoracic healthcare, education and research in the *Université Paris-Sud.* TORINO will structure and enhance cross-talk between disciplines from major hospitals, doctoral schools and research institutes. The ambition of TORINO is to become a European leader in the field through the promotion of open dialogues and interaction between partners from the *Université Paris-Sud,* the *Assistance Publique Hôpitaux de Paris (Hôpitaux Universitaires Paris-Sud),* the *Institut Gustave Roussy,* the *Centre Chirurgical Marie Lannelongue* and the Inserm/LERMIT mixed research units.

Grouping these centres into a single entity will be instrumental in creating a driving force behind the university/hospital dynamics, in establishing new synergism and in helping to innovate and revolutionize site policy. TORINO represents a major opportunity for the Hospitals, the University and Inserm to gain enhanced visibility over the three dimensions of quality of care, teaching and research, thus reinforcing the established appeal of the university/hospital sites.

Département **H**ospitalo-**U**niversitaire

TORINO

THORAX INNOVATION

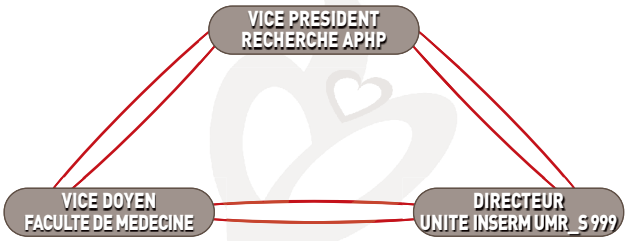
COORDINATOR: MARC HUMBERT, MD, PhD

UNIVERSITE PARIS-SUD
AP-HP, IGR, CCML
Inserm

APPENDIX

Closing date for the call for proposals:
21/10/2011

Call for proposals published on:
http://rechercheclinique.aphp.fr/



Marc HUMBERT, MD, PhD

Professor of Respiratory Medicine, Université Paris-Sud
- French Reference Centre for Pulmonary Hypertension
- Severe Asthma Clinic

Director, Inserm UMR_S 999
- Pulmonary Hypertension: Pathophysiology
- Pulmonary Hypertension: Novel Therapies

Member of the Board of Directors (*Directoire*), Assistance Publique Hôpitaux de Paris
- President of the Research Committee
- Vice President of the Board of Directors

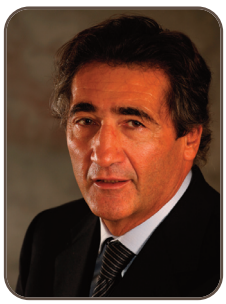
South Paris University Medical School
- Vice Dean

h-index: 65 (web of science, October 2011)

SIGAPS score 2001-2011: 4842 (SIGAPS 2010: 667)

Ten selected publications (2001-2011):

1. Hara Y, et al. Inhibition of MRP4 prevents and reverses pulmonary hypertension in mice. **J Clin Invest** 2011; 121:2888-2897.
2. Humbert M, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. **Circulation** 2010; 122:156-163.
3. Izikki M, et al. Endothelial-derived FGF2 contributes to the progression of pulmonary hypertension in humans and rodents. **J Clin Invest** 2009; 119:512-523.
4. Humbert M, et al. Pulmonary arterial hypertension in France: results from a national registry. **Am J Respir Crit Care Med** 2006; 173:1023-1030.
5. Sitbon O, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. **Circulation** 2005; 111:3105-3111.
6. Humbert M, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. **J Am Coll Cardiol** 2004; 43:13S-24S.
7. Humbert M, et al. Treatment of pulmonary arterial hypertension. **N Engl J Med** 2004; 351:1425-1436.
8. Sitbon O, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. **J Am Coll Cardiol** 2002; 40:780-788.
9. Trembath RC, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. **N Engl J Med** 2001; 345:325-334.
10. Eddahibi S, et al. Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. **J Clin Invest** 2001; 108:1141-1150.



HEALTHCARE COMMITTEE

Gérald SIMONNEAU, MD

Professor of Respiratory Medicine, *Université Paris-Sud*

Head, Department of Pneumology, *Hôpitaux Universitaires Paris-Sud,* AP-HP

Head of French Reference Centre for Pulmonary Hypertension

Inserm UMR_S 999, Head of Team 2 "Pulmonary hypertension: novel therapies"

h-index : 74 (web of science, October 2011)

SIGAPS score 2001-2011: 2517 (SIGAPS 2010: 313)

Ten selected publications:

1. Parent F, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. **N Engl J Med** 2011; 365:44-53.
2. Pepke-Zaba J, et al. Chronic thromboembolic pulmonary hypertension: results from an international prospective registry. **Circulation** 2011; Oct 3.
3. Simonneau G, et al. Updated clinical classification of pulmonary hypertension. **J Am Coll Cardiol** 2009; 54:S43-54.
4. Simonneau G, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. **Ann Int Med** 2008; 149:521-530.
5. Galie N, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. **N Engl J Med** 2005; 353:2148-2157.
6. Humbert M, et al. Treatment of pulmonary arterial hypertension. **N Engl J Med** 2004; 351:1425-1436.
7. Rubin LJ, et al. Bosentan therapy for pulmonary arterial hypertension. **N Engl J Med** 2002; 346:896-903
8. Olschewski H, et al. Inhaled iloprost for severe pulmonary hypertension. **N Engl J Med** 2002; 347:322-9.
9. Simonneau G, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. **N Engl J Med** 1997; 337:663-669.
10. Simonneau G, et al. Lockhart A. Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. **N Engl J Med** 1981; 304:1582-1585.

HEALTHCARE COMMITTEE

Philippe DARTEVELLE, MD

Professor of Thoracic and Cardiovascular Surgery

Head of the Department of Thoracic and Vascular surgery and Heart-lung Transplantation of Marie Lannelongue Hospital

Scientific Director of Marie Lannelongue Hospital

Member of the Council of the European association for Cardiothoracic Surgery

Honorary Member of the American Society of Thoracic Surgery

h-index : 30 (Web of Science, October 2011)

Ten selected publications (2001-2011):

1. Fadel E, et al. Long-term outcomes of en bloc resection of non-small cell lung cancer invading the thoracic inlet and spine. **Ann Thorac Surg** 2011; 92:1024-1030.
2. Fabre D, et al. Long-term outcome of pleuropneumonectomy for Masaoka stage IVa thymoma. **Eur J Cardiothorac Surg** 2011; 39:e133-8.
3. Mayer E, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. **J Thorac Cardiovasc Surg** 2011; 141:702-710.
4. Montani D, et al. Cautious use of epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease. **Eur Respir J** 2009; 34:1348-1356.
5. Fabre D, et al. Complete resection of pulmonary inflammatory pseudotumors has excellent long-term prognosis. **J Thorac Cardiovasc Surg** 2009; 37:4
6. Izzikki M, et al. Endothelial-derived FGF2 contributes to the progression of pulmonary hypertension in humans and rodents. **J Clin Invest** 2009; 119:512-523.
7. Yildizeli B, et al. Results of primary surgery with T4 non-small cell lung cancer during a 25-year period in a single center: the benefit is worth the risk. **Ann Thorac Surg** 2008; 86:1065-1075.
8. Yildizeli B, Morbidity, mortality, and long-term survival after sleeve lobectomy for non-small cell lung cancer. **Eur J Cardiothorac Surg** 2007; 31:95-102.
9. de Perrot M, Long-term results after carinal resection for carcinoma: does the benefit warrant the risk? **J Thorac Cardiovasc Surg** 2006; 131:81-89.
10. Eddahibi S, et al. Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. **J Clin Invest** 2001; 108:1141-1150.

HEALTHCARE COMMITTEE

Jean Charles SORIA, MD, PhD

Professor of Cancerology, *Université Paris-Sud*
- Chairman Early Drug development program, *Institut Gustave Roussy*

Group leader, Inserm UMR_S 981
- Molecular predictors of the efficacy of anti-cancer therapy
- DNA repair dysfunctionality in lung cancer

Member of the Scientific Advisory Board of the French National Cancer Institute (INCa)

European Society of Medical Oncology (ESMO)
- 2008-2009: Member of the executive Committee
- 2011 Scientific chairman of the ECCO-ESMO multidisciplinary meeting

h-index: 61 (web of science, October 2011)

SIGAPS score 2001-2011: 2461(SIGAPS 2010: 485)

Ten selected publications (2001-2011):

1. Friboulet L, et al. Molecular Characteristics of ERCC1-Negative versus ERCC1-Positive Tumors in Resected NSCLC. **Clin Cancer Res** 2011; 17:5562-5572.
2. Sequist LV, et al. Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. **J Clin Oncol** 2010; 28:3076-83.
3. Soria JC, et al. Phase 1b study of dulanermin (recombinant human Apo2L/TRAIL) in combination with paclitaxel, carboplatin, and bevacizumab in patients with advanced non-squamous non-small-cell lung cancer. **J Clin Oncol** 2010; 28:1527-1533.
4. Olaussen KA, et al. Validation of ERCC1-XPF immunodetection. **Cancer Res** 2010; 70:3851-3852.
5. Saintigny P, et al. Erythropoietin and erythropoietin receptor coexpression is associated with poor survival in stage I non-small cell lung cancer. **Clin Cancer Res** 2007; 13:4825-4831.
6. Giaccone G, et al. Erlotinib for frontline treatment of advanced non-small cell lung cancer: a phase II study. **Clin Cancer Res** 2006; 12:6049-6055.
7. Olaussen KA, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. **N Engl J Med** 2006; 355:983-901.
8. Soria JC, et al.. Retinoic acid receptor beta and telomerase catalytic subunit expression in bronchial epithelium of heavy smokers. **J Natl Cancer Inst** 2003; 95:165-168.
9. Soria JC, et al. Aberrant promoter methylation of multiple genes in bronchial brush samples from former cigarettes smokers. **Cancer Res** 2002; 62:351-355.
10. Soria JC, et al. Effects of N-(4-hydroxyphenyl)retinamide on hTERT expression in the bronchial epithelium of cigarette smokers. **J Natl Cancer Inst** 2001; 93:1257-1263.

EDUCATION COMMITTEE

Marc PALLARDY, Pharm. D, PhD

Professor of Toxicology, Faculty of Pharmacy, *Université Paris-Sud*
- Head of the Department
- Research Director

Director Inserm UMR_S 996
- Cytokines, chemokines and Immunopathology

Faculty of Pharmacy, *Université Paris Sud*
- Vice-Dean
- Director PhD Program, "Therapeutic innovation"
- Director Master Program, "Toxicology, risk assessment and vigilances"

Member of the committee for marketing authorization of medicinal products (AFSSAPS)
Chairman of the AFSSAPS preclinical working party
Co-chairman of the gene therapy working party (AFSSAPS)
Member of the clinical trials authorization and cellular therapy working party (AFSSAPS).
Member of the "Safety Working Party" of the EMA (European Medicinal Agency).

h-index : 21 (Web of Science, October 2011)

Ten selected publications (2001-2011):

1. Zimmer A, et al. Identification of a new phenotype of tolerogenic human dendritic cells induced by fungal proteases from Aspergillus oryzae. **J Immunol** 2011; 186:3966-3976.
2. Antonioset D, etal. Mechanisms of IL-12 synthesis by human dendritic cells treated with the chemical sensitizer NiSO4. **J. Immunol** 2010; 185:89-98.
3. Latre de Late P, et al. Glucocorticoid-induced leucine zipper (GILZ) promotes the nuclear exclusion of FOXO3 in a CRM1-dependent manner. **J Biol Chem** 2010; 285:5594-5605.
4. Ade N, et al HMOX1 and NQO1 genes are upregulated in response to contact sensitizers in dendritic cells and THP-1 cell line: role of the Keap1/Nrf2 pathway. **Toxicol Sci** 2009; 107:451-460.
5. Ade N, et al. NF-{kappa}B Plays a Major Role in the Maturation of Human Dendritic Cells Induced by NiSO4 but not by DNCB. **Toxicol Sci** 2007; 99:488-501.
6. Cohen N, et al. GILZ expression in human dendritic cells redirects their maturation and prevents antigen-specific T lymphocyte response. **Blood** 2006; 107:2037-2044.
7. Asselin-Labat ML, et al FoxO3 mediates antagonistic effects of glucocorticoids and interleukin-2 on glucocorticoid-induced leucine zipper expression. **Mol Endocrinol** 2005; 19:1752-1764.
8. Boislève F, et al. Nickel and DNCB induce CCR7 expression on human dendritic cells through different signalling pathways: role of TNF-alpha and MAPK. **J Invest Dermatol** 2004 123:494-502.
9. Asselin-Labat ML, et al. GILZ, a new target for the transcription factor FoxO3, protects T lymphocytes from interleukin-2 withdrawal-induced apoptosis. **Blood** 2004; 104:215-223.
10. Biola A, et al. Interleukin-2 inhibits glucocorticoid receptor transcriptional activity through a mechanism involving STAT5 (signal transducer and activator of transcription 5) but not AP-1. **Mol Endocrinol** 2001; 15:1062-1076.

EDUCATION COMMITTEE

Philippe BROËT, MD, PhD

Associate Professor in Public Health, *Université Paris-Sud*

Adjunct group Leader, Genome Institute of Singapore, Singapore

Team Leader: Genomics and Genetic Statistics team, Inserm UMR_S 669

Member of the Scientific Committee, Faculty of Medicine, *Université Paris-Sud*

h-index: 28 (Web of Science, October 2011)

Ten selected publications (2001-2011):

1. Broët P, et al, Finding exclusively deleted or amplified genomic areas in lung adenocarcinomas using a novel chromosomal pattern analysis. **BMC Med Genomics** 2009; 2:43.
2. Broët P, et al. Prediction of clinical outcome in multiple lung Ccancer cohorts by integrative genomics: implications for chemotherapy selection. **Cancer Res** 2009; 69:1055-1062.
3. Dalmasso C et al. distinct genetic loci control plasma HIV-RNA and cellular HIV-DNA levels in HIV-1 infection: The ANRS genome wide association 01 study. **PLoS One** 2008; 3:e3907.
4. Camilleri S et al, A uniform activated B-cell-like in-immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. **Blood** 2006; 107:190-196.
5. Broët P, et al. Identifying gene expression changes in breast cancer that distinguish early and late relapse among uncured patients. **Bioinformatics** 2006; 22:1477-1485.
6. Broët P, et al. A mixture model-based strategy for selecting sets of genes in multiclass response microarray experiments. **Bioinformatics** 2004; 20:2562-2571.
7. Dalmasso C, et al. A simple procedure for estimating the false discovery rate. **Bioinformatics** 2005; 21:660-668.
8. Broët P, et al. Two-sample statistics for testing the equality of survival functions against improper semi-parametric accelerated failure time alternatives: An application to the analysis of a breast cancer clinical trial. **Lifetime Data Analysis** 2004; 10:103-120
9. Look MP, et al. Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 8377 breast cancer patients. **J Natl Cancer Inst** 2002; 94:116-128.
10. Broët P, et al. Bayesian hierarchical model for identifying changes in gene expression from microarray experiments J. **Comput Biol** 2002; 9:671-683.

RESEARCH COMMITTEE

Rodolphe FISCHMEISTER, PhD

Inserm Director of Research - Exceptional Class

Director, Inserm UMR_S 769, Signalling and Cardiac Pathophysiology

Coordinator, Laboratory of Excellence LERMIT

President, Inserm Study Section 4

Elected member, Academia Europaea

h-index: 46 (Web of Science, October 2011)

Ten selected publications (2001-2011):

1. Maillet M, et al. Crosstalk between Rap1 and Rac regulates secretion of sAPP alpha. **Nat Cell Biol** 2003; 5:633-639.
2. Rochais F, et al. Negative feedback exerted by cAMP-dependent protein kinase and cAMP phosphodiesterase on subsarcolemmal cAMP signals in intact cardiac myocytes: an in vivo study using adenovirus-mediated expression of CNG channels. **J Biol Chem** 2004; 279:52095-52105.
3. Rochais F, et al. A specific pattern of phosphodiesterases controls the cAMP signals generated by different G(s)-coupled receptors in adult rat ventricular myocytes. **Circ Res** 2006; 98:1081-1088.
4. Fischmeister R, et al. Compartmentation of cyclic nucleotide signaling in the heart - The role of cyclic nucleotide phosphodiesterases. **Circ Res** 2006; 99:816-828.
5. Castro LRV, et al. Cyclic guanosine monophosphate compartmentation in rat cardiac myocytes. **Circulation** 2006; 113:2221-2228.
6. Leroy J, et al. Spatiotemporal dynamics of beta-adrenergic cAMP signals and L-type Ca2+ channel regulation in adult rat ventricular myocytes: role of phosphodiesterases. **Circ Res** 2008; 102:1091-1100.
7. Skeberdis VA, et al. beta(3)-adrenergic receptor activation increases human atrial tissue contractility and stimulates the L-type Ca2+ current. **J Clin Invest** 2008; 118:3219-3227.
8. Abi-Gerges A, et al. Decreased expression and ectivity of cAMP phosphodiesterases in cardiac hypertrophy and its impact on beta-adrenergic cAMP signals. **Circ Res** 2009; 105:784-792.
9. Castro LRV, et al. Feedback control through cGMP-dependent protein kinase contributes to differential regulation and compartmentation of cGMP in rat cardiac myocytes. **Circ Res** 2010; 107:1232-1240.
10. Leroy J, et al. Phosphodiesterase 4B in the cardiac L-type Ca(2+) channel complex regulates Ca(2+) current and protects against ventricular arrhythmias in mice. **J Clin Invest** 2011; 121:2651-2661.

RESEARCH COMMITTEE

Eric DEUTSCH, MD, PhD

Professor of Radiation Oncology, *Université Paris-Sud*
- Novel drugs combined to radiotherapy phase I trials
- Gastro intestinal tumor board

Group leader, Inserm UMR_S 1030
- Pharmacological modulation of tumor response to ionizing radiation
- HPV related malignancies

Member of the scientific boards of European Society of Therapeutic Radiation Oncology and gastro-instestinal and gynecological board at INCa

h-index: 24 (web of science, October 2011)

SIGAPS score 2001-2011: 1220

Ten selected publications (2001-2011):

1. Mordant, P et al. Bioluminescent orthotopic mouse models of human localized non-small cell lung cancer: feasibility and identification of circulating tumour cells. **PLoS One** 2011; 6:10.
2. Tao Y, et al. Enhancement of radiation response in p53-deficient cancer cells by the Aurora-B kinase inhibitor AZD1152. **Oncogene** 2008; 27:3244-3255.
3. Prevo R, et al. Class I PI3 kinase inhibition by the pyridinylfuranopyrimidine inhibitor PI-103 enhances tumor radiosensitivity. **Cancer Res** 2008; 68, 14:5915-5923.
4. Tao Y, et al. Mechanisms of disease: signaling of the insulin-like growth factor 1 receptor pathway--therapeutic perspectives in cancer. **Nat Clin Pract Oncol** 2007; 4:591-602.
5. Massard, C., et al. Tumour stem cell-targeted treatment: elimination or differentiation. **Ann Oncol** 2006; 17:1620-4.
6. Deutsch E, et al. New concepts for phase I trials: evaluating new drugs combined with radiation therapy. **Nature Clin Pract Oncol** 2005; 2:456-465.
7. Abdulkarim B, et al. Antiviral agent cidofovir restores p53 function and enhances the radiosensitivity in HPV-associated cancers. **Oncogene** 2002; 21:2334-2346.
8. Wen B, et al. Tyrphostin AG 1024 modulates radiosensitivity in human breast cancer cells. **Br J Cancer** 2001; 85:2017-2021.
9. Deutsch E, et al. Down-regulation of BRCA1 in BCR-ABL-expressing hematopoietic cells. **Blood** 2003; 101:4583-4588.
10. Deutsch E, et al. BCR-ABL down-regulates the DNA repair protein DNA-PKcs. **Blood** 2001; 97:2084-2090.

RESEARCH COMMITTEE

Annelise BENNACEUR-GRISCELLI, MD, PhD

Professor of Heamatology, *Université Paris-Sud*

Head, laboratory of hematology Hospital Paul Brousse and IGR
- Hematopoietic stem cells and cancer stem cells
- Onco-molecular diagnosis

Director, Inserm UMR_S 995, IAL Villejuif
- Embryonic and pluripotent stem cells
- Hematopoiesis / endothelial cells

Head of ESTeam Paris Sud / Pluripotent Stem cell
- Patient specific iPS modelling diseases and drug discovery
- Mesenchymal stem cells and cell repair
- Cell therapy models

Member of the Scientific Board, Faculty of Medicine, *Université Paris-Sud*
Member of Inserm commitee translational research

h-index: 17 (Web of Science, October 2011)

Ten selected publications (2001-2011):

1. Chomel JC and al. Leukemic stem cell persistence in chronic myeloid leukemia patients with sustained undetectable molecular residual disease. **Blood** 2011; 118:3657-3660.
2. Giuliani M, et al. Human mesenchymal stem cells derived from induced pluripotent stem cells down-regulate NK-cell cytolytic machinery. **Blood** 2011; 118:3254-3262.
3. Mitjavila-Garcia MT, et al. Partial reversal of the methylation pattern of the X-linked gene HUMARA during hematopoietic differentiation of human embryonic stem cells. **J Mol Cell Biol** 2010; 2:291-298.
4. Capron C, et al. A major role of TGF-beta1 in the homing capacities of murine hematopoietic stem cell/progenitors. **Blood** 2010; 116:1244-1253.
5. Chio-Srichan S, et al.Toxicity and phototoxicity of hypocrellin A on malignant human cell lines: evidence of a synergistic action of photodynamic therapy with imatinib mesylate. **J Photochem Photobiol B** 2010; 99:100-104.
6. Frydman N, et al. Characterization of human PGD blastocysts with unbalanced chromosomal translocations and human embryonic stem cell line derivation. **Reprod Biomed Online** 2009; 19 Suppl 4:4199.
7. Pierre-Louis O, et al. Dual SP/ALDH functionalities refine the human hematopoietic Lin-CD34+CD38- stem/progenitor cell compartment. **Stem Cells** 2009; 27:2552-2562.
8. N Lefort, et al. Human embryonic stem cells reveal recurrent genomic instability at 20q11.21. **Nat Biotechnol** 2008; 26:1364-1366.
9. James C, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. **Nature** 2005; 434:1144-1148.
10. Sekkaï D, et al. Microarray analysis of LIF/Stat3 transcriptional targets in embryonic stem cells. **Stem Cells** 2005; 23:1634-1642.

RESEARCH COMMITTEE

Francine KAUFFMANN, MD

Director of Research, Inserm, exceptional class

Director, Team Respiratory and Environmental Epidemiology, Inserm UMR_S 1018

Co-director of the International Associated laboratory between Inserm and Centre of Research in Environmental Epidemiology in Barcelona

h-index: 31 (web of science, October 2011)

Ten recent publications :

1. Jacquemin B, et al. Air pollution and asthma control in the Epidemiological study on Genetics and Environment of Asthma. **J Epidemiol Community Health** 2011 Jun 20 [Epub ahead of print].
2. Dumas O, et al. Do young adults with childhood asthma avoid occupational exposures at first hire ? **Eur Respir J** 2011; 37:1043-1049.
3. Varraso R, et al. Farming in childhood, diet in adulthood and asthma history. **Eur Respir J** 2011 Jun 9
4. Smit LAM, et al. Mold allergen sensitization in adult asthma according to ITGB3 polymorphisms and TLR2/+596 genotype. **J Allergy Clin Immunol** 2011; 128:185-191.
5. Siroux V, et al. Identifying clinical phenotypes of asthma using clustering approach. **Eur Respir J** 2011; 38:310-317.
6. Cambon-Thomsen A, et al. The role of a bioresource research impact factor as an incentive to share human bioresources. **Nat Genet** 2011; 43:503-504.
7. Moffatt MF, et al. A large-scale, consortium-based genomewide association study of asthma. **N Engl J Med** 2010; 363:1211-21.
8. Nadif R, et al. Heterogeneity of asthma according to blood inflammatory patterns. **Thorax** 2009; 64:374-380.
9. Smit LAM, et al. CD14 and Toll-like receptor gene polymorphisms, country living during childhood, and asthma in adults. **Am J Respir Crit Care Med** 2009; 179:363-368.
10. Bouzigon E, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. **N Engl J Med** 2008; 359:1985-1994.

TORINO

THORAX INNOVATION

COORDINATOR : MARC HUMBERT, MD, PhD

UNIVERSITE PARIS-SUD • AP-HP, IGR, CCML • Inserm