Evaluation DHU FIRE

I) The DHU FIRE

Title: Département Hospitalo-Universitaire Fibrosis Inflammation Remodeling in cardiovascular respiratory and renal diseases

Date of creation: The convention between AP-HP, Inserm and the University Paris Diderot was signed on July, 5th 2012

CV of the coordinator: Professor Bruno Crestani, MD,PhD

Academic functions:

Since 2009:	Member-elect of the executive committee of Paris Diderot University School of Medicine
2009-2015	Deputy Dean for research, Paris Diderot University School of Medicine
1998:	Professor of Pneumology – Paris Diderot University – France
1995:	PhD -University Paris 11
1991:	MD University Paris XI

Hospital position:

Since 2016:	President of the Medical resource committee of Hôpitaux UNiversitaires Paris Nord Val de Seine
Since 2015:	Head of the Pneumology A department, Coordinator of Reference Center for rare pulmonary diseases (centre constitutif), Bichat Hospital, Assistance Publique Hôpitaux de Paris, France

Clinical research experience

Principal investigator in asthma (1), pulmonary embolism (2), IPF (12) therapeutic trials. Coordinator in IPF phase 2 study (1). Coordinator of the IFRA study (supported by APHP). Member of the Scientific committee of the french IPF cohort (COFI) and the French Rare Disease Cohort for ILD (RADICO-PID). Member of the ATS/ERS committee for the Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias (2013).

Basic Research experience

Director of the team 3 of INSERM 1152 research unit: "Inflammation and Lung fibrogenesis". Founding member of the EurIPFnet (funded by the EU, FP7). Member of the LabEx INFLAMEX.

Scientific Society Member: Société de Pneumologie de Langue Française (past scientific secretary); European Respiratory Society (past secretary of group 3.1, secretary of assembly 3, past Conference and Seminars Director 2016-2016); American Thoracic Society (past member of the Respiratory Cell and Molecular Biology scientific committee).

Reviewer for Science Translational Medicine, Lancet Respiratory Medicine, Am J Respir Crit Care Med, Am J Respir Cell Mol Biol, Thorax, Eur Respir J, Am J Physiol, Laboratory Investigation, Allergy, Intensive care medicine, Respiratory Medicine, Lung, Respiration.

Member of the editorial board for Am J Physiol Lung

Associate editor for Respir Res, Eur Respir J.

DHU objectives

Fibrosis, inflammation and remodeling are major targets for new preventive and curative therapeutic strategies. This DHU aims to develop an integrated approach to the management of cardiovascular,

renal and respiratory diseases, from prevention, early detection, treatment of acute and chronic complications, and management of late phases, up to organ transplantation.

Composition

The DHU FIRE brings together clinicians and staff from four academic hospitals (Bichat, Saint Louis, Robert Debré and Lariboisière), scientists and epidemiologists from 5 research units, all located within the perimeter of Université Paris Diderot. This original structure overcomes the barriers between medical specialties, hospitals and research areas, and promotes multidisciplinary work. The research groups of DHU FIRE are the following:

- **CRI:** Research Centre for Inflammation, (UMR 1149, Bichat), specifically the teams focused on the pathophysiology of inflammatory diseases, including renal diseases with strengths in cardiovascular and neurovascular disease.
- **LVTS UMR 1148**, Bichat, coordinated by D.Letourneur. This is a large research group with 5 teams, and includes the FACT (French Alliance for cardiovascular Clinical Trials) academic clinical research network created in 2012 with CeNGEPS support, and accredited by F-CRIN.
- **PHERE**: Pathophysiology and epidemiology of respiratory diseases (UMR 1152-Bichat)
- **BIOCANVAS**: Cardiovascular Biomarkers (UMR 942-Lariboisiere),
- **FRIM**: Federative Research for Multimodality Iimaging, supported by University Paris Diderot
- **Vascular and Renal complications related to diabetes and nutrition** (Ronan Roussel team, UMR 1138).

The DHU is also supported by **LabEx INFLAMEX** coordinated by Renato Monteiro.

Striking Facts

This is a non comprehensive list of scientific or organizational facts which are considered as important for the life of the DHU

1-The funding of RHU iVASC

iVASC (Innovations in VAscular SCience) is a consortium of scientists, clinicians, and industry (AAA, AstraZeneca, ResMed, Colgate), assembled around the DHU FIRE, to tackle research on atherothrombosis. Gabriel Steg is the scientific coordinator of the consortium, which has been funded via the RHU funding call by PIA-2 and ANR for 5 years (8.5 Million Euros grant) and will lead the effort from 2017 till 2021.

iVASC aims to:

-Establish a large multicenter continuous French cohort of MI patients (approximately 15,000 patients), to be linked (in collaboration with the CONSTANCES infrastructure, INSERM and UVSQ) to databases (including PMSI, CépiDC and SNIIRAM), allowing automated low-cost follow up of outcomes and healthcare consumption. It will allow prospective studies and nested registry-based randomized trials. Long term support will come from pivotal trials, particularly European ones.

-Improve selection of patients (particularly for antithrombotics) using risk assessment tools developed in large databases, imaging or biomarkers.

-Improve molecular imaging of atherothrombosis

- Using the French cohort and novel molecular imaging methods, study the association and impact of poor oral health and sleep-disordered breathing on atherothrombosis

(see more on www.ivasc.eu)

2-The funding of 20 « Emergence » projects, promoting innovative research and young investigators.

3-dentification of RTEL1 (regulator of telomere elongation helicase 1), a new gene responsible for about 10% of familial pulmonary fibroses-> Heterozygous RTEL1 mutations are associated with familial pulmonary fibrosis, Kannengiesser, et al., Crestani, *Eur Respir J*, 2015 ; DOI: 10.1183/09031936.00040115

4-Identification of seven new genes involved in the pathophysiology of thoracic aortic aneurysms by Catherine Boileau and her team, in close and direct collaboration with D. Milewicz (Houston) (TGFB2, PRKG1, MFAP5, MAT2A, LOX, FOXE3 and the new ADAMTSLX) -> Boileau C et al 2012 *Nat Genet*; Guo DC et al 2013 *Am J Hum Genet*; Barbier M et al 2014 *Am J Hum Genet*; Guo DC et al 2015 *Am J Hum Genet*; Guo D et a. 2016 Circ Res; Kuang SQ et al 2016 J Clin Invest.

5-Identification of new markers for glomerulopathies by Renato Monteiro (service d'immunologie, UF dysfonctionnements immunitaires) in collaboration with Eric Daugas (Nephrology, Bichat) (Ben Mkaddem et al J Clin Invest 2014 ; Nat Commun 2017)

6-Innovative care for TIA (Transient Ischemic Attack) by Pierre Amarenco and his team (Neurology,Bichat)

-> One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke, Pierre Amarenco, et al. , *N Engl J Med* 2016; 374:1533-1542 April 21, 2016 DOI: 10.1056/NEJMoa1412981

7-Development of transversal clinical activities with significant inputs in terms of quality of care, and science **(Appendix 3; 4; 5;6;7)**

II) Governance

The governance of the DHU has three levels:

1) A DHU council including one representative from each of the clinical scientific and educational partners (one annual meeting)

2) An Operations Committee running day to day operations and consisting of the DHU lead and work-package leaders (once a month meeting)

3) A strategic advisory board: P.Barnes (Imperial College, London, UK), G.London (Université Paris Descartes), and DL.Bhatt (Harvard Medical School, Boston, MA, USA) which advise on the DHU scientific strategy (phone meeting on midterm).

Use of credits (see Appendix 12)

The DHU was granted 500,000€ over five years

- The DHU has launched and funded Emergence Call for young investigators and transversal projects **(see Appendix 2)**
- The DHU hired a project manager (Delphine Azama)
- The DHU hired consultants to answer RHU calls: IMS health in 2015 for the project SINATRA which was not funded and Inserm Transfert in 2015 for the selected RHU iVASC

DHU FIRE Conference (see Appendix 8)

The DHU holds an annual FIRE conference in Bichat Medical school to gather its members and present the work in progress. The FIRE conferences are supported by industry (Intermune, Roche, Boehringer Ingelheim). Guests are invited for keynote lectures and the DHU funded Emergence projects re presented by the investigators. The list of FIRE conferences is in the annex.

The 5th FIRE conference is scheduled on November 30th. The keynote speaker is Dr Remy Burcelin, (Institut des Maladies Métaboliques et Cardiovasculaires (I2MC), U1048 INSERM Toulouse) : *Le microbiote, les maladies métaboliques et leurs traitements.*

III) Activity report

The DHU FIRE project was built around 6 work packages (WPs), which are the backbone of the DHU. We decided to present our report through a synthetic view of the WPs considering this as more relevant for our DHU. We associate to this WPs report the most relevant collaborative publications, the key teaching activities, and innovations in patient care.

WP1- Fight Fibrosis – Coordinator: B. Crestani

Fibrosis is a key determinant of many chronic diseases. To inhibit the development of tissular fibrosis, and eventually obtain its reversal, are key targets of the basic and translational research performed in this DHU. This collaborative project was fruitful in some areas where we had important expertise at the initiation of the project.

- Dissecting the link between inflammation and Fibrosis. **(1)** Activation of the proteases of the coagulation cascade was explored in the lung through a collaboration between the thrombosis group and the lung fibrosis group. We extended these studies to the evaluation of the protease/antiprotease imbalance in the lung. This allowed us to identify the profibrotic action of protease nexin 1 and matriptase, and the antifibrotic actions of Human airway trypsin-like (HAT) (Menou et al, in revision). **(2)** the role of Platelets was supported by the DHU as an "emergence" project to B Ho-Tin-Noé who was recruited by Inserm as a full-time scientist. **(3)** the involvement of basophils and mast cells was specifically studied in the kidney. **(4)** Lymphoid neogenesis and fibrosis evolution, was studied in the vessels in atherosclerosis, in Takayasu arteritis, and in the lung. **(5)** Altered crosstalk of epithelial cells and fibroblasts is being explored in the lung and the kidney.

- Deciphering the genetic basis of fibrosis. Our DHU was very successful in this area. Beside the genetic susceptibility to aortic aneurysms, and renal fibrosis in diabetes, where the DHU is very active, we developed a dedicated research to identify new susceptibility genes gene in familial pulmonary fibrosis. We identified the role of a new gene, RTEL1, and demonstrated the shared genetic susceptibility to pulmonary fibrosis in rheumatoid arthritis and idiopathic pulmonary fibrosis through a collaboration between the genetics department (C Kannengiesser), the rheumatology department (Ph Dieudé) and the Pneumology department (R Borie, B Crestani). This led to the identification of a group aiming at the identification of genes involved in the development of pulmonary fibrosis in the Inserm1152 unit, and was very helpful in the recognition of the Pulmonology department as a Reference Center (constitutive) for Rare Pulmonary Diseases. We set up a dedicated out-patient clinic for genetic pulmonary fibrosis. Identification of new genes, definition of the genotype-phenotype relationships, identification of therapeutic targets, are ongoing.

- Identification of fibrosis biomarkers is very active in the diabetic kidney field where two groups of the DHU are collaborating (R Roussel, JF Gautier), in heart remodeling in acute and chronic conditions (A Mebazaa and colleagues), and in lung fibrosis.

- Imaging of fibrosis in vivo is still an emerging area. We recently showed that FDG-uptake in the lung in IPF patients was associated with more severe pulmonary fibrosis as assessed by altered lung function test results (Justet 2017). Improving imaging of cardiac sarcoidosis is also an important area of progress. R Sinkus, an expert in the development of new MRI methods for tissue remodeling is joining the DHU after a 4 year stay in London and will develop this area. A collaboration is ongoing to develop new molecules for nuclear imaging of cardiac fibrosis (F Rouzet).

- Developing clinical trials in tissue fibrosis. The DHU members were very active in including patients in phase 2-3 industry-sponsored trials for lung fibrosis, particularly IPF (B Crestani is coordinating the INPULSIS-ON trial, which is the extension phase of the INPULSIS phase 3 trials at the world level). The DHU members coordinate two PHRC-supported therapeutic trials in IPF exacerbation: the KEFI trial (treatment of IPF exacerbation with recombinant KGF-early stop because the company decided not to provide the molecule) and the EXCHANGE IPF trial (treatment of IPF exacerbation with plasma exchange-supported by the PHRC 2016).

Publications: See Appendix 1 References 1 to 22

WP2 - Diabetes in chronic remodeling diseases– Coordinator: Ronan Roussel

1 Integration of care

-The two diabetology departments of the DHU (Bichat and Lariboisière, formerly-St Louis) joined their efforts to have on the same basis a systematic assessment of vascular complications of diabetes. In that purpose, the CUDC (University Center for Diabetes and its Complications) opened up in 2014, with facilities for outpatients visits and one-day admissions for up to 15 patients, including an antenna of the cardiology department (Pr Henry and Pr Cohen-Solal) of the DHU in Lariboisière, and the outpatient facility of diabetology department in Bichat hospital was up-sized to 200% of its initial capacity.

-Reciprocally, in cardiology departments of WP4, was implemented systematic assessment of cardio-metabolic diseases, as a collaboration between the Diabetology/nutrition and Cardiology groups, with routine cardiovascular assessment of patients with advanced diabetes or severe obesity (in particular in the context of preoperative assessment of bariatric surgery candidates), but also routine metabolic assessment of patients admitted to the Coronary Care Unit with acute coronary syndromes. (approximately 350 patients/year).

-A new integrated team was initiated around the expertise required for patients with severe or morbid obesity, diabetes, and chronic kidney disease. This group of patients has a particularly poor prognosis regarding early need of renal replacement therapy, access to renal graft, cardiovascular disease, and overall survival. Bariatric surgery is of potential benefit, in specialized center. We gathered the expertise from the Diabetology/nutrition, Physiology, Cardiology, and Nephrology departments of the DHU in a dedicated team in 2017 for coordination of care.

Shared d*atabase*

The two diabetology departments of the DHU now have sharable databases, with the ability to conduct similar assessment of activities or indicators related to care, but also to be able to reply on a shared basis to requests from clinical research entities regarding the ability for recruitment of patients with a given profile.

2- Research

Research structures

The frame of the DHU had been an opportunity to organize the research activity related to diabetology and nutrition locally. A new research team was created in 2014 (leader Pr Roussel, WP2), dedicated to « Pathophysiology and therapeutics of vascular and renal diseases related to diabetes and nutrition ». This INSERM team, located in the Cordeliers Research Center, joined the DHU in 2015. It will extend its perimeter to the other clinical members of WP2 in 2019 (Pr Gautier, Pr Riveline), and to Nicolas Venteclef, who was awarded an ERC consolidator grant in 2017 (epigenetics of diabetes and its complications) and future leader of the team.

Dr Hansel, expert in nutrition in WP2, will create a new research team in the frame of INSERMU1148 (Didier Letourneur, WP4), dedicated to connected tools and e-medicine related to nutrition and cardiovascular disease.

Research objectives

The WP2 fulfilled its predefined objectives:

-Identification of a new therapeutic target in diabetes complications (deliverable 1)

See Appendix 1 references 23 to 26

-Role of diabetes in valvular disease GENERAC/SOFRASA cohorts (delivrable 2.2)

Pr Messika-Zeitoun showed the detrimental effect of metabolic syndrome in valvular patients. **(Appendix 1 reference 27)**

- Heart failure in diabetes, therapeutic issues in diabetes and CVD (deliverable 3)

Members of WP 2 and 4 conducted several studies in the therapeutics of diabetes with CVD in the large REACH cohort. **(See Appendix 1 References 28 to 34)**

- Epidemiology and genetics of vascular and renal complications of (délivrable 2.4)

A number of studies were conducted, especially with the purpose of evidencing causality in epidemiological studies, using Mendelian randomization techniques.
(Appendix 1 References 35 to 43)

3. Teaching

Since the launch of the DHU, the WP2 members have initiated two new third cycle training programs related to care of patients with diabetes and complications (« Inter-University Diploma for Diabetes Care Coordination » and « Inter-University Diploma for Diabetes Care ») with more than 60 students each year, and members of all the WPs of the DHU participating to the faculty. Moreover, in November 2017 will be launched the first third cycle training program dedicated to « Development of e-medicine programs and tools », led by Dr Hansel (WP2) and Pr Nataf (WP4).

WP3- Chronic Graft Failure – Coordinator: Denis Glotz

1-Chronic graft failure in kidney and heart transplantation . From rejection to arteriosclerosis: Vascular remodeling in organ transplantation

In the last years, the pathophysiology of chronic allograft failure has been re-evaluated, due to novel data pointing to the role of alloreactive antibodies directed against the graft, so called donor specific antibodies (DSAs). In kidney transplantation, we and others have shown that the existence of such DSA significantly impact the survival of the transplanted kidney (99).

Our recent results include the following:

1) We have demonstrated in a large prospective study that DSAs exert a deleterious effect on allograft outcome even in stable-state kidney transplant recipient (100) and we have extended these results to heart transplantation (101).

2) We have previously shown that the non-specific lesion of arteriosclerosis is accelerated in the presence of DSA in kidney allografts (102), suggesting an important role for immune processes in the progression of arteriosclerosis. To address this hypothesis, we first studied the role of DSAs in the interaction between immune system and endothelial cell in vitro. We showed that the activation of endothelial cells by DSA promotes Th17 and disrupts regulatory T lymphocyte expansion (103). Second, in a large prospective cohort of kidney transplant recipients, we identified a new rejection entity characterized by acute vascular lesions induced by DSAs (104). Third, using organ transplantation as a human model of immunologically induced arteriosclerosis, we demonstrated in a prospective population-based study that circulating DSAs are major determinants of premature, severe kidney allograft arteriosclerosis, independent of traditional cardiovascular risk factors, and induce a distinct phenotype of arteriosclerosis characterized by prominent arterial intimal thickening and hypercellularity associated with allograft endothelial activation and complement deposition in capillaries and arteries (105). We also showed that DSAs strongly determine the progression of cardiac allograft vasculopathy in a large cohort of 723 heart transplant recipients (manuscript in preparation).

3) Beyond the effect of DSAs on allograft arteriosclerosis, we have provided new insights into the relationships between DSA pathogenicity and allograft injury phenotype with important consequences for prognostication and therapeutics in kidney transplantation. We have

demonstrated that i) the capacity of circulating DSAs to activate complement is associated with a more severe rejection clinical and histological phenotype, and decreased allograft survival in kidney recipients (106); ii) the IgG subtype composition of DSAs influence the clinical and histological phenotype of kidney allograft injury (107); and iii) a comprehensive characterization of DSA including their capacity to activate complement and IgG subtype profile improves the risk stratification for long-term kidney allograft loss (108). Finally, using kidney allograft gene expression profiling by microarray at large scale, we sowed that complement-activating DSAs induce a specific molecular phenotype of allograft rejection that predicts the response to complement inhibition therapy (JASN, in press).

2-Early identification of chronic allograft dysfunction.

Clinical, physiological and molecular markers of chronic allograft dysfunction will be sought for and integrated in a mathematical model (Thabut, AJRCCM 2008). This model will allow for early identification of chronic allograft dysfunction and for early intervention before irreversible damage. This modeling approach will take advantage of the large biocollection available in the prospective multicenter national cohort of lung transplantation (COLT) and of the expertise of the epidemiology team of U700 in statistical modeling. Similar modelisation can be applied to the process of chronic rejection in renal and heart transplant. (deliverable 3.2. Timeline 2014)

3-Undestanding the mechanisms responsible for the development of bronchiolitis obliterans (BO) post-lung transplant.

Pathophysiology of chronic lung allograft failure, which mainly manifests as the development of bronchiolitis obliterans (BO), has been re-evaluated in the last decade.

1) Similarly to kidney Tx, the pivotal role of humoral immunity in the pathophysiology of BO has recently been identified. We showed the deleterious role of preformed anti-HLA donor-specific antibodies (DSA) on post-lung Tx outcome, with both an increased incidence of bronchiolitis obliterans and lower survival in case of pre-Tx DSA detection (109). We also investigated the role of post-Tx DSAs detected by the new C1q assay as a predictor of long-term outcome in a multicenter study, and demonstrated that the C1q assay allows for a better identification of lung-transplant recipients with the highest risk of graft failure (110, in submission).

2) We investigated the immunological mechanisms involved in bronchial epithelial injury of BO, including the role of the tolerogenic molecule HLA-G. We first showed in a multicenter study that early graft HLA-G expression was a predictor of graft acceptance in the long-term, associated with a lower risk of alloimmunization (111). In addition, using primary bronchial cells culture in an *ex-vivo* model, we observed that inhibition of T Cell alloreactivity by bronchial epithelium was impaired in lung Tx recipients (through pathways involving TGF-beta, IL-10 and HLA-G) (112), which suggests a potential role of targeted inhaled therapies directed towards bronchial epithelium.

In the next future, we plan 2 research topics: 1- To investigate the role of the complement-independent injury of anti-class II DQ abs on bronchial epithelium, using primary BECs cultures from lung Tx recipients. 2- To identify non-HLA antigen targets of bronchial epithelial cells in BOS, suspected to play a major role in BO, using protein arrays to query de novo or augmented post-lung Tx antibody responses against a selection of non-HLA targets.

See Appendix 1: references 99 to 112

WP4 – Atherothrombosis – Coordinator: Gabriel Steg

1- Patient care:

Integration of care between the HU partners has involved the following:

a. Coordinated pan-vascular assessment of atherothrombosis (and specifically of coronary artery disease) among stroke survivors. Initially performed within a research study (the AMISTAD study), this has become integrated into routine clinical care integrating the Neurology and Cardiology groups.
b. A multidisciplinary group for the management of resistant hypertension, coordinated by E.Vidal Petiot, and involving the Physiology, Nephrology, Cardiology and Imaging groups, with a monthly joint review of difficult cases
c. Systematic assessment of cardio-metabolic diseases, as a collaboration between the Diabetology/nutritrion and Cardiology groups, with routine cardiovascular assessment of patients with advanced diabetes or severe obesity (in particular in the context of preoperative assessment of bariatric surgery candidates), but also routine metabolic assessment of patients admitted to the Coronary Care Unit with acute coronary syndromes. (approximately 350 patients/year).

2- Teaching: There has been integration of first second and third cycle curriculum between the various specialties of the DHU, with integrated seminar on cardio-metabolic risk (eg the seminar on athero-thrombosis, hypertension and diabetes is fully integrated) Likewise, in the 3rd cycle, the curriculum of the DIU on cardiovascular emergency care fully integrates cardiovascular medicine, vascular neurology, diabetology/nutrition.

3- Research. several themes reflect the integrated multidisciplinary research **approach**

3.A. Vascular Neurology/Cardiology interface **(See Appendix 1 references 44 to 58):** it has been centered around 3 themes

- Overlap between cerebrovascular disease and coronary artery disease
- Antiplatelet strategies in cerebral ischemia
- Epidemiology and management of TIA and ischemic stroke.

3.B. Diabetology/nutrition/Cardiology interface **(See Appendix 1 references 28 to 36):** has been focused on cardiovascular safety assessment of glucose lowering medications

3.C. Physiology/Cardiology/Nephrology interface **(See Appendix 1 references 59 to 64):** has focused mainly on clinical studies in hypertension and cardiorenal physiology.

WP5- CardioRenal Syndrome– Coordinator: E. Daugas

Interactions between kidney and heart emerged as an individualized entity named cardiorenal syndrome (CRS). CRS constitutes a true clinical threat, renal failure being responsible for increased duration of hospitalization of patients with acute heart failure or limitation of therapy in patients with chronic HF. About 25% of patients hospitalized for decompensated heart failure have an eGFR < 60 mL/min/1.73 m2 and most of them develop at least a mild alteration of renal function during the early phase of treatment. Conversely congestive heart failure recurrently complicates acute or chronic renal failure. Our Cardiorenal project had been be conducted at different levels.

1-Patient care

All patients with CRS discharged from hospital (more than 20 pts/month) were proposed to a dedicated outpatient follow-up by nephrologists and cardiologists.

The cardiology departments in Bichat (G. Jondeau) and Lariboisiere (D Logeart), and nephrology department in Bichat (F Vrtovsnik) initiated an active collaboration for the treatment of refractory congestive heart failure (RCHF) by haemodialysis or peritoneal dialysis. RCHF is associated with a short-term lethality that is significantly reduced by dialysis. A growing number of RCHF patients are proposed to dialysis with a preferential orientation to peritoneal dialysis, which is the most beneficial when possible.
From 2015, a project had been initiated involving the physiology department, and the cardiac surgery department (Martin Flamant, Richard Dorent) aiming to improvement of renal outcome in heart transplant recipients. All patients are now routinely evaluated to determine the renal functional reserve in the context of RCHF in patients for whom a project of heart allograft is proposed. The main objective is to improve the diagnostic performance to determine whether renal failure should be related to CRS type 1 or to CRS type 2 or type 4. The reversibility of renal failure is expected following heart transplantation in patients with type 1 CRS but not in others in whom combined heart+kidney transplantation represents the best treatment option.

2-Research projects

Cardiology and Nephrology departments acquired a large expertise in the field with a large recruitment of patients with CRS (600 patients hospitalized every year with acute heart failure, including 40% with significant renal failure). A prospective cohort of patients with CRS type 1 and type 2 is now ongoing with the most severe patients requiring extrarenal therapy with dialysis, haemodialysis or peritoneal dialysis (F. Vrtovsnik and G. Jondeau).
The VOLEMIC project (G Jondeau and E Daugas) evaluated the performance of impedancemetry to quantify overhydration and as a treatment monitoring in patients referred for acute heart failure. In a first step study (VOLEMIC I), clinical data had been repeatedly recorded as well as echocardiographic and biological parameters (including renal function assessment) before, during and after the treatment of heart failure. In parallel, body composition will be estimated by impedancemetry. A secondary objective of VOLEMIC I had been the characterization of patients presenting with a CRS and developing an acute renal failure. The main objective of VOLEMIC 1 was the validation of impedancemetry as a clinical tool for improvement of right hydration state of patients with CRS. Then we planned to conduct a prospective interventional trial (VOLEMIC II) to demonstrate the additive value of impedancemetry as a guide of depletion therapy for heart failure, especially in patients at risk for acute renal failure. However, the VOLEMIC I study was negative as it failed to demonstrate an improvement of the diagnosis value of overhydration state in patients with CRS when compared to usual clinical evaluation coupled to heart ultrasonography. Repeated impedancemetry records during extracellular depletion therapy were showed to be directly and only related to variations of total body weight. The VOLEMIC II trial was not conducted.

3-Teaching

There has been integration of first second and third cycle curriculum between the various specialties of the DHU, with integrated seminar on cardio-metabolic risk including renal risk.

Publications: See Appendix 1 References 59; 61; 64 to 81

WP6 - Sleep disordered breathing and tissue remodeling– Coordinator: MP d'Ortho

The increasing prevalence of sleep disordered breathing (SDB) in the general community makes it a public health problem. Patients with SAS exhibit increased cardiovascular morbidity and mortality,

including systemic hypertension and ischemic heart and brain diseases, increased risk to develop diabetes and steato-hepatitis. SAS could participate in the development of these associated pathologies through intermittent hypoxia, which induces oxidative stress and inflammation, increase in sympathetic activity and renin-angiotensin activity.

1-Patient care

Sleep center of Bichat hospital has been launched in 2009; in 2013 its capacity has been extended to better face increased demand. It is certified by the French Sleep Research (2011, renewed in 2016) and Medical Society and complies with standards of the European Sleep Research Society (MP d'Ortho is member of the board of Sleep Medicine Committee of the ESRS). It has been recognized as a Competence Center for rare hypersomnia diseases in 2017 (BrainTeam ; AFS H 1730222 AB3).
To date, patient pathway is clearly identified to allow routine screening and diagnosis regarding sleep pathologies especially in patients from the Cardiology-, Nephrology-, Pulmonology-departments. We have included systematic SDB screening in resistant hypertension and comprehensive sleep evaluation in orthostatic hypotension.
Once diagnosed patients are treated, the active file includes 3000 patients, with 300 patients newly treated and followed-up in the Sleep Center each year. To favor treatment compliance and adherence we set up a specific patient educational program, certified by Agence Regionale de Santé (n° BCB 10/303, renewed in 2015).

2-Research projects

a- Assessing the role of SDB in chronic diseases

Taking advantage of the already available cohorts, where SDB screening is part of the phenotyping of patients, we aimed at systematically evaluate how SAS can contribute:

- To left ventricular remodelling following an acute coronary event (ongoing screening based on questionnaires), initially based on the PREGICA cohort this deliverable was re-oriented to address SDB in prospective registry of acute coronary disease (RHU iVASC PG Steg, WP5 Sleep, ongoing) and in an interventional study in atrial fibrillation (see below)
- To lung and airways remodelling (ongoing patient screening, study of airways neutrophilic inflammation 2012-2013) (COFI and COBRA cohorts) (deliverable 6.3. Timeline 2013), two papers published (Taille ... d'Ortho, PLoS One 2016; Gille et al. Eur Respir J 2017 Jun 8;49(6). pii: 1601934)
- To kidney function loss over time and to aortic remodeling in Marfan's disease, the PHRC grant proposal to be submitted in 2012 were not met, due to re-orientation (respectively deliverable 6.1. Timeline 2012; deliverable 6.2. Timeline 2013);

We participate in a French National registry of central sleep apnea in Heart Failure (FACE, industry promotor, MPO member of scientific committee, first patient enrolled in 2013, to be ended in 2018), and we set up a French National registry of central sleep apnea whatever etiologies (FAACIL VAA, SFRMS promotor, MPO member of scientific committee, first patients enrolled in 2017)

b- Interventional studies according to the results of cohort studies.

Observational therapeutic study: ORCADES is a French multisite registry assessing the long term consequences of SAS treatment with mandibular advancement repositioning device (as an alternative to continuous positive airway pressure, CPAP). Interim results of the 1st semester of follow-up have been published (Vecchierini ../.. d'Ortho et al., Sleep Med, 2016), results of the 2nd year are presented in European and US meetings in 2017 & 2018.

Clinical randomized studies have been achieved: SERVE-HF study: that addressed central sleep apnea treatment impact on morbi-mortality of chronic heart failure, published (Cowie …/… d'Ortho et al. NEJM 2015) ; PHRC P071227 which addressed the question of optimal treatment for both HT and SAS on macular edema in type 2 diabetes (MP.d'Ortho, scientific committee). (deliverable 6.4. Timeline 2014, ended, not published yet).
Two studies are ongoing: SAAFIR: intervention study addressing the impact of systematic SDB screening on atrial fibrillation recurrence (multicenter study, first patients enrolled in 2017, PHRC AOM 15529, MPO PI); ADVENT-HF: addresses obstructive sleep apnea treatment impact on morbi-mortality of chronic systolic heart failure

c- Basic research:
Recent data suggest that perinatal oxidative stress may be the initiating trigger in long-term programming of cardiovascular and renal function in the adulthood. A collaboration has been set up (MP.d'Ortho) with INSERM U1141 (Paris Diderot University), we have developed an in vivo model of chronic intermittent hypoxia exposition of pregnant mice, in order to examine its consequence on cerebral development and learning capacities. Our collaboration aimed at characterizing adult mice exposed to chronic intermittent hypoxia when pups, in terms of myocardial and vascular remodeling, in collaboration with Centre for Mouse Imaging and Functional Phenotyping (CEFI, IFR2, Bichat). 3 MSc students have been supervised on the topics (deliverable 6.5. Timeline 2014). MS in preparation.

3-Teaching
1- Internship in pulmonology: since 2013 one resident shared between pulmonology and Sleep Center
2- University Diploma in Sleep Medicine: MPO is the national coordinator.
3- MSc in Biology Physiology & Pharmacology in Respiratory system and Sleep, MPO is the national coordinator.
(See Appendix 1 References 63; 82 to 98)

IV) Joint scientific productions
See WP presentation; **Appendix 1**

V) National and International positioning of the DHU

The DHU positioning comes from its high level of publication, the international visibility of its team leaders, the excellence of its clinical and research teams. For instance, according to the APHP evaluation, between creation in June 2012 and first evaluation in June 2014, the DHU produced 1736 manuscripts, and had the highest scientific impact all DHUs evaluated (H-index of 35).
The large cohorts developed by the DHU teams are part of the international visibility of the DHU.

Cohorts
DHU teams coordinates large cohorts, (non exhaustive list)

- EGEA (Epidemiological study on the genetics and environment of asthma, bronchial hyperresponsiveness and atopy, G. Thabut),
- COBRA (COhort of BRonchial obstruction and Asthma, > 1500 patients, PI: M. Aubier & M. Pretolani). The COBRA cohort was recently published (Pretolani et al. Clinical and biological characteristics of the French COBRA cohort of adult subjects with asthma. Eur Respir J. 2017 Aug 24;50(2). PMID: 28838976;

- CONEDAT (National cohort of alpha-1 antitrypsin-deficient emphysematous patients, G. Thabut),
- Marfan et maladies apparentées (G. Jondeau),
- The TIA registry (Transient Ischemic Attack, > 4500 sujets, PI: P. Amarenco),
- The CLARIFY registry, PI: G. Steg),
- COFRASA/GENERAC (French cohort of aortic stenosis PI : A. Vahanian et D. Messika-Zeitoun)

See Appendix 9: Selection of congress organized by DHU members
See Appendix 10: Participation in Networks (non- exhaustive list)

VI) Teaching

The teaching is developed in the Work Packages reports section (chapter III).
See Appendix 11: Thesis

VII) Care innovation

In order to present the added value of the DHU for daily patient care, we identified 9 transversal activities initiated or developed by the DHU

- **Cardiology-Neurology Interaction (see WP4)**
- **Heart Kidney Interaction** **(see Appendix 3)**
- **Resistant hypertension**

One of the innovative activities developed thanks to the dynamic of the DHU was the creation of a multidisciplinary structure for the management of severe or resistant arterial hypertension, integrating care and research (detailed in appendix). This activity, on its research side, was supported by the DHU under the "Emergence" program. **(see Appendix 4)**

- **Heart Vessels Diabetes**

Complicated diabetes is the unifying pathology top example of the care activity of the DHU. The diabetology department of Bichat is integrated into the *Pôle Coeur Vaisseaux* and has continued its integration in the context of the DHU. The diabetology department of Lariboisière also organized its outpatient care within the framework of the DHU, with the opening of the CUDC (University Center for Diabetes and its Complications) in 2014, on the occasion of its move from Saint-Louis. **(see WP2)**

- **Endocarditis**

On this multidisciplinary theme, the dynamic of the DHU has contributed to the establishment of a care organization and transversal research projects, which are detailed in the attached appendix **(see Appendix 5)**

- **Obesity**

The nutrition activity of the DHU (within the Department of Diabetology-Endocrinology-Nutrition, Hôpital Bichat) is labeled Centre Intégré Nord Francilien de l'Obésité by the Regional Health Agency of Île de France. **(see Appendix 6)**

- **Cardiac sarcoidosis**

The DHU FIRE identified cardiac sarcoidosis as a disease where the expertise of the members of the DHU FIRE was most important for patient care. We set up a quarterly meeting involving expert clinicains (pneumology, cardiology, internal medicine), cardiac nuclear medicine and cardiac MRI experts, where sarcoidosis patients with suspected cardiac involvement are discussed. One manuscript was published on the basis of this initiative (Agoston-Coldea L, et al Int J Cardiol. 2016 Nov 1;222:950-6).

- **Systemic diseases**

Care for patients with immune-inflammatory diseases takes advantage of the collaborative dynamics of the DHU. We set up a quarterly multidisciplinary meeting called « Maladies Systémiques ».

Difficult cases from all participating teams of the hospital are discussed and some are included in clinical trials (systemic sclerosis for instance).

- **Genetics of connective tissue diseases**

The DHU teams developed a genetic research project on systemic autoimmune diseases, exploiting the local patient cohorts, developing national cohorts, in relation to the projects on this topic. This transversal research benefits from the excellence of the interdisciplinary interaction developed within the DHU. **(see Appendix 7)**

- **Shared platform for heart and lung transplantation.**

The DHU FIRE is an active member of the Transplant Federation of University Paris Diderot. We set up in 2015 a shared day care facility for the evaluation of heart and lung transplant patients (8th floor, Bichat Hospital).

VIII) SWOT Analysis

STRENGTHS	WEAKNESSES
- Its location at Bichat University Hospital, a large tertiary academic center, which allows efficient and competitive translational research through close interaction of clinicians and scientists and access to patient cohorts - The inter-disciplinary nature of DHU FIRE - Excellent collaborative spirit between participants - The clinical expertise of the participating clinical sites, many of which are international leaders. - The availability of large clinical cohorts and the associated biobanks. -Support of young investigators through the Emergence program - Strong scientific output: e.g., between creation in June 2012 and first evaluation in June 2014, the DHU produced 1736 peer reviewed manuscripts, and had the highest scientific impact all DHUs evaluated (H-index of 35).	- Transversal activities of the DHU may appear in conflict with specific activities of the members - Multisite geography of the DHU limits the interaction with the non-Bichat members - Heterogeneity of the members and activities - Annual consumption of credits
OPPORTUNITIES	**THREATS**
- A new Campus in 2025 - Further calls for RHU - Develop new integrative activities - Increase in the prevalence of chronic non-communicable diseases, which are the core of DHU FIRE	- Difficulties to recruit new teams and young investigators due to the uncertainty, pending building the new Campus - Aging of the University and Hospital infrastructures - Demotivation of the partners if the DHU is not renewed after 2017

IX) Perspectives

The creation of the DHU FIRE in 2012 (first DHU call) was a very positive move. As the DHU FIRE is built around common pathophysiological pathways (Fibrosis, Inflammation and tissular Remodeling),

it allowed us to break boundaries between disciplines and develop successful transversal multidisciplinary projects in terms of clinical investigation, translational research and improvement of care. It also resulted, via the personal interactions, in creating new links between clinicians and scientists across various fields.
The new DHU FIRE will build on its past success, leveraging the prospect of the Campus Hospitalier Paris Nord and Olympic Games (both set in 2024) as new impulse for its development. In the short term, the DHU teams will apply to the next call for RHU as this is an important funding source, and will apply for its own renewal.

DHU FIRE Appendices

Appendix 1: DHU FIRE WP Publications (a non exhaustive list)

Pink: Pneumology
Red: Cardiology
Purple: Diabetology/Nutrition
Blue: Vascular Neurology
Green: Physiology
Orange: Nephrology
Yellow: Rheumatology

1. **Melboucy-Belkhir S, Pradère** P, Tadbiri S, **Habib S**, Bacrot A, Brayer S, Mari B, Besnard V, Mailleux AA, Guenther A, **Castier Y**, Mal H, **Crestani B, Plantier L**. Forkhead Box F1 (FOXF1) represses cell growth, COL1 and ARPC2 expression in lung fibroblasts in vitro. Am J Physiol Lung Cell Mol Physiol. 2014 Sep 26. pii: ajplung.00012.2014. [Epub ahead of print]

2. **Cigna N, Farrokhi Moshai E, Brayer S, Marchal-Somme J, Wémeau-Stervinou L**, Fabre A, **Mal H**, **Lesèche G**, Dehoux M, Soler P, **Crestani B**, **Mailleux A**. The hedgehog system machinery controls transforming growth factor-β-dependent myofibroblastic differentiation in humans: involvement in idiopathic pulmonary fibrosis. Am J Pathol. 2012 Dec;181(6):2126-37.

3. Moshai EF, Wémeau-Stervinou L, Cigna N, Brayer S, Sommé JM, **Crestani B**, Mailleux A. Targeting the hedgehog-glioma-associated oncogene homolog pathway inhibits bleomycin-induced lung fibrosis in mice. Am J Respir Cell Mol Biol. 2014 Jul;51(1):11-25.

4. **François D, Venisse L, Marchal-Somme J, Jandrot-Perrus M, Crestani B, Arocas V, Bouton MC**. Increased expression of protease nexin-1 in fibroblasts during idiopathic pulmonary fibrosis regulates thrombin activity and fibronectin expression. Lab Invest. 2014 Sep 8. doi: 10.1038/labinvest.2014.111. [Epub ahead of print]

5. Beghdadi W, Madjene LC, Claver J, Pejler G, Beaudoin L, Lehuen A, **Daugas E**, **Blank U.** Mast cell chymase protects against renal fibrosis in murine unilateral ureteral obstruction. Kidney Int. 2013 Aug;84(2):317-26.

6. Madjene LC, Pons M, Danelli L, Claver J, Ali L, Madera-Salcedo IK, Kassas A, Pellefigues C, Marquet F, Dadah A, Attout T, El-Ghoneimi A, Gautier G, Benhamou M, Charles N, **Daugas E**, **Launay P**, **Blank U.** Mast cells in renal inflammation and fibrosis: Lessons learnt from animal studies. Mol Immunol. 2015 Jan;63(1):86-93.

7. **Borie R**, Quesnel C, Phin S, Debray MP, Marchal-Somme J, Tiev K, **Bonay M,** Fabre A, Soler P, Dehoux M, **Crestani B**. Detection of alveolar fibrocytes in idiopathic pulmonary fibrosis and systemic sclerosis. PLoS One. 2013;8(1):e53736.

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9. Suzuki M, Bachelet-Violette L, **Rouzet F**, Beilvert A, Autret G, Maire M, Menager C, Louedec L, Choqueux C, Sabourel P, Haddad O, Chauvierre C, Chaubet F, **Michel JB**, Serfaty JM, **Letourneur D**. Ultrasmall superparamagnetic iron oxide nanoparticles coated with fucoidan for molecular MRI of intraluminal thrombus. Nanomedicine (Lond). 2014 Jun 24:1-15.

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12. **Juge PA**, **Borie R**, Kannengiesser C, Gazal S, Revy P, Wemeau-Stervinou L, Debray MP, Ottaviani S, Marchand-Adam S, Nathan N, **Thabut G**, Richez C, Nunes H, Callebaut I, Justet A, Leulliot N, Bonnefond A, Salgado D, Richette P, Desvignes JP, Lioté H, Froguel P, Allanore Y, Sand O, Dromer C, Flipo RM, Clément A, Béroud C, Sibilia J, Coustet B, Cottin V, Boissier MC, Wallaert B, Schaeverbeke T, Dastot le Moal F, Frazier A, Ménard C, Soubrier M, Saidenberg N, Valeyre D, Amselem S; FREX consortium, Boileau C, **Crestani B**, **Dieudé P**. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. Eur Respir J. 2017 May 11;49(5). pii: 1602314.

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30. **Hansel B, Roussel R, Elbez Y, Marre M,** Krempf M, Ikeda Y, Eagle KA, Elisaf M, Bhatt DL, **Steg PG;** REACH Registry Investigators. Cardiovascular risk in relation to body mass index and use of evidence-based preventive medications in patients with or at risk of atherothrombosis. ***Eur Heart J.*** 2015 Oct 21;36(40):2716-28.

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coronary artery disease undergoing drug-eluting stent placement. ***Am Heart J***. 2014 Dec;168(6):940-7.e5.

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Appendix 2: Emergence Call Awardees

Emergence 1- 2013

Jonathan Chemouny (Unité Inserm 1149)
Étude de l'intérêt de marqueurs biologiques et histologiques dans la prédiction de l'évolution et de la réponse au traitement dans la néphropathie à IgA de l'adulte.

Benoît Ho-Tin-Noé (Unité Inserm 1148 et Cardiologie Bichat)
Régulation des activités des neutrophiles par les plaquettes dans le remodelage vasculaire

Séverine Letuvé (Unité Inserm 1152 et Pneumologie Bichat)
Rôle de la Transglutaminase 2 (TG2) dans le remodelage épithélial et la fibrogenèse tissulaire dans l'asthme

Louis Potier (Unité Inserm 1138 et Diabétologie Bichat)
Nouveaux traitements pharmacologiques des complications cardiaques et rénales du diabète : les agonistes des récepteurs des kinines

Karim Sacré (Unité Inserm U1149, Médecine interne Bichat)
Rôle de l'immunité T dans l'athérome associé au lupus

Nicolas Vodovar (Unité Inserm 942 – Lariboisière)
Evaluation of the role of QSOX1 in the establishment of cardiac fibrosis

Emergence 2- 2014

Emmanuelle Vidal-Petiot (Unité Inserm 1149)
Mesure de l'activité nerveuse sympathique par microneurographie chez les patients bénéficiant d'une dénervation rénale

Arnaud Mailleux (Unité Inserm 1152)
Identification des fonctions non-apoptotiques de la forme nucléaire de la protéine proapoptotique BAX au cours de la fibrose pulmonaire idiopathique

Mélodie Aubart (Unité Inserm 1148)
Variabilité phénotypique du syndrome de Marfan : recherche de facteurs génétiques modificateurs par étude eQTL

Nicolas Charles (Unité Inserm 1149)
Les basophiles dans le développement de la néphrite lupique – Approche Transcriptomique

Marie Le Borgne-Moynier (Unité Inserm 1148)
Rôle des mastocytes et des basophiles dans l'athérosclérose

Emergence 3 – 2015

Yacine Boulaftali (Unité Inserm 1148 LVTS)
Intéractions plaquettes- Leucocytes dans le développement des anévrismes de l'aorte abdominale

Anaïs Gardette (Service de Rhumatologie, Hôpital Bichat)
Rôle de la tyrosine phosphatase Lyp (PTPN22) dans l'activation des polynucléaires neutrophiles humains et dans la polyarthrite rhumatoïde

Boris Hansel (Service de Diabétologie-Endocrinologie-Nutrition, Hôpital Bichat)
Étude de la fonction rénale et des marqueurs de fibrose avant et après chirurgie bariatrique (Néphrobaria)

Nidaa Mikaïl (Service de Médecine Nucléaire, GH Bichat-Claude Bernard - LVTS (Inserm U1148), Equipe 4)
Imagerie moléculaire de la mémoire ischémique myocardique chez le rat par le 99mTc-Fucoïdane

Emergence 4- 2016

Pierre-Antoine JUGE (Service de rhumatologie- Bichat)
Etude de l'implication du gène SFTPC dans la pneumopathie interstitielle diffuse au cours de la polyarthrite rhumatoïde

Aurélien Justet (U1152 Equipe 3- Pneumologie A Bichat)
FGFR 4 : une nouvelle voie thérapeutique dans la fibrose pulmonaire idiopathique.

Fanny Saidoune (U1149 – Médecine interne Bichat)
Rôle des lymphocytes B dans l'athérome accéléré associé au lupus systémique

Alexy Tran Dinh (U1148 - Département Anesthésie réanimation Bichat)
Rôle du CD31 dans la dysfonction primaire du greffon pulmonaire

Appendix 3: Heart and Kidney Axis – Pr François Vrtovsnik

1) Projects and cohorts

1.1. The Heart Module from the French Speaking Peritoneal Dialysis Registry (*RDPLF*)

Refractory Heart Failure is a not uncommon indication for peritoneal ultrafiltration although its benefits have been unconsistently reported through mainly retrospective or monocentric studies. The main objectives of the "heart module" are to prospectively collect data related to cardiac status in PD pts and to allow longitudinal follow-up of cardiac- and dialysis-related parameters in HF pts

The RDPLF constitutes the largest recruiting observational cohort of French speaking PD pts, with coverage estimated at 98,3% of PD in France. All centers complete a set of core modules covering socio-demographics and basic clinical information, peritonitis episodes, and outcomes. Optional specialized modules are available. The heart module consists of baseline followed by quarterly collection of information related to cardiac disease, hospitalization rate, and dialysis-related parameters.

A total number of 232 pts have been included in the heart module by 44 centers, constituting the largest prospective cohort in the field. PD was initiated because of HF in 73%. Mean eGFR was 22±14 ml/mn/1.73m^2 with GFR>15ml/mn/1.73m^2 in 69%. Half of the pts had echocardiographic Left Ventricular Ejection Fraction (LVEF)<30% and 71% pts had NYHA III-IV status. Mean rate of hospitalization the previous year was 30.8 days/pts/yr. Follow-up data indicate à 45% decreased rate of hospitalization.

Comparison analysis will be based on pts from the FRESH Registry (pts with heart failure and no peritoneal ultrafiltration) and pts from the RDPLF with heart failure as a comorbidity and not included in the heart module. Statistical analysis is ongoing.

1.2. Autosomal polycystic kidney disease a risk of aortic root aneurysm

Simple renal cysts have been linked to an increased risk of aortic aneurysm but there is little evidence regarding aortic root dilatation in ADPKD.

Sinuses of Valsalva (SoV) diameters were measured by 2 echographers blinded to the clinical status in 61 ADPKD patients and 61 controls matched 1:1 for sex, age, blood pressure and beta-blocker therapy. Mean age was 56±12 years, 54% were men, 35% under beta-blocker therapy, mean body surface area was 1.8±0.2 m2 and mean systolic/diastolic BP were 136±24/79±16 mmHg. Mean SoV diameters were significantly higher in ADPKD patients than in controls (36.3±4.1 versus 34.1±3.7 mm, p< 0.0001). The Campens Z-scores (normalized on sex, age and body surface area) were higher in ADPKD patients (1.2±1.2 versus 0.4±1.0, p<0.0001). More importantly, aortic aneurysms, as defined by a Z score>2 Standard Deviations, were present in 44% of ADPKD patients (44%) versus 15% of controls (p<0.001).

These results establish an increased prevalence of aortic aneurysms in ADPKD patients as compared with controls, matched for common confounding factors for aortic dilatation. Systematic echocardiography is currently not recommended in ADPKD patients, however, our results strongly support aortic aneurysms echocardiographic screening and follow-up in this population.

2) Publications

Peritoneal dialysis and heart failure: designing of the heart module in the French speaking peritoneal dialysis registry (RDPLF). F Vrtovsnik[1,2], G Jondeau[1,2], C Verger[3] and the "groupe Coeur" du RDPLF[4]. University Paris-Diderot, Paris, France. ISPD 2014

Insuffisance cardiaque et dialyse péritonéale: le module cœur du RDPLF. 16ème Réunion Commune SN-SFD, Saint Etienne 30/09-3/10/2014

Insuffisance cardiaque et dialyse péritonéale: le module cœur du RDPLF. 13ème Symposium du RDPLF. Montvillargene 15-17 avril 2015

Peritoneal ultrafiltration and heart failure: data from the heart module in the RDPLF. 4ème symposium de dialyse extra-hospitalière. 6-7 juin 2018, Bruxelles

Autosomal polycystic kidney disease carries an increased risk of aortic root aneurysm. C. Bouleti, M. Flamant, B. Escoubet, F. Arnoult, O. Milleron, E. Vidal-Petiot, M. Langeois, F. Vrtovsnik, G. Jondeau. ESC 2017

Augmentation du risque d'anévrysme de la racine de l'aorte au cours de la polykystose rénale autosomique dominante. C. Bouleti, M. Flamant, B. Escoubet, F. Arnoult, O. Milleron, E. Vidal-Petiot, M. Langeois, F. Vrtovsnik, G. Jondeau. 2ème Réunion de la SNSFD 11-13 octobre 2017, Nice

3) Research projects

3.1. Renal failure in the Cardio-Renal syndrome : determinants and reversibility

Renal failure is a marker of severity in patients with heart failure; it limits the access and efficacy of medical therapies and questions the need for transplantation. In contrast, reversibility of renal failure may ensue from correction of venous congestion highlighting the role of hemodynamic factors. Determinants of glomerular filtration rate will be analyzed in 650 pts who underwent simultaneous measurement of 51Cr-EDTA clearance and echocardiography in the physiology department with special attention to volemic and hemodynamic parameters in order to better identify markers of reversibility of renal failure in this setting.

3.2. Hyperkaliemia in chronic heart failure.

Common treatment of heart failure relies on diuretics, renin-angiotensin system blockers and aldosteron antagonists; however, this therapeutic approach may induce severe hyperkalemia which prevent further use. Novel therapeutic agents are being developed to treat hyperkalemia. Whether inclusion of these agents to standard heart failure treatment reduces the occurrence of this adverse event and improves adherence to therapy and clinical results is not known.

4) Funding

The « Heart module in the RDPLF » received a 20.000 € grant from the Société Francophone de dialyse in 2015

Appendix 4: Resistant and secondary hypertension-Dr E. Vidal-Petiot

Coordinator: Dr Emmanuelle Vidal-Petiot, MCU-PH (Physiology Department, Bichat Hospital)

Collaborators (Bichat Hospital, Paris, France): Pr M. Flamant, Physiology Department - Pr M-P d'Ortho, Physiology Department - Dr F. Arnoult, Physiology Department - Dr B. Touraut, Physiology Department - Pr F. Vrtovsnik, Nephrology Department - Pr PG Steg, Cardiology Department - Dr P. Fernandez, Radiology Department - Pr A. Khalil, Radiology Department - Dr JF Hermieu, Urology Department

Introduction

Since January 2012, a multidisciplinary program for the care of patients with resistant or secondary forms of hypertension has been implemented, coordinated by Dr Emmanuelle Vidal-Petiot. This program relies on a tight collaboration between the physiology department (renal, cardiology and sleep disorders units), the medical departments (nephrology, cardiology, and neurology in particular), as well as the radiology, nuclear imaging and urology departments.

Patient care

Outpatient clinic

Hypertension is a very common co-morbidity and risk factor, concerning 60-80% of patients followed-up in the outpatient department of Bichat hospital, in particular in the cardiology (~10000 outpatient visits/year), nephrology (~14600 outpatient visits/year), diabetology and neurology departments. In some cases hypertension requires expert medical advice, either because of resistance or suspicion of secondary form. Since 2012, specialized consulting activities dedicated to the care of such patients have been opened (Dr E. Vidal-Petiot, Hypertension specialist, since 2012, and Dr F. Arnoult and Dr B. Touraut, cardiologists, since 2015), with ~100 patients/ year in 2012, ~450 patients/year in 2017. Patients are referred either from our hospital or surrounding hospitals, or by private practioners

Day hospital admissions

Patients requiring specialized explorations are explored during a day hospital with two frames of explorations in search of:

- secondary forms of hypertension, this activity increased from 70 patients/year in 2012, to ~140 patients/year (stable since 2014)
- end organ damage in case of very severe forms of hypertension (~5/month since 2016)

Adrenal venous sampling

This technically challenging procedure is pivotal in the care of patients with primary hyperaldosteronism (10% of patients with resistant hypertension). No patient has been referred to another center for the past 6 months, snice this procedure was successfully implemented by Pr A. Khalil (head of the radiology department). 25 patients underwent adrenal venous sampling in our center and this number is expected to increase markedly in the coming years as more and more patients are referred to our center from surrounding hospitals.

Those with lateralized hyperaldosteronism (40%) undergo coelioscopic adrenalectomy which cures hypertension.

Other forms of secondary hypertension

Other less frequent diagnoses of secondary hypertension can lead to endovascular or surgical procedures, all available locally in Bichat hospital (pheochromocytoma, renin tumor, renal artery stenosis, urological disorders, genetic forms of hypertension…)

Multidisciplinary meeting

Along with this specialized care, we run a monthly multidisciplinary discussion group meeting with radiologists, nephrologists, cardiologists, endocrinologists. 15 patients are discussed monthly.

New activities developed

Since May 2016, an entirely new activity has been developed. We completed our expertise in hypertension with an expertise in severe forms of orthostatic hypotension, and especially in patients with pure autonomic failure. We are now following up 15 patients with this very rare disease and have seen about the same number of patients for severe OH of various other etiologies. This multidisciplinary expert care relies on an outpatient clinic (Dr Vidal-Petiot) as well as on a 1-day hospital exploration for orthostatic hypotension with no etiology identified and a 5-day hospital stay for patients with a high suspicion of dysautonomia. Patients are addressed from all over France with a national coverage.

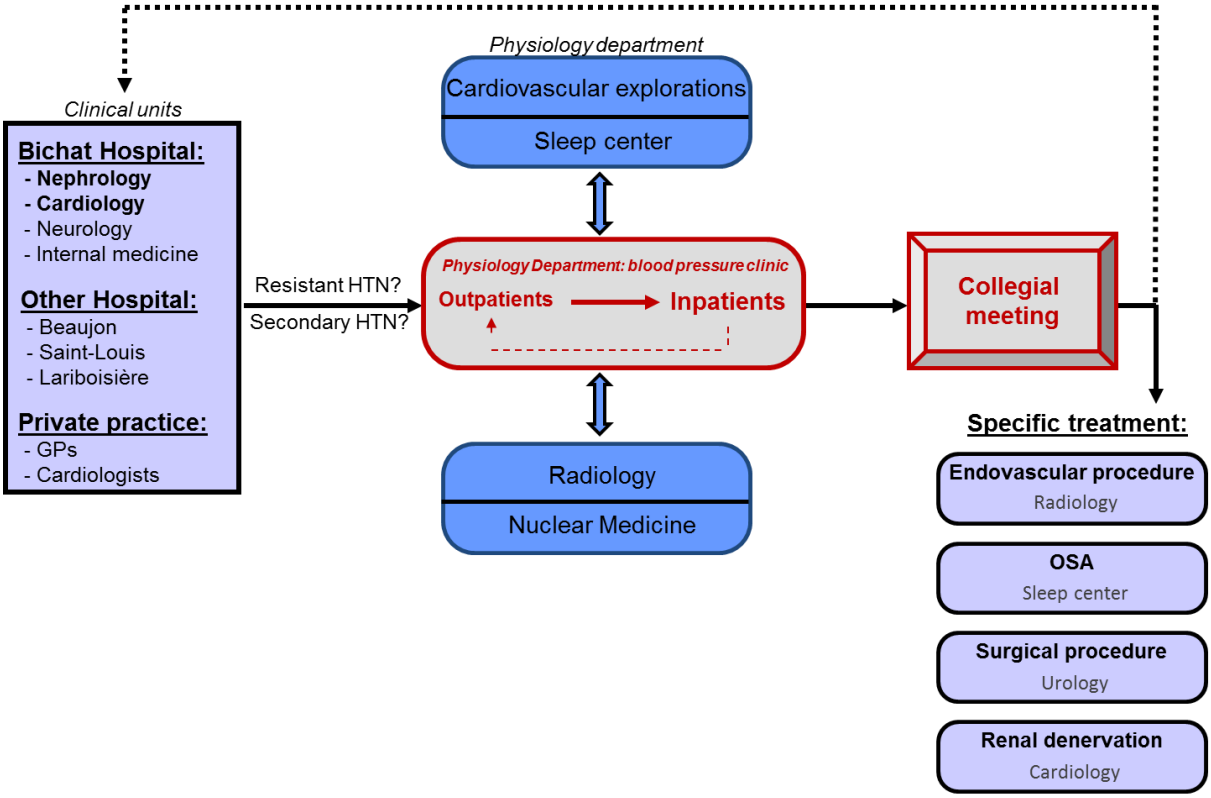

Figure: Hypertension Care Circuit

"Blood Pressure Clinic" accreditation

Dr Vidal-Petiot was certified European Hypertension Specialist in 2014. This year, our structure is applying for the title of « Blood pressure Clinic », credited by the European Society of Hypertension to centres with a particular expertise in the care of hypertensive patients. This coordinated network of specialized centres facilitates the set-up of multicentric trials for instance. The selected structures for 2017 will be announced in December.

Research projects and databases

1. **Hypertension during chronic kidney disease (Dr Vidal-Petiot, Pr Flamant, Pr Vrtovsnik)**

NephroTest study cohort: prospective hospital-based chronic kidney disease (CKD) which enrolled 2084 adult patients with CKD of various etiologies, stages 1 to 5, from January 2000 to December 2012. A urine and plasma biobanking has been prospectively collected and funded by Inserm (Inserm GIS-IReSP AO 8113LS TGIR and Inserm AO 8022LS).
In the context of the development of research in hypertension within the DHU fire, we started new research projects focusing on the links between hypertension and chronic disease based on the Nephrotest cohort study.
1/ Determinants of uncontrolled and resistant hypertension during CKD.
Status: completed, manuscript draft under revision by co-authors
2/ Interactions between CKD and Hypertension. Role of extracellular water.
Research project of Dr Anne-Laure Faucon, PhD student, , co-direction by Dr Vidal-Petiot and Dr Geri from the CESP/Inserm UMR 1018 (statistical laboratory of the Nephrotest study). Dr Faucon was awarded a 3-year grant from nov, 2017, to oct, 2020, by Ecole Doctorale de Santé Publique Paris XI for this project.

Hypertension in patients with coronary artery disease (Pr Steg)

1/ Analyses from the prospective observational registry of patients with stable coronary artery disease (CLARIFY), including 32703 outpatients receiving standard care. These studies are registered with clarify-registry.com, number ISRCTN43070564.
1.1 - Cardiovascular event rates and mortality according to systolic and diastolic blood pressure
Status: presented in the hotline session as ESC congress in August 2016 and published simultaneously (Vidal-Petiot et al, Lancet 2016)
1.2 - Relationships between components of blood pressure and cardiovascular events: is pulse pressure responsible for the J-curve phenomenon?
Status: presented in the hotline session at ESC congress 2017. Currently in revision in *Hypertension*.
2/ Visit-to-visit variability as a predictor of cardiovascular outcomes in patients with stable coronary heart disease: a post-hoc analysis of the Stability trial (darapladib vs placebo in 15828 patients, ClinicalTrials.gov number NCT00799903).
Status: presentation as an oral communication at AHA scientific sessions 2016 and published. (Vidal-Petiot et al, Eur Heart J 2017)

Orthostatic hypotension (coordination Dr Vidal-Petiot, Pr d'Ortho)

Several research projects are ongoing in our cohorts of patients with PAF. Dr Wanono, neurologist, is studying sleep disorders in patients with PAF as a research project of his master's degree in 2016-2017 (Biologie, Physiologie et Pharmacologie de la Respiration et du Sommeil). Other projects are ongoing to describe the cardiovascular alterations in these patients. The database has been declared (CNIL MR003), as a standard care cohort.

Renal denervation (Inserm U1149, Pr Monteiro)

The clinical project on renal denervation in patient with resistant hypertension (2013-2014) has been interrupted after the publication of simplicity HTN 3 trial; the results of other ongoing trials are awaited to define the potential future indications of this procedure.
A DHU Fire "Emergence grant" was obtained on this topic in 2014. We have, in part thanks to this grant, developed a mouse model of renal denervation (Inserm U1149, CRI, Pr R. Monteiro). The surgical procedure is now routinely performed, with a 95% reduction of intra-renal norepinephrine content. We are currently testing the potential protecting role of renal denervation in several models

of glomerulonephritis. This is part of the PhD project of Amaya Murua, Ecole Doctorale Bio SPC, Immunology department (3-year MRT grant, Oct 2015-Sept 2018).

Renal physiology and hypertension

All patients explored in the renal physiology unit, including for resistant and secondary hypertension, are registered in a database (CNIL MR003), with several ongoing or future related clinical research projects. One project on salt intake evaluation, approved by the institutional review Board IRB 00006477, N°14-051, is completed. The manuscript is currently under review in *J. Hypertens.*

Sleep disorders and hypertension (Coordination Pr d'Ortho)

ORCADES is a prospective observational study underway at 28 centers (including Bichat Hospital) in France (ClinicalTrials.gov identifier: NCT01326143), sponsored by ResMed, including patients treated with mandibular repositioning devices for an obstructive sleep apnea syndrome. We are studying the effect of the device on blood pressure. The manuscript is currently being validated by co-authors and should be submitted by Nov 2017.

Publications related to the Hypertension Program

E. Vidal-Petiot, N. Greenlaw, I. Ford, R. Ferrari, KM. Fox, J-C. Tardif, M. Tendera, A. Parkhomenko, DL. Bhatt, PG. Steg, for the CLARIFY Investigators, Relationships between components of blood pressure and cardiovascular events in patients with stable coronary artery disease and hypertension, *in revision*

E. Vidal-Petiot, Adrien Joseph, Matthieu Resche-Rigon, Anne Boutten, Jimmy Mullaert, MP d' Ortho, F. Vrtovsnik, PG Steg, and M. Flamant, External validation and comparison of formulae estimating 24-hour sodium intake from a fasting morning urine sample, *in revision*

E. Vidal-Petiot, A. Stebbins, K. Chiswell, D. Ardissino, PE. Aylward, CP. Cannon, MR. Corrales, C. Held, JL. López-Sendón, RA. Stewart, L. Wallentin, HD. White, Ph. G.Steg, on behalf of the STABILITY Investigators, Visit-to-visit variability of blood pressure and cardiovascular outcomes in patients with stable coronary heart disease. Insights from the STABILITY trial, *Eur Heart J* 2017, doi: 10.1093/eurheartj/ehx250 [Epub ahead of print] (IF 15.1 – SIGAPS A)

E. Vidal-Petiot, DL. Bhatt, KM. Fox, and Ph. G. Steg, Blood pressure and cardiovascular outcomes: authors' reply (correspondence), *Lancet* 2017; 389:1296-97 (IF 45 – SIGAPS A)

A. Joseph, R. Wanono, M. Flamant and E. Vidal-Petiot, Orthostatic Hypotension: A review, *Néphrologie & Thérapeutique* 2017, 13 Suppl 1 :S55-S67.

E. Vidal-Petiot, « Hypertension artérielle : quels objectifs en 2017 ? » - *Nutritions et Endocrinologie, Hors série Cardiologie N°8,* 2017

A. Lorthioir et E. Vidal-Petiot, « Physiologie du système rénine-angiotensine-aldostérone et des peptides natriurétiques » - *Traité d'Endocrinologie 2ème édition,* Editions Lavoisier, coordination Pr P. Chanson et J. Young, 2017

E. Vidal-Petiot, A. Joseph, M. Flamant, Estimation of populational 24-h urinary sodium and potassium excretion from spot urine samples: evaluation of four formulas in a large national representative population (letter), *J. Hypertens* 2017; 35(5):119-20 (IF 5.1 – SIGAPS B)

L. Amar, Y. Sharabi, GP. Rossi, E. Vidal-Petiot, AF. Dominiczak, P. Mulatero, AL. Faucon, N. Dhaun, RM. Touyz, M. Barigou, A. Lorthioir, Case of Primary Aldosteronism With Discordant Hormonal and Computed Tomographic Findings, *Hypertension* 2017; 69(4):529-35 (IF 6.3 – SIGAPS A)

E. Vidal-Petiot, I. Ford, N. Greenlaw, R. Ferrari, KM Fox, JC Tardif, M. Tendera, L. Tavazzi, DL Bhatt, PG Steg, Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study, *Lancet* 2016; 388:2142–525 (IF 45 – SIGAPS A)

E. Vidal-Petiot, M. Bens, L. Choudat, P. Fernandez, F. Rouzet, J-F. Hermieu, P. Bruneval**,** JM. Goujon, M. Flamant**,** A. Vandewalle**,** A case report of reninoma: radiological and pathological features of the tumor and characterisation of tumor-derived juxtaglomerular cells in culture**,** *J. Hypertens.* 2015; 33(8): 1709-15. (IF:5.1-SIGAPS B)

Appendix 5: Endocarditis - Pr Bernard Iung

Patient management and organization of clinical research on infective endocarditis in Bichat Hospital

1. Organisation of patient management

Patients with infective endocarditis are referred in different departments of Bichat Hospital, mainly in cardiology, cardiovascular surgery, infectious disease and intensive care.

A multidisciplinary management is organized according to the recommendations of the European Society of Cardiology with regards to Endocarditis Teams. A weekly meeting is organized with practitioners representing clinical departments (cardiology, cardiovascular surgery, infectious disease and intensive care departments), specialists in imaging (echocardiography, nuclear medicine) and microbiology. A written report is provided summarizing the presentation of the patient and the therapeutic decision. Additional multidisciplinary meetings can be organized if there is a need for an emergency decision.

Following the results of the IMAGE study (Duval et al. Ann Intern Med 2010), cerebral magnetic resonance imaging is systematically performed, if not-contra-indicated, in patients hospitalised for infective endocarditis. Patients are proposed to consent for inclusion in the IMAGE / Echo-IMAGE cohort.

2. Clinical research: Cohorts

The IMAGE / Echo-IMAGE cohort collects clinical, biological, microbiological and imaging data and therapeutic management of patients hospitalized in Bichat Hospital because of infective endocarditis. Blood samples are collected and stored for patients of the Echo-IMAGE cohort. This cohort presently includes 395 patients. An annual follow-up is performed on this cohort, up to 5 years.

The substudy Post-IMAGE consists in a specific follow-up of patients from the IMAGE / Echo-IMAGE cohort who undergo a standardized clinical examination and odontologic evaluation, a follow-up cerebral MRI and psychometric tests. The recruitment of Post-IMAGE ended in June 2017 and it comprises 100 patients.

Research projects on infective endocarditis are coordinated by the Clinical Investigation Centre (Pr Xavier Duval).

The Bichat multidiscipinary endocarditis team is also involved in multicenter studies (EVAMICA study) and studies performed by the AEPEI (Association pour l'Etude et la Prévention de l'Endocardite Infectieuse) (see publications):
- Subanalyses of the French survey on infective endocarditis performed in 2008
- VIRSTA study
- AEPEI French multicentre registry of endocarditis (beginning in 2017).

Bichat participates to the Eurobservational research Programme on infective endocarditis (European registry) headed by the European Society of Cardiology and Pr Bernard Iung is the national coordinator for France.

3. Publications related to infective endocarditis (since 2014)

3.1. Original articles

1. Rouzet F, Chequer R, Benali K, Lepage L, Ghodbane W, Duval X, Iung B, Vahanian A, Le Guludec D, Hyafil F. Respective Performance of 18F-FDG PET and Radiolabeled Leukocyte Scintigraphy for the Diagnosis of Prosthetic Valve Endocarditis. J Nucl Med. 2014;55:1980-1985.
2. Endocarditis due to gram-negative bacilli at a French teaching hospital over a 6-year period: clinical characteristics and outcome. Loubet P, Lescure FX, Lepage L, Kirsch M, Armand-Lefevre L, Bouadma L, Lariven S, Duval X, Yazdanpanah Y, Joly V. Infect Dis (Lond) 2015;47:889-895
3. Staphylococcus aureus infective endocarditis versus bacteremia strains: Subtle genetic differences at stake. Bouchiat C, Moreau K, Devillard S, Rasigade JP, Mosnier A, Geissmann T, Bes M, Tristan A, Lina G, Laurent F, Piroth L, Aissa N, Duval X, Le Moing V, Vandenesch F; French VIRSTA Study Group. Infect Genet Evol 2015;36:524-530.
4. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, Kapadia S, Lerakis S, Cheema A, Gutiérrez-Ibanes E, Munoz-Garcia A, Pan M, Webb JG, Herrmann H, Kodali S, Nombela-Franco L, Tamburino C, Jilaihawi H, Masson JB, Sandoli de Brito F, Ferreira MC, Correa Lima V, Mangione JA, Iung B, Durand E, Vahanian A, Tuzcu M, Hayek SS, Angulo-Llanos R, Gómez-Doblas JJ, Castillo JC, Dvir D, Leon MB, Garcia E, Cobiella J, Vilacosta I, Barbanti M, Makkar R, Barbosa Ribeiro H, Urena M, Dumont E, Pibarot P, Lopez J, San Roman A, Rodés-Cabau J. Infective Endocarditis Following Transcatheter Aortic Valve Implantation: Results from a Large Multicenter Registry. Circulation 2015;13:1566-1574.
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6. Mirabel M, André R, Barsoum Mikhaïl P, Colboc H, Lacassin F, Noël B, Robert J, Nadra M, Braunstein C, Gervolino S, Marijon E, Iung B, Jouven X. Infective endocarditis in the Pacific: clinical characteristics, treatment and long-term outcomes. Open Heart 2015;2(1):e000183.
7. Le Moing V, Alla F, Doco-Lecompte T, Delahaye F, Piroth L, Chirouze C, Tattevin P, Lavigne JP, Erpelding ML, Hoen B, Vandenesch F, Duval X; VIRSTA study group. Staphylococcus aureus Bloodstream Infection and Endocarditis—A Prospective Cohort Study. PloS One 2015;10:e0127385.
8. Braquet P, Alla F, Cornu C, Goehringer F, Piroth L, Chirouze C, Revest M, Lechiche C, Duval X, Le Moing V; VIRSTA-AEPEI study group. Factors associated with 12 week case-fatality in Staphylococcus aureus bacteraemia: a prospective cohort study. Clin Microbiol Infect 2016; 22: 948.e1-948.e7.
9. Symptomatic and Asymptomatic Neurological Complications of Infective Endocarditis: Impact on Surgical Management and Prognosis.. Selton-Suty C, Delahaye F, Tattevin P, Federspiel C, Le Moing V, Chirouze C, Nazeyrollas P, Vernet-Garnier V, Bernard Y, Chocron S, Obadia JF, Alla F, Hoen B, Duval X; PLoS One 2016; 11:e0158522
10. Time Interval between Infective Endocarditis First Symptoms and Diagnosis: Relationship to Infective Endocarditis characteristics, Microorganisms and Prognosis. N'Guyen Y, Duval X, Revest M, Saada M, Erpelding ML, Selton-Suty C, Bouchiat C, Delahaye F, Chirouze C, Alla F, Strady C, Hoen B; AEPEI study group. Ann Med. 2016;49:117-112.
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12. Tubiana S, Duval X, Alla F, Selton-Suty C, Tattevin P, Delahaye F, Piroth L, Chirouze C, Lavigne JP, Erpelding ML, Hoen B, Vandenesch F, Iung B, Le Moing V; VIRSTA/AEPEI study group. The VIRSTA score, a prediction score to estimate risk of infective endocarditis and determine priority for echocardiography in patients with Staphylococcus aureus bacteremia. J Infect 2016;72:544-553
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14. Oral streptococcal endocarditis, oral hygiene habits and recent dental procedures: a case-control study.. Duval X, Millot S, Chirouze C, Selton-Suty C, Moby V, Tattevin P, Strady C, Euvrard E, Agrinier N, Thomas D, Hoen B, Alla F; EI-dents AEPEI study group. Clin Infect Dis. 2017;64:1678-1685.
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16. Cambau E, Durand-Zaleski I, Bretagne S, Buisson CB, Cordonnier C, Duval X, Herwegh S, Pottecher J, Courcol R, Bastuji-Garin S; EVAMICA study team. Performance and economic evaluation of the molecular detection of pathogens for patients with severe infections: the EVAMICA open-label, cluster-randomised, interventional crossover trial. Intensive Care Med. 2017 Apr 3 [Epub ahead of print]

17. Tubiana S, Blotière PO, Hoen B, Lesclous P, Millot S, Rudant J, Weill A, Coste J, Alla F, Duval X. Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: nationwide population based cohort and a case crossover study. BMJ 2017;358:j3776

3.2 Guidelines and literature reviews

1. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 26:3075-3128.
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3. Duval X, Iung B. Extracardiac imaging of infective endocarditis. Curr Infect Dis Rep 2017;19:24.
4. Millot S, Lesclous P, Colombier ML, Radoi L, Messeca C, Ballanger M, Charrier JL, Tramba P, Simon S, Berrebi A, Doguet F, Lansac E, Tribouilloy C, Habib G, Duval X, Iung B. Position paper for the evaluation and management of oral status in patients with valvular disease: Groupe de Travail Valvulopathies de la Société Française de Cardiologie, Société Française de Chirurgie Orale, Société Française de Parodontologie et d'Implantologie Orale, Société Française d'Endodontie et Société de Pathologie Infectieuse de Langue Française. Arch Cardiovasc Dis 2017;110:482-494.

3.3 Editorials

1. Duval X, Hoen B. Prophylaxis for infective endocarditis: let's end the debate. Lancet 2015;385:1164-1165.
2. Habib G, Lancellotti P, Iung B. 2015 ESC Guidelines on the management of infective endocarditis: a big step forward for an old disease. Heart 2016;102: 992-994

3.4 Letters to the editor

1. Iung B, Tubiana S, Alla F, Lavielle M. Infective endocarditis and antibiotic prophylaxis. Lancet 2015; 386:529-530.
2. Tubiana S, Le Moing V, Duval X. Echocardiography in Patients With Enterococcal Bacteremia. Clin Infect Dis 2015;61:132.
3. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, Kapadia S, Lerakis S, Cheema AN, Gutiérrez-Ibanes E, Munoz A, Pan M, Webb JG, Herrmann H, Kodali S, Nombela-Franco L, Tamburino C, Jilaihawi H, Masson JB, Sandoli de Brito F, Cristina Ferreira M, Lima VC, Mangione JA, Iung B, Vahanian A, Durand E, Tuzcu M, Hayek SS, Angulo-Llanos R, Gómez-Doblas JJ, Castillo JC, Dvir D, Leon MB, Garcia E, Cobiella J, Barbanti M, Makkar R, Barbosa Ribeiro H, Urena M, Dumont E, Pibarot P, Lopez J, Roman AS, Rodés-Cabau J. Response to Letters Regarding Article, "Infective Endocarditis After Transcatheter Aortic Valve Implantation: Results From a Large Multicenter Registry". Circulation 2015; 132: e372-4.
4. Millot S, Colombier ML, Iung B, Lancellotti P, Habib G. Response to the letter of Diz et al.: Prophylaxis against infective endocarditis in the dental setting. New ESC guidelines, albeit with old problems. Eur Heart J 2016 http://eurheartj.oxfordjournals.org/content/early/2015/08/28/eurheartj.ehv319.explore
5. Mathieu C, Mikaïl N, Benali K, Iung B, Duval X, Nataf P, Jondeau G, Hyafil F, Le Guludec D, Rouzet F. Response by Mathieu et al to Letter Regarding Article, "Characterization of 18F-Fluorodeoxyglucose Uptake Pattern in Noninfected Prosthetic Heart Valves".Circ Cardiovasc Imaging. 2017; 10.pii: e006720. doi:10.1161/CIRCIMAGING.117.006720.

4. Research projects and funding

Public funding was obtained for the cohorts IMAGE / Echo-IMAGE and Post-IMAGE (PHRC National 2004 and CRC 2012).

TEPVENDO is multicentre prospective evaluation of the impact of 18-FDG PET/CT imaging on clinical decision making during the acute phase of infective endocarditis (public funding PHRC National 2013). 150 patients have been recruited and the analysis is ongoing.

CHIRENDO is a multicenter randomized trial comparing early valve surgery versus conventional treatment in infective endocarditis patients with high risk of embolism (public funding PHRC National 2016). Recruitment will start in 2018.

Appendix 6: Obesity – Dr B. Hansel

At the Bichat hospital, the medical management of obesity is organized by the Department of Diabetology-Endocrinology-Nutrition, which is part of the "Centre Intégré Nord-Francilien de l'Obésité", labeled by the Regional Health Agency of Île-de-France. In this context and in the recognition of the DHU, we have developed different pathways for patient care, adapted to specific needs and profiles.

1) Structuring the supply of care

The flow of patients is constantly increasing. During the year 2016, it was about 400 new patients. In 2017 it will be 500+ patients. Three types of care programs have been implemented over the past three years.

- **Therapeutic Education Program (ETAPES)** for patients who wish to invest in a non-surgical, structured multidisciplinary, quite demanding, care program. This program includes 3 new patients / week.
- The "**EQUILIBRE" program** for patients who do not wish to undergo bariatric surgery or benefit from the ETAPES program. It is centered by management of comorbidities and includes nutritional advice (diet and physical activity). This program recruits 3 to 4 new patients per week currently.
- **Medical and surgical program** for patients for whom bariatric surgery is indicated (3 new patients per week currently). Eligibility assessment is organized in a one-day hospital stay before bariatric surgery; monitoring of patients after surgery is organized through outpatient visits, one-day stay, and increasingly telemedicine. This activity is carried out jointly with the bariatric surgery department led by Professor Simon MSIKA.

In addition, in 2017, we created a care program specifically dedicated to obese patients with impaired renal function. The interest of our team for this theme was reinforced by the Nephrobaria and BOKID clinical studies implemented in our department. Nephrobaria is an observational study carried out thanks to the funding obtained in the framework of the EMERGENCE call for proposals of the DHU. BOKID is a clinical multicentric trial conducted as part of a national PHRC, co-lead by our team with Nice University hospital.

Finally, since 2012, we have been developing and experimenting connected care programs for the management of obese and / or cardiometabolic patients in the context of routine care and research (see below).

1) Cohorts and biobanks associated with obese patient management

In 2013, we organized follow-up of the cohort of obese patients benefiting from bariatric surgery. Our database, including preoperative and post-operative clinical and biological data at 6 months and 1 year, contains about 300 patients. In addition, since 2015, a collection of biological material (plasma and urine) is carried out for any patient benefiting from bariatric surgery. This biobank was set up thanks to the funding obtained in the framework of the EMERGENCE call for projects.

2) Publications resulting from this activity

1. Arapis K, Tammaro P, Parenti LR, et al. Long-Term Results After Laparoscopic Adjustable Gastric Banding for Morbid Obesity: 18-Year Follow-Up in a Single University Unit. *Obesity surgery* 2017; **27**(3): 630-40.
2. Belhatem N, Mohammedi K, Rouzet F, et al. Impact of morbid obesity on the kidney function of patients with type 2 diabetes. *Diabetes Res Clin Pract* 2015; **108**(1): 143-9.

3. Hansel B, Roussel R, Elbez Y, et al. Cardiovascular risk in relation to body mass index and use of evidence-based preventive medications in patients with or at risk of atherothrombosis. *European heart journal* 2015; **36**(40): 2716-28.
4. Mohammedi K, Compaore A, Potier L, et al. Outpatient measurement of arterial stiffness in patients with type 2 diabetes and obesity. *J Diabetes* 2017; **9**(3): 237-42.
5. Tammaro P, Hansel B, Police A, et al. Laparoscopic Adjustable Gastric Banding: Predictive Factors for Weight Loss and Band Removal After More than 10 Years' Follow-Up in a Single University Unit. *World J Surg* 2017; **41**(8): 2078-86.
6. Hansel N, Giral B, Gambotti L, et al. A fully automated web-based program improves lifestyle habits and HbA1c in patients with type 2 diabetes and abdominal obesity: Randomized trial of e-coaching nutritional support for obesity and diabetes (The ANODE Study). *J Med Int Res,* in press.

1) Research projects and funding obtained through this activity

- Three research projects are underway on the theme **Kidney and Obesity**
  1- **Nephrobaria** is an observational study launched thanks to the funding obtained in the framework of the **DHU call EMERGENCE.** Its purpose is to examine the evolution of renal function (measured) and fibrosis markers during a weight loss obtained with bariatric surgery.
  2- **BOKID** is a multicentric national clinical trial evaluating the impact of bariatric surgery on renal function, col-lead by Bichat and Nice University hospitals. Up to now, 15 of the 84 subjects required for the study were included in Bichat.
  3- Study of the **effectiveness of bariatric surgery** in patients with severe renal insufficiency. This observational study carried out on the basis of our database is the subject of a publication (manuscript in preparation):

- A clinical trial (ANODE) to evaluate the effect of a **connected health program in diabetic** patients with abdominal obesity was carried out thanks to funding from the Clinical Research Contract (DRCD).

- A clinical trial (TOOLBAR) is under preparation (conducted as part of a national PHRC). It aims to compare the impact of a **connected health program (OBECOACH) on weight** versus usual care.

Appendix 7: Genetics of connective tissue diseases – Pr Philippe Dieudé

1-Delivery of comprehensive health care dedicated to rheumatoid arthritis - associated interstitial lung disease

Outside the projects ongoing previously described in the last report 2012-mid 2014, during this last three years we have focused our activities on deciphering the genetic background of the rheumatoid arthritis – associated interstitial lung disease (RA-ILD), which is oneof the most severe complications of the rheumatism.

The routing of patients has been accordingly modified as follows:

- Identification of RA patients during medical consultations and hospitalized patients in the rheumatology department. Each new RA patients identified being assessed for functional pulmonary symptoms.
- In case of pulmonary functional symptoms and/or if the RA activity requires a biotherapy, both high-resolution computed tomography (HRCT) chest scan and Pulmonary Functional Tests are systematically performed and analyzed by a senior pulmonologist. All these procedures, including biobanking (serum and DNA) at the Centre de Ressources Biologiques of the Bichat hospital are performed within the day care unit of the Rheumatology department for both RAILDpositive and RA-ILDnegative patients.
- All the HRCT chest scan are systematically rewieved by a senior radiologist (Dr MP Debray, Radiology department, Bichat)
- To date more than 75 RA-ILDpositive patients and 100 RA-ILDnegative patients were included, all admitted at the Bichat hospital.
- For RA-ILDpositive patients the appropriate therapeutic strategy is systematically decided with the pulmonologists (Pr B Crestani, Dr R Borie) during a dedicated staff or during the hospitalization in the daily care unit of rheumatology.

All these procedures allow us to systematically detect RA-ILDpositive patients and to provide a better management through the close interaction between the rheumatology and pulmonology departments of the Bichat Hospital.

2- Samples and related biobanking

To date, through the TRANSLATE (DECIPHERING RHEUMATOID ARTHRITIS- ASSOCIATED INTERSTITIAL LUNG DISEASE PATHOGENESIS) project (PI Dieudé Ph). A large RA-ILD cohort has been constituted through a national collaborative project. The project includes baseline phenotypic and biologic biobanking, a total follow-up period of 3 years with a systematic annual evaluation of RAILDpositive patients. To date more than 240 RA RA-ILDpositive patients and 200 RA-ILDnegative patients have been included (DNA and serum), allowing us, taking advantage of 1245 healthy controls already available to provide evidence for a share genetic background between pulmonary fibrosis and RA-ILD.

A second phase of the project (TRANSLATE 2) will be started soon with the objective of including 500 RA-ILDpositive patients and 500 RA-ILDnegative patients, with a total follow-up periodof 5 years.

3- RelatedPublications

1- Juge PA, Gazal S, Constantin A, Mariette X, Combe B, Tebib J, Dougados M, Sibilia J, Le Loet X, **Dieude P**. Variants of genes implicated in type 1 interferon pathway and B-cell activation modulate the EULAR response to rituximab at week 24 in rheumatoid arthritis. RMD open. 2017;in press.

2- Juge PA, Borie R, Kannengiesser C, Gazal S, Revy P, Wemeau-Stervinou L, Debray MP, Ottaviani S, Marchand-Adam S, Nathan N, **Thabut G**, Richez C, Nunes H, Callebaut I, Justet A, Leulliot N, Bonnefond A, Salgado D, Richette P, Desvignes JP,

Lioté H, Froguel P, Allanore Y, Sand O, Dromer C, Flipo RM, Clément A, Béroud C, Sibilia J, Coustet B, Cottin V, Boissier MC, Wallaert B, Schaeverbeke T, Dastot le Moal F, Frazier A, Ménard C, Soubrier M, Saidenberg N, Valeyre D, Amselem S; FREX consortium, **Boileau C, Crestani B**, **Dieudé P**. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. Eur Respir J. 2017 May 11;49(5). pii: 1602314.

3- Terao C, Kawaguchi T, **Dieude P**, et al Transethnic meta-analysis identifies GSDMA and PRDM1 as susceptibility genes to systemic sclerosis. Ann Rheum Dis. 2017 Jun;76(6):1150-1158. doi: 10.1136/annrheumdis-2016-210645. Epub 2017 Mar 17.

4- Ruyssen-Witrand A, Degboé Y, Cantagrel A, Nigon D, Lukas C, Scaramuzzino S, Allanore Y, Vittecoq O, Schaeverbeke T, Morel J, Sibilia J, Cambon-Thomsen A, **Dieudé P,** Constantin A. Association between RANK, RANKL and OPG polymorphisms with ACPA and erosions in rheumatoid arthritis: results from a meta-analysis involving three French cohorts. RMD Open. 2016 Sep 8;2(2):e000226. doi: 10.1136/rmdopen-2015-000226. eCollection 2016.

5- Koumakis E, Bouaziz M, **Dieudé P**, et alA candidate gene study identifies a haplotype of CD2 as novel susceptibility factor for systemic sclerosis. Clin Exp Rheumatol. 2016 Sep-Oct;34 Suppl 100(5):43-48. Epub 2016 Jul 1.

6- Ruyssen-Witrand A, van Steenbergen HW, van Heemst J, Gourraud PA, Nigon D, Lukas C, Miceli-Richard C, Jamard B, Cambon-Thomsen A, Cantagrel A, Dieudé P, van der Helm-van Mil AH, Constantin A1. A new classification of HLA-DRB1 alleles based on acid-base properties of the amino acids located at positions 13, 70 and 71: impact on ACPA status or structural progression, and meta-analysis on 1235 patients with rheumatoid from two cohorts (ESPOIR and EAC cohort). RMD Open. 2015 Nov 19;1(1):e000099. doi: 10.1136/rmdopen-2015-000099. eCollection 2015.

7- Ochoa E, Martin JE, Assasi S, Beretta L, Carreira P, Guillén A, Simeón CP, Koumakis E, **Dieude P**, et al ; Spanish Scleroderma Group. Confirmation of CCR6 as a risk factor for anti-topoisomerase I antibodies in systemic sclerosis. Clin Exp Rheumatol. 2015 Jul-Aug;33(4 Suppl 91):S31-5. Epub 2015 Aug 27.

8- Miceli-Richard C1, Taylor KE, Nititham J, Seror R, Nocturne G, Boudaoud S, **Dieude P**, Constantin A, Devauchelle-Pensec V, Tobón GJ, Mariette X, Criswell LA. Genetic contribution of DKK-1 polymorphisms to RA structural severity and DKK-1 level of expression. Ann Rheum Dis. 2015 Jul;74(7):1480-1. doi: 10.1136/annrheumdis-2014-206530. Epub 2015 Mar 24.

9- Marangoni RG, Korman BD, Allanore Y, **Dieude P**, et al. A candidate gene study reveals association between a variant of the Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) gene and systemic sclerosis. Arthritis Res Ther. 2015 May 19;17:128. doi: 10.1186/s13075-015-0641-2.

10- Gazal S, **Sacre K**, Allanore Y, Teruel M, Goodall AH5; (The CARDIOGENICS consortium), Tohma S, Alfredsson L, Okada Y, Xie G, Constantin A, Balsa A, Kawasaki A, Nicaise P, Amos C, Rodriguez-Rodriguez L, Chiocchia G, **Boileau C,** Zhang J, Vittecoq O, Barnetche T, Gonzalez Gay MA, Furukawa H, Cantagrel A, Le Loët X, Sumida T, Hurtado-Nedelec M, Richez C, **Chollet-Martin S**, Schaeverbeke T, Combe B, Khoryati L, Coustet B, **El-Benna J**, Siminovitch K, Plenge R, Padyukov L, Martin J, Tsuchiya, **Dieudé P**. Identification of secreted phosphoprotein 1 gene as a new rheumatoid arthritis susceptibility gene. Ann Rheum Dis. 2015 Mar;74(3):e19. doi: 10.1136/annrheumdis-2013-204581. Epub 2014 Jan 21.

11- Arismendi M, Giraud M, Ruzehaji N, Dieudé P, et al. Identification of NF-κB and PLCL2 as new susceptibility genes and highlights on a potential role of IRF8 through interferon signature modulation in systemic sclerosis. Arthritis Res Ther. 2015 Mar 21;17:71. doi: 10.1186/s13075-015-0572-y.

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13- Ruyssen-Witrand A, Lukas C, Nigon D, Dawidowicz K, Morel J, Sibilia J, Jamard B, Cambon-Thomsen A, Cantagrel A, Dieudé P, Constantin A. Association of IL-2RA and IL-2RB genes with erosive status in early rheumatoid arthritis patients (ESPOIR and RMP cohorts). Joint Bone Spine. 2014 May;81(3):228-34. doi: 10.1016/j.jbspin.2013.10.002. Epub 2013 Nov 5.

14- Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, Yoshida S, Graham RR, Manoharan A, Ortmann W, Bhangale T, Denny JC, Carroll RJ, Eyler AE, Greenberg JD, Kremer JM, Pappas DA, Jiang L, Yin J, Ye L, Su DF, Yang J, Xie G, Keystone E, Westra HJ, Esko T, Metspalu A, Zhou X, Gupta N, Mirel D, Stahl EA, Diogo D, Cui J, Liao K, Guo MH, Myouzen K, Kawaguchi T, Coenen MJ, van Riel PL, van de Laar MA, Guchelaar HJ, Huizinga TW, Dieudé P,
RACI consortium; GARNET consortium. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature. 2014 Feb 20;506(7488):376-81. doi: 10.1038/nature12873. Epub 2013 Dec 25.

15- Okada Y1, Diogo D2, Greenberg JD3, Mouassess F4, Achkar WA4, Fulton RS5, Denny JC6, Gupta N7, Mirel D7, Gabriel S7, Li G8, Kremer JM9, Pappas DA10, Carroll RJ6, Eyler AE11, Trynka G2, Stahl EA12, Cui J8, Saxena R13, Coenen MJ14, Guchelaar HJ15, Huizinga TW16, **Dieudé P17**, et al. Integration of sequence data from a Consanguineous family with genetic data from an outbred population identifies PLB1 as a candidate rheumatoid arthritis risk gene. PLoS One. 2014 Feb 10;9(2):e87645. doi: 10.1371/journal.pone.0087645. eCollection 2014.

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4- Funding

TRANSLATE 1	PFIZER 40 000€ ROCHE 20 000€
TRANSLATE 2	BMS 300 000€ PFIZER 40 000€ Société Française de Rhumatologie 5000€

Appendix 8: FIRE Conference program

(dates and list of keynote speakers)

1st FIRE Conference-September 5th 2013

- *ARN non codants dans les maladies respiratoires*, Pascal Barbry (Institut de Pharmacologie Cellulaire et Moléculaire, Univ. Nice Sophia Antipolis),
- *Génétique et épigénétique des formes familiales des anévrysmes de l'aorte*, Catherine Boileau **(**UMR 1148, Université Paris Diderot-Bichat),
- *Peptidomique urinaire : un nouvel outil pour le pronostic des néphropathies obstructives,* Jean Loup Bascands (Institute of Metabolic and Cardiovascular Disease, Toulouse).

2nd FIRE Conference-September 4th 2014

- *Mécanismes de l'athérosclérose au cours de l'insuffisance rénale,* Ziad MASSY **(**Hôpital Ambroise Paré **-** INSERM U1088**-** Université Versailles Saint Quentin),
- *Inflammation et remodelage vasculaire pulmonaire,* Christophe GUIGNABERT (Unité Inserm 999 **-**Université Paris Sud- LabEx LERMIT**-** DHU TORINO)

-

3rd FIRE Conference-October 8th 2015

- *New pathways in idiopathic pulmonary fibrosis,* Andreas GÜNTHER (Giessen University, Allemagne)
- *Microfluidique en gouttes : un nouvel outil pour l'étude monocellule,* Pierre BRUHNS (Institut Pasteur)
- *Conséquences cardiovasculaires de l'hypoxie intermittente : de la souris au syndrome d'apnées du sommeil,* Diane GODIN-RIBUOT (INSERM U1042 Hypoxie : Physiopathologie Cardiovasculaire et Respiratoire **-** Faculté de Médecine de Grenoble)
- *Inhiber IRF5 : une nouvelle piste dans le traitement du syndrome métabolique ?* Nicolas VENTECLEF (Centre de Recherche des Cordeliers- Team Diabetes cellular and clinical pathogenesis)

-

4th FIRE Conference: Kick off RHU iVASC, October 4th 2016: special conference to launch the DHU Fire's RHU iVASC coordinated by Gabriel Steg, it gathered all the consortium members.

-

5th FIRE Conference-November 30th 2017

- *Le microbiote, les maladies métaboliques et leurs traitements,* Rémy BURCELIN (Institut des Maladies Métaboliques et Cardiovasculaires (I2MC), U1048 INSERM Toulouse)

Appendix 9: Selection of congress organized by DHU members

- Bruno Crestani. Seminar director and organizer of the « Lung Science Conferences » (European Respiratory Society) from 2013 to 2016.
- Gabriel Thabut. Organization of the « Séminaire d'épidémiologie respiratoire », every two years in Bichat (20122014-2016) (every two other years by Inserm U1168, Villejuif).
- Camille Taillé: Organization of the Journées d'échanges sur l'asthme sévère from 2012 (national meeting for young physicians involved in severe asthma care)
- Keren Borensztajn, Seminar co-director and co-organiser of the ERS Research Seminar "Proteases at the cutting edge: friends or foes in chronic lung diseases? », Amsterdam 2015
- Philippe Dieudé. Organization of scientific meetings Since 2012 : Journées des Actualités Rhumatologiques, Paris
- Bruno Crestani and Jean-Michel Sallenave - Member of the organizing committe of the 15th Lung Science Conference 'Mechanistic overlap between chronic lung injury and cancer, 23-26 Mars 2017, Estoril, Portugal
- Renato Monteiro: 1st Challenge in Inflammation: regulatory checkpoints and resolution meeting, in Florence (Italy), March 30-April 1st 2016 R Monteiro : « 14th international symposium on IgA nephropathy, Tours, September 15-17, 2016 ».
- Ulrich Blank and Marc Benhamou. Organizing committee 7th EMBRN International Mast cell and Basophil meeting, October 2015
- Ulrich Blank and Jenny Halgren, Organizers, Uppsala COST Action 1007 Training School, Uppsala, Sweden, February 2015
- Organization (Laurent Gouya G, Hervé Puy) and chair (Jean-Charles Deybach) of the Porphyrins and Porphyrias Congress 2017
- Loredana Saveanu participated to the organizing committee for: the First Symposium of the Center for Research on Inflammation "Endocytic pathways, autophagy and inflammatory diseases", Paris, Oct 2016 and the "3rd IRAP meeting" Paris, August 2017
- Jamel El-Benna-Organization of the du 8th oxydase club meeting, international, organized the 30-31 May 2013, FIAP, Paris.
- Organization of the 1st neutrophil club meeting «Neutrophils onstage and offstage», organized the 10th April 2015, FIAP, Paris.
- Organization of the "GREMI Meeting" on "Vascular Inflammation: Blood vessels under attack", the 13th November 2015 at Pasteur Institute, Paris.
- Organization of the "50th Scientific Meeting of the European Society for Clinical Investigation", and the joining "Phagocyte Workshop" 27-29 April 2016, Cochin Institute, Paris.
- Gabriel Steg Co-President of the annual congress TUC (Thrombose et Urgence Cardiologique)
- Pierre Amarenco is the president of the international Congress on Heart and Brain (biannual)
- Xavier Norel : Meeting organizator : 4th-7th European Workshop on Lipid Mediators, (3 days in 2012-Paris, 2014-Istanbul)
- Catherine Boileau and Guillaume Jondeau organized in Paris the 9th International Research Symposium on Marfan Syndrome and Related Diseases (Paris, 25-27 september 2014)

Appendix 10: Participation in Networks (non-comprehensive list)

- Gabriel Steg

Principal Investigator of the RHU iVASC (Innovations in Atherothrombosis Science) consortium, funded by PIA-2 and selected by ANR in 2016.
Founder (with T.Simon and N.Danchin) and chair of the French Alliance for Cardiovascular Trials (FACT) Academic Research Network, affiliated with F-CRIN.
Member of the ATLAS (Antithrombotic Trials Leadership and Steering Group), an academic research network of experts in thrombosis

- Michel Aubier is a member of the National Academy of Medicine since 2015
- Marina Pretolani is member of the National Academy of Pharmacy since 2016
- Renato Monteiro president of Steering Comittee of International IgA Nephropathy Network
- G Deschênes, president de la Société de Néphrologie Pédiatrique, 2011-2014.
- Georges Deschênes, Chair leader of idiopathic nephrotic syndrome working group at the European Society for Pediatric Nephrology, January 2012 – January 2016.
- François Vrtovsnik F. CA de la Société Francophone de Néphrologie, Dialyse et Transplantation.
- François Vrtovsnik F. CA de la Société Francophone de Dialyse.
- Laurent Gouya (U1149) Direction Centre National de Référence Maladies Rares Porphyries
- Hervé Puy (U1149) Président du collège National des professeurs d'université– praticiens hospitaliers de Biochimie et biologie moléculaire des UFRs de Médecine (CNBBMM) : HP (2015-2019)
- Pierre Guermonprez (U1149) is part of the Medical Research Club, a London-based society founded in 1891
- Jean-Charles Deybach is the coordinator of the European Porphyria Network (Epnet)
- Fabien Hyafil. Member of the Board of the European Society of Molecular Imaging.
- Marie-Christine Bouton: Elected Member of the SAB for the French Society of Hemostasis & Thrombosis (GFHT) 2013-2020
- Nadine Ajzenberg: Elected Member of the SAB for the French Society of Hematology (SFH) 2017-2020
- Mikael Mazhigi: Member of the Scientific board of "Société Francaise Neurovasculaire" (2012->); Member of the scientific board of "Fondation AVC" (2016->); Nucleus member of Stroke Council for the European Society of Cardiology (2016->);
- Martine Jandrot-Perrus: Vice-president of the " Groupe Français de l'Hémostase et la Thrombose "(GFHT) 2006-2012; Member (expert in Haemostasis) of the scientific desk of the "Institut Thématique Multi Organisme" (ITMO) Immunology, Haematology, Pneumology (2008-2014); Member of the Scientific Cardiovascular Committee of the Fondation de France (2015->); Member of the Scientific Council of the Fondation de Recherche sur les Accidents Vasculaires Cérébraux, FRM (2015->); Member of the Scientific Council of Force Hémato (2016->).

UMR1152 belongs to the "RESPIRE" (Marie Curie Post-doctoral Research Fellowships of the European Respiratory Society). RESPIRE is an international and inter-disciplinary program providing post-doctoral research fellowships to early stage scientists with the potential to become the leaders of tomorrow in the respiratory field. UMR1152 has already obtained 2 fellowships since 2013;

Appendix 11: Thesis defences

Name	First Name	Doctoral School	Thesis director	Date	DHU Team
AL SALIH	Ghada		JB Michel	2013	U1148 Team 2
ATLAN	Michael	P7	D Letourneur	2015	U1148 Team 3
AUBART	Melodie	P7	C Boileau	2016	U1148 Team 2
AUFAURE	Romain	ESCOM	E Guénin/Y. Lalatonne	2016	U1148 Team 3
BEN AZZOUNA	Rana	P13	D Le Guludec	2016	U1148 Team 4
BENYAHIA	Chabba	P13	D Longrois	2015	U1148 Team 5
BONNARD	Thomas	P13	C Levisage	2014	U1148 Team 3
BOUKAIS	Kamel	P7	JB Michel/MC Bouton	2016	U1148 Team 2
CIFUENTES CEPEDA	DianaRocio	P11	N Kubis	2016	U1148 Team 6
CLEMENT	Marc	EPHE	G Caligiuri	2014	U1148 Team 1
DELATTRE	Cecilia	arts et metier	A Pelle	2015	U1148 Team 3
DESILLES	Jean-Philippe	P7	M Mazighi	2017	U1148 Team 6
DIALLO	Devy		O Meilhac	2015	U1148 Team 5
DUCROC	Grégory	P7	PG Steg	2015	U1148 Team 5
FRANCOIS	Deborah	P7	MC Bouton	2014	U1148 Team 6
GHEBOULI	Radouane	P5	JB Michel	2016	U1148 Team 2
GOMEZ	Ingrid	P13	X Norel	2013	U1148 Team 5
GROS	Angele	P6	M Jandrot Perrus/B Ho Tin Noe	2017	U1148 Team 6
GUEDJ	Kevin	P7	A Nicoletti	2014	U1148 Team 1
HADDAD	Soumaya		l Mora	2015	U1148 Team 3
HILAL	Rose	P5	N Kubis	2015	U1148 Team 6
HOANG QUOC	Thang	P7	JB Michel	2016	U1148 Team 2
INO	Julia	P13	D Letourneur	2012	U1148 Team 3
JIANG	Peng	chine	M Jandrot Perrus	2014	U1148 Team 6
KESSLER	Ketty	P7	JB Michel	2014	U1148 Team 2
LAMRANI	Lamia	P7	M Jandrot Perrus	2014	U1148 Team 6
LI	Bo	chine	C Chauvierre	2017	U1148 Team 3
MAILLARD	Loic	P13	A Sutton	2015	U1148 Team 3
MARINVAL	Nicolas	P13	N Charnaux	2016	U1148 Team 3
MICHELE	Eleonore	Ingenieur galilee	D Letourneur	2016	U1148 Team 3
OZEN	Gulsev	universite Istanbul	G Topal	2016	U1148 Team 5
POITTEVIN	Marine	P5	N Kubis	2013	U1148 Team 6
POPOVIC	Batric	Université	F Zannad/ V	2016	U1148 Team 5

		Nancy	Regnault		
RANGE	Helene		O Meilhac/P Bouchard	2016	U1148 Team 2
RIMA	Belibel	P12	C Barbaud	2015	U1148 Team 3
ROUCHAUD	Aymeric		L Spelle	2017	U1148 Team 1
SABOURAL	Pierre		C Chauvierre	2015	U1148 Team 3
SELBONNE	Sonia	P7	M Jandrot Perrus	2014	U1148 Team 6
TRAN DINH	Alexy	P7	O Meilhac	2015	U1148 Team 1
VO	Sophie	P13	N Charnaux	2015	U1148 Team 3
LEONE	Nathalie	Paris XI	M. Zureik	2014	U1152 Team 1
ARUMUGAM	Garthiga	Paris Diderot	M.Pretolani/ S. Letuvé	2014	U1152 team2
FARROKI MOSHAI	Elika	Paris Est	B. Crestani/ A. Mailleux	2013	U1152 Team 3
BRAYER	Stéphanie	Paris Est	B. Crestani/ A. Mailleux	2013	U1152 Team 3
GARNIER	Marc	Paris Diderot	C. Quesnel/ M. Dehoux	2016	U1152 Team 3
MENOU	Awen	Paris Diderot	B. Crestani	2017	U1152 Team 3
BORIE	Raphael	Paris Diderot	B. Crestani	2017	U1152 Team 3
BASTAERT	Fabien	Paris Diderot	JM Sallenave	2016	U1152 Team 4
DIEU	Alexandra	Paris Diderot	I. Garcia-Verugo	2016	U1152 Team 4
Azibani	Feriel	U Paris 6	C Delcayre, JL Samuel	2012	U942 Team1
Fazal	Loubina	U Paris 7	C Delcayre	2013	U942 Team1
Seronde	Marie-France	U Dijon	A Mebazaa	2013	U942 Team1
Laribi	Saïd	U Paris 7	A Mebazaa	2014	U942 Team1
Rebillat	Anne Sophie	U Paris 6	J Hugon	2014	U942 Team 2
Gourmaud	Sarah	U Paris 7	J Hugon	2014	U942 Team 2
Taga	Mariko	U Paris 7	J Hugon	2015	U942 Team 2
Dillinger	Jean Guillaume	U Paris 7	P Henry	2015	U942 Team1
Sideris	Giorgios	U Paris 7	P Henry	2016	U942 Team1
Ragot	Hélène	U Paris 6	JL Samuel	2016	U942 Team1
Blet	Alice	U Paris 7	A Mebazaa	2016	U942 Team1
Vergaro	Giuseppe	U Paris 7 / Pisa Univ.	A Cohen Solal, M Emdin	2017	U942 Team1
Caillard	Anais	U Paris 7	A Mebazaa	2017	U942 Team1
CHEDID	Pia	Université Denis-Diderot P7	MARIE Jean-Claude	2012	U1149 Team EL BENNA
MAKNI-MAALEJ	Karama	Université Paris11	EL BENNA Jamel	2012	U1149 Team EL BENNA

ABDESSAMED	Mahmoud	Université Paris11	CHASTRE Eric	2012	U1149 Team EL BENNA
MOUZAOUI	Souad	Université d'Alger	DANG Pham My-Chan	2014	U1149 Team EL BENNA
BELAMBRI	Amel-Sahra	Université de Sétif	EL BENNA Jamel	2014	U1149 Team EL BENNA
ELATRECH	Imen	Université Denis-Diderot P7	MARIE Jean-Claude	2014	U1149 Team EL BENNA
ROLAS	Loic	Université Denis-Diderot P7	PERIANIN Axel	2015	U1149 Team EL BENNA
BOUDIAF	Kaouthar	Université de Sétif	DANG Pham My-Chan	2017	U1149 Team EL BENNA
BOUSSIF	Abdelali	Université de Sétif	PERIANIN Axel	2017	U1149 Team EL BENNA
BOUKEMARA	Hanane	Université de Guelma	MARIE Jean-Claude	2017	U1149 Team EL BENNA
ABDELSSAMAD	Mahmoud	Paris 7 - Denis Diderot	CHASTRE	2012	U1149 Team EL BENNA
BELDI-FERCHIOU	Asma		CAILLAT	2014	U1149 Team CAILLAT ZUCMAN
BELAMBRI	Sahra	Paris 7 - Denis Diderot	EL BENNA	2014	U1149 Team EL BENNA
BOUSSIF	Abdelali	Université d'Alger	PERIANIN	2017	U1149 Team EL BENNA
BOUKEMARA	Hanane	Université d'Alger	MARIE	2017	U1149 Team EL BENNA
BOUDIAF	Kaouthar	Université d'Alger	DANG	2017	U1149 Team EL BENNA
CHEDID	Pia	Paris 7 - Denis Diderot	MARIE	2012	U1149 Team EL BENNA
ELATRECH	Imen	Paris 7 - Denis Diderot	MARIE	2014	U1149 Team EL BENNA
PAPISTA	Christina	Paris 7 - Denis Diderot	MONTEIRO	2015	U1149 Team MONTEIRO
HEMING	Nicholas	Paris 7 - Denis Diderot	MONTEIRO	2015	U1149 Team MONTEIRO
HOUAMEL	Dounia	Paris 7 - Denis Diderot	KARIM	2014	U149 Team GOUYA / PUY
KASSAS	Asma	Paris 7 - Denis Diderot	BENHAMOU	2015	U1149 Team EL BENNA
LECHNER	Sébastian	Paris 7 - Denis Diderot	MONTEIRO	2016	U1149 Team MONTEIRO
LEFEBVRE	Thibaud	Paris 5 - René Descartes	PUY	2016	U149 Team GOUYA / PUY
MADJENE	Lydia Celia	Paris 7 - Denis Diderot	BLANK	2013	U1149 Team EL BENNA
MAKNI-MAALEJ	Karama	Paris-Sud 11	EL BENNA	2012	U1149 Team EL

					BENNA
MIRMIRAN	Arienne	Paris 7 - Denis Diderot	GOUYA	2017	U149 Team GOUYA / PUY
PELLEFIGUES	Christophe	Paris 7 - Denis Diderot	CHARLES	2015	U149 Team BLANK / LAUNAY
PONS	Maguelonne	Paris 7 - Denis Diderot	BLANK	2016	U149 Team BLANK / LAUNAY
MOULOUEL	Boualem	Paris 7 - Denis Diderot		2014	U149 Team GOUYA / PUY
RIO	Sarah	Paris 5 - René Descartes	DA COSTA	2016	U149 Team GOUYA / PUY
ROLAS	Loïc	Paris-Sud 11	PERIANIN	2016	U1149 Team EL BENNA
CHEMOUNY	Jonathan	Paris 7 - Denis Diderot	MONTEIRO	2016	U1149 Team MONTEIRO
ROSSATO	Elisabetta	Paris 7 - Denis Diderot	MONTEIRO	2014	U1149 Team MONTEIRO

Appendix 12: State of finance June 2017

Note: The last awardees of the Emergence Call received their grant in March 2017 and have until December 2017 to spend it for their project.

Ventilation des crédits

ANNEE	DOTATION	DEPENSES	SOLDE	
2012	0,00 €	0,00	0,00	
2013	50 693,73 €	50 693,73	0,00	
2014	83 979,20 €	83 979,20	0,00	
2015	121 705,29 €	81 376,14	40 329,14	Solde non reporté
2016	121 705,29 €	103 014,88	18 690,40	Financement contrat Delphine AZAMA
2017	121 705,29 €	15 130,27	106 575,01	
	499 788,79 €	334 194,23 €	165 594,56 €	

DATE_COMMANDE	FOURNISSEUR	CODE_IMPUTATION	EXERCICE	N_FACTURE_FOURNISSEUR	ENGAGEMENT	DEGAGEMENT	LIQUIDATION	DEPENSE Prévisionnel	DEPENSE REELLE
26/06/2013	@VIREMENT@	65	2013	FIRE0001/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**13 431,87**
26/06/2013	@VIREMENT@	65	2013	FIRE0002/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**15 261,23**
26/06/2013	@VIREMENT@	65	2013	FIRE0003/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 817,30**
26/06/2013	@VIREMENT@	65	2013	FIRE0004/FINANCEMENT BOURSE	10 000,00	10 000,00	10 000,00	**10 000,00**	**10 396,43**
26/06/2013	@VIREMENT@	65	2013	FIRE0005/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 532,00**
26/06/2013	@VIREMENT@	65	2013	FIRE0006/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 510,23**
01/09/2013	BICHAT-CLAUDE BERNARD (CHARG MISS	641	2013	DE GELIS A. SEP-DEC	11 267,70	11 267,70	11 267,70	**11 267,70**	**11 267,70**
01/09/2013	#VIREMENT#	641387	2013	MUTU-APE/DE GELIS A. SEP-DEC	375,53	375,53	375,53	**375,53**	**375,53**
25/01/2014	BICHAT-CLAUDE BERNARD (CHARG MISS	641	2014	DE GELIS A. JAN-AVR	11 124,39	11 124,39	11 124,39	**11 124,39**	**11 124,39**
25/01/2014	#VIREMENT#	641387	2014	MUTU-APE/DE GELIS A. JAN-AVR	370,75	370,75	370,75	**370,75**	**370,75**
25/07/2014	#VIREMENT#	641387	2014	MUTU-APE/AZAMA D.	462,39	462,39	462,39	**462,39**	**462,39**
25/07/2014	BICHAT-CLAUDE BERNARD (CHARG MISS	641	2014	AZAMA D. JUL-DEC	13 873,95	13 873,95	13 873,95	**13 873,95**	**13 873,95**
16/09/2014	@VIREMENT@	65	2014	FIRE0010/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 941,37**
16/09/2014	@VIREMENT@	65	2014	FIRE0011/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 272,79**
16/09/2014	@VIREMENT@	65	2014	FIRE0007/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 549,94**
16/09/2014	@VIREMENT@	65	2014	FIRE0008/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**5 401,72**
16/09/2014	@VIREMENT@	65	2014	FIRE0009/FINANCEMENT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 988,22**
01/01/2015	BICHAT-CLAUDE BERNARD (CHARG MISS	641	2015	AZAMA D. JAN-DEC	28 258,62	28 258,62	28 258,62	**28 258,62**	**28 258,62**

01/01/2015	#VIREMENT#	641387	2015	MUTU-APE/AZAMA D.	941,80	941,80	941,80	**941,80**	**941,80**
01/01/2016	BICHAT-CLAUDE BERNARD (CHARG MISS	641	2016	AZAMA D. JAN-DEC	28 424,85	28 424,85	28 424,85	**28 424,85**	**28 424,85**
01/01/2016	#VIREMENT#	641387	2016	MUTU-APE/AZAMA D.	947,34	947,34	947,34	**947,34**	**947,34**
02/01/2015	@VIREMENT@	65	2014	FIRE0002/RALLONGE BUDGETAIRE	340,00	340,00	340,00	**340,00**	**340,00**
18/06/2015	@VIREMENT@	65	2015	FIRE0012/VRT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**5 676,03**
18/06/2015	@VIREMENT@	65	2015	FIRE0013/VRT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 143,76**
18/06/2015	@VIREMENT@	65	2015	FIRE0014/VRT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**0,00**
18/06/2015	@VIREMENT@	65	2015	FIRE0015/VRT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**0,00**
18/06/2015	@VIREMENT@	65	2015	FIRE0016/VRT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**14 289,85**
18/06/2015	@VIREMENT@	65	2016	FIRE0017/VRT BOURSE	11 000,00	11 000,00	11 000,00	**11 000,00**	**0,00**
18/06/2015	@VIREMENT@	65	2016	FIRE0018/VRT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**0,00**
18/06/2015	@VIREMENT@	65	2016	FIRE0019/VRT BOURSE	10 000,00	10 000,00	10 000,00	**10 000,00**	**0,00**
18/06/2015	@VIREMENT@	65	2016	FIRE0020/VRT BOURSE	15 000,00	15 000,00	15 000,00	**15 000,00**	**0,00**
01/01/2017	BICHAT-CLAUDE BERNARD (CHARG MISS	641	2017	AZAMA D. JAN-JUN	15 780,14	10 520,09	9 551,88	**14 811,93**	**14 811,93**
01/01/2017	#VIREMENT#	641387	2017	MUTU-APE/AZAMA D.	318,34	318,34	318,34	**318,34**	**318,34**
								0,00	
				TOTAL :	**398 485,81**	**393 225,76**	**392 257,55**	**397 517,60**	**292 730,34**

UA ETABLISSEMENT 000 (UA 1)

DATE_COMMAND	FOURNISSEUR	DE_IMPUTAT	EXERCICE	FACTURE_FOURNISSE	ENGAGEMENT	DEGAGEMENT	LIQUIDATION	DEPENSE
28/10/2013	NEIGE ET SOLEIL VOYAG	62561	2013	4502390690_10	14,21	14,21	14,21	**14,21**
28/10/2013	NEIGE ET SOLEIL VOYAG	62511	2013	4502390690_20	450,25	450,25	450,25	**450,25**
16/12/2013	EBIOSCIENCE	6066	2013	4502568761_10	540,80	201,58	201,58	**540,80**
16/12/2013	EBIOSCIENCE	6066	2013	4502568761_20	540,80	540,80	540,80	**540,80**
16/12/2013	EBIOSCIENCE	6066	2013	4502568761_30	442,22	442,22	442,22	**442,22**
31/12/2013	PARTEC	6066	2013	4502568762_10	146,85	146,85	146,85	**146,85**
31/12/2013	PARTEC	6066	2013	4502568762_20	45,71	45,71	45,71	**45,71**
29/07/2015	IMS HEALTH	62888	2015	4503901687_10	17 582,00	17 582,00	17 582,00	**17 582,00**
24/09/2015	LOTUS VOYAGES	62561	2015	4504006895_10	523,00	523,00	523,00	**523,00**
24/09/2015	LOTUS VOYAGES	62562	2015	4504006895_20	12,50	12,50	12,50	**12,50**
24/09/2015	LOTUS VOYAGES	62561	2015	4504006895_30	223,65	223,65	223,65	**223,65**
24/09/2015	LOTUS VOYAGES	62561	2015	4504006895_40	5,90	5,90	5,90	**5,90**
21/06/2016	INSERM TRANSFERT	65887	2016	4504411667_10	21 276,00	21 276,00	21 276,00	**21 276,00**
								0,00
								0,00
				TOTAL :	**41 803,89**	**41 464,67**	**41 464,67**	**41 803,89**

Appendix 13: Autoévaluation Octobre 2014

Le rapport d'auto-évaluation et ses annexes sont disponibles sur le site web du DHU : www.dhuFIRE.org

Le DHU FIRE a été créé en Juin 2012, au terme du premier appel à projet DHU. Il est centré sur le diagnostic, le traitement, la prévention et l'identification des mécanismes physiopathologiques de maladies chroniques particulièrement fréquentes que sont les maladies cardiovasculaires, neuro-vasculaires, rénales et respiratoires,

Les maladies chroniques sont les principales causes de décès dans les pays développés, et leur prévalence est en croissance rapide dans le monde entier. La transition épidémiologique annoncée au début des années 1970 (Omran, 1971) décrivant un changement radical dans la répartition des décès a eu lieu (Hunter NEJM 2013). Dans les 15 prochaines années, les maladies cardiaques ischémiques, cérébrovasculaires, et pulmonaires chroniques (principalement BPCO) seront respectivement la première, la deuxième et la quatrième cause de décès dans le monde (Mathers, Plos Med 2006).

Dans le même temps, le diabète sera la septième, la cardiopathie hypertensive la onzième et les maladies chroniques rénales, la treizième. Au total, les maladies cardiovasculaires, neuro-vasculaires, rénales et respiratoires, que nous appellerons « les maladies chroniques », représentent une menace majeure pour le système de santé mondial. (European observatory on health systems and policy, 2009, "Health in the European union").

Malgré leur diversité, ces maladies ont des facteurs de risque communs, et partagent d'importants processus physiopathologiques, que sont la fibrose, l'inflammation et le remodelage chronique qui modifient progressivement la structure des organes natifs ou greffés, et entravent leur fonctionnement, conduisant à des insuffisances aiguës, chroniques et finalement au décès. La fibrose, l'inflammation et le remodelage sont les cibles majeures des nouvelles stratégies thérapeutiques préventives et curatives dans ces maladies.

Le DHU FIRE rassemble les cliniciens et le personnel de quatre hôpitaux universitaires (Bichat, Saint Louis, Robert Debré et Lariboisière), des scientifiques et des épidémiologistes de 5 unités de recherche, toutes situées dans le périmètre de l'Université Paris Diderot, et soutenues par les hôpitaux, l'Université et l'Inserm. Cette structure originale permet de surmonter la division fréquente entre les sous-spécialités médicales, les hôpitaux et les domaines de recherche, en s'appuyant sur des processus physiopathologiques communs à diverses maladies pour travailler de façon pluridisciplinaire et en optimisant les moyens.

Depuis sa création, le DHU s'est lui-même « remodelé » :

- les unités de recherche fondatrices ont été évaluées par l'AERES et recréées au 1er Janvier 2014 par l'université Paris Diderot, le CNRS et l'Inserm, pour certaines sous d'autres numéros et de nouvelles dénominations mais en conservant leurs thématiques de recherche :
    - **CRI** : Centre de Recherche sur l'Inflammation, (UMR 1149), notamment les équipes dont l'activité porte sur la physiopathologie des maladies inflammatoires, en particulier rénales, situé sur le site Bichat
    - **LVTS** : Laboratoire de Recherche Vasculaire Translationnelle (UMR 1148), qui réunit les forces de recherche en cardiovasculaire et neurovasculaire, situé sur le site Bichat, et qui s'appuie, pour la recherche clinique multicentrique, sur le réseau de recherche clinique académique FACT (French Alliance for cardiovascular Clinical Trials), créé en 2012 avec le soutien du CENGEPS et labellisé par F-CRIN en 2013.

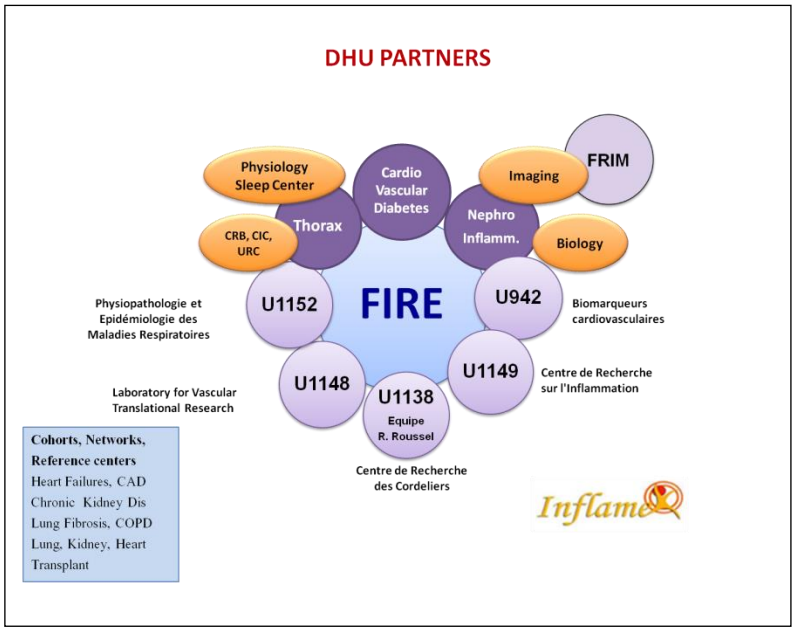
- **PHERE** : Physiopathologie et épidémiologie des maladies respiratoires (UMR 1152), qui coordonne la recherche dans ce domaine, situé sur le site Bichat
- **BIOCANVAS** : Biomarqueurs cardiovasculaires (UMR 942), dont la dénomination n'a pas changé, situé sur le site Lariboisière.

- Le DHU a intégré deux nouvelles structures de recherche labellisées :
  - **FRIM**, Fédération de Recherche en Imagerie multimodalités, labellisée par l'Université Paris Diderot, qui a pris la suite de l'IFR 02 pour la gestion des plateformes d'imagerie sur le site Bichat
  - **Complications vasculaires et rénales liées au diabète et à la nutrition** (équipe Ronan Roussel, UMR 1138). Cette équipe est située dans le Centre des Cordeliers. Elle est dirigée par Ronan Roussel qui exerce son activité clinique dans l'hôpital Bichat et coordonne le work package 2 du DHU FIRE.

Le DHU bénéficie du dynamisme supplémentaire insufflé par le **LabEx INFLAMEX**, coordonné par Renato Monteiro, qui est également un des coordonnateurs scientifiques du DHU FIRE.

Nos points forts:

1) Le cœur du DHU est situé dans un vaste site académique: l'Hôpital Bichat, rassemblant dans un seul et même site les ressources nécessaires pour renforcer une recherche translationnelle, efficace et concurrentielle. L'ensemble du DHU est sur un campus universitaire: l'Université Paris Diderot, réunissant les groupes cliniques, universitaires et de recherche à proximité.
2) Une collaboration étroite entre les groupes clinique et recherche,
3) La nature trans-disciplinaire du DHU aide les groupes cliniques et de recherche à aborder de nouvelles questions
4) L'expertise clinique internationalement reconnue des sites cliniques participants, dont plusieurs sont des leaders internationaux dans leur domaine
5) L'existence de grandes cohortes cliniques et des biobanques associées
6) L'expertise en recherche translationnelle des groupes participants.



Pour cette évaluation à mi-parcours du DHU FIRE, nous avons souhaité mettre en exergue l'activité des work packages, qui constituent le cœur du projet du DHU, et certaines activités de soins qui reflètent la valeur ajoutée du DHU par leur caractère transversal. De ce fait, les informations contenues dans ce rapport d'autoévaluation sont non exhaustives.

I- LE SOIN

L'activité de soin au sein du DHU est très importante, les maladies traitées étant fréquentes. Afin de présenter la valeur ajoutée liée au DHU, nous avons identifié 9 activités de soins (et de recherche), transversales, initiées ou développées dans le cadre du DHU, en complément des activités décrites dans les work packages.

- **Interaction Cardiologie-Neurologie** (détaillée dans le WP4)
- **Interaction rein cœur**

L'insuffisance cardiaque réfractaire est associée à un pronostic particulièrement péjoratif à court terme. Les équipes de cardiologie et de néphrologie du DHU FIRE ont développé un axe spécifique de soin ayant pour objectif l'accès des patients à un traitement par épuration extrarénale, dialyse péritonéale et hémodialyse. Les résultats préliminaires montrent déjà une réduction des durées d'hospitalisation et une réduction de la mortalité. (Annexe 1)

- **HTA Résistante**

Une des activités novatrices développées grâce à la dynamique du DHU a été la création d'une structure pluridisciplinaire de prise en charge des hypertensions artérielles sévères ou résistantes, intégrant soins et recherche (elle est détaillée en annexe). Cette activité, sur son versant recherche, a fait l'objet d'un soutien du DHU dans le cadre du programme « Émergence ». (Annexe 2)

- **Cœur Vaisseau diabète**

Le diabète compliqué est la pathologie unificatrice par excellence de l'activité de soin du DHU. Le service de diabétologie de Bichat est intégré au pôle hospitalier Coeur Vaisseaux et a poursuivi son intégration dans le contexte du DHU. Le service de diabétologie de Lariboisière a également organisé son soin ambulatoire dans le cadre du DHU, avec l'ouverture du CUDC (Centre Universitaire du Diabète et de ses Complications) en 2014, à l'occasion de son déménagement depuis Saint_Louis. Les protocoles communs, trans-hospitaliers, et les projets de recherche en thérapeutique des complications du diabète sont présentés dans le WP2.

- **Endocardite**

Sur cette thématique, pluridisciplinaire par excellence, la dynamique du DHU a contribué à la mise en place d'une organisation des soins et de projets de recherche transversaux qui sont détaillés dans l'annexe jointe. (Annexe 3)

- **Obésité**

L'activité de nutrition du DHU (au sein du service de Diabétologie-Endocrinologie-Nutrition, hôpital Bichat) est labellisée Centre Intégré Nord Francilien de l'Obésité par l'Agence Régionale de Santé d'Île de France. Elle se développe autour de 3 axes : prise en charge médicale de l'obésité, incluant une activité physique adaptée ; prise en charge chirurgicale (filière de chirurgie bariatrique), en particulier des patients fragiles avec pathologies pneumologiques, cardiologiques médicales et chirurgicales, et avec insuffisance rénale ; développement d'outils innovants d'intervention et de suivi (télémédecine, suivi par internet). (Annexe 4)

- **Sarcoïdose cardiaque**

Le DHU FIRE a identifié la sarcoïdose cardiaque comme étant un problème spécifique de prise en charge des patients, qui pourrait bénéficier de l'expertise clinique et paraclinique des partenaires du DHU. Nous avons mis en place 1) un protocole commun d'évaluation, 2) une réunion multidisciplinaire dédiée à cette pathologie (réunions mensuelles depuis Juin 2014). Un travail rétrospectif sur plus de 50 patients explorés a été réalisé (Phalla OU, Radiologie) et sert de base à un second travail prospectif.

- **Maladies systémiques**

La prise en charge des patients atteints de maladies systémiques est une des spécificités des équipes du DHU FIRE. Un réseau de soins spécifiques a été mis en place avec des interactions transdisciplinaires jamais observées jusqu'alors. L'ensemble est matérialisé sur le site Bichat par l'avènement prochain d'un hôpital de jour multidisciplinaire dédié à cette filière de soin, et par la mise en place d'une RCP « maladies systémiques » mensuelle. (Annexe 5)

- **Génétique des maladies systémiques**

En lien avec le projet de prise en charge coordonnée des maladies systémiques, les équipes du DHU ont développé un projet de recherche génétique concernant les maladies systémiques dysimmunitaires, en exploitant les cohortes de patients locales, en développant des cohortes

nationales, en lien avec les projets internationaux sur ce thème. Cette recherche transversale bénéficie de l'excellence de l'interaction interdisciplinaire développée au sein du DHU. (Annexe 6)

- **Transplantation cardiaque et transplantation pulmonaire**

Le DHU FIRE participe à la Fédération de Transplantation des hôpitaux universitaires de l'UFR de Médecine Paris Diderot. Dans ce cadre, les partenaires du DHU développent 1) une prise en charge commune des greffés du cœur et du poumon (respectivement n=30 et n=22 pour l'année 2014, au 1er septembre 2014) avec la création d'un hôpital de jour commun, et 2) des séminaires communs d'enseignement avec la première journée scientifique de la Fédération de Transplantation prévue le 15 Janvier 2015.

II- LA RECHERCHE

1- Les résultats aux appels à projets

Le DHU présente dans l'autoévaluation 84 projets financés. Quatre projets en cours d'évaluation figurent dans la liste. Ils ne représentent qu'une minime fraction des projets actuellement soumis aux différents appels à projets 2014 (Horizon 2020, ANR). Sur les 84 projets actifs, 19 sont internationaux, 43 nationaux et 22 sont locaux. (Annexe 7).

2- Les publications du DHU

a- Les publications du DHU à partir d'une base de données validée par le coordinateur du DHU Cf : DHU SIGAPS

Nombre de publications par catégorie et par position

Position	A	B	C	D	E	NC	Total
1	119	88	66	29	46	30	**378**
2	43	37	30	15	25	12	**162**
3	34	45	26	11	21	7	**144**
IL	90	23	11	6	6	1	**137**
k	220	152	85	42	21	13	**533**
ADA	23	28	25	11	11	5	**103**
DA	60	76	50	39	29	25	**279**
Total	**589**	**449**	**293**	**153**	**159**	**93**	**1736**

DA = Dernier Auteur, ADA = Avant Dernier Auteur, IL = Liste Investigateur

Nombre de publications par année et par catégorie

Année	A	B	C	D	E	NC	Total
2012	192	143	97	48	64	25	**569**
2013	207	156	92	51	45	37	**588**
2014	190	150	104	54	50	31	**579**
Total	**589**	**449**	**293**	**153**	**159**	**93**	**1736**

b- Une analyse qualitative effectuée par le coordinateur

Les partenaires du DHU continuent à publier dans les meilleures revues des spécialités ainsi que dans les meilleures revues généralistes (New Engl J Med, n=30 ; Lancet, n=12 ; Nature, n=2 ; Nat Med, n=2 ; Nat Genet, n=14 ; J Clin Invest, n=5) sur le thème central du DHU FIRE. On peut noter le caractère exceptionnel de l'activité de publication dans le domaine cardiovasculaire, Gabriel Steg et

Alec Vahanian, deux des membres du DHU, faisant partie des scientifiques ayant la plus importante production scientifique dans le monde. (http://highlycited.com)

3- Les conférences invitées dans les congrès nationaux et internationaux

Plus de 88 conférences nationales: Aix-en-Provence (1), Asnières (1), Biarritz (2), Bobigny (1), Bordeaux (6), Chamonix (1), La Ciotat (1), Lille (8), Lyon (6), Maffliers (1), Marseille (11), Nice (1), Paris (47), Toulouse (1). (Annexe 8)

Plus de 156 conférences internationales invitées:
Allemagne (22), Argentine (2), Bahamas (1), Belgique (5), Brésil (1), Canada (1),Chine (3), Espagne (8), Etats-Unis (20), France (25), Grande Bretagne (9), Grèce (3), Hongrie (1), Irlande (1), Israël (2), Italie (13), Japon (4), Liban (2), Luxembourg (1), Maroc (2), Pays Bas (9), Pologne (2), Portugal (1), République Tchèque (1), Sénégal (2), Serbie (1), Slovénie (1), Suède (1),Suisse (3), Thaïlande (2), Tunisie (3), Turquie (4). (Annexe 9)

4- Les indicateurs de valorisations

- Partenariat avec des entreprises ou des Institutions

Les équipes du DHU ont formé 31 partenariats depuis sa création. (Annexe 10)

- Brevets ou Licences

10 brevets déposés. (Annexe 11)

- Création de Start up

2 créations de start up en 2013 : Acticor Biotech et IMMATIS (Annexe 12)

III- LA FORMATION

1- Les étudiants du DHU

Le DHU a accueilli 134 étudiants dans ses structures de recherche, provenant de différents pays et continents : Algérie (8), Australie (1), Brésil (1), Cameroun (1), Chine (2), Colombie (1), Emirats Arabes (2), Espagne (2), Finlande (1), France (95), Grèce (2), Italie (2), Liban (2), Mexique (1), Portugal (1), RDC (1), Sénégal (1), Syrie (1), Tunisie (3), Turquie (2), Vietnam (1) Etats-Unis (1)(l'information est manquante dans 2 cas). (Annexe 13)

2- La responsabilité de la formation à/par la recherche et la responsabilité/ participation à un ou plusieurs master

Les membres du DHU coordonnent 14 masters (Annexe 14) et assurent collectivement plus de 96 cours de master (Annexe 15) chaque année.

3- Les thèses

24 thèses de science soutenues depuis Juin 2012. (Annexe 16)

4- Les publications d'ouvrage et de revues de synthèses

Le recensement des ouvrages et des revues de synthèse a été difficile. Nous avons identifié 33 publications de ce type, mais ce chiffre sous-estime probablement la réalité de ce type d'activité. (Annexe 17)

5- L'organisation de colloque ou de séminaires nationaux et internationaux

Les équipes du DHU ont organisé 14 colloques nationaux ou internationaux, sans compter la Fire Conférence annuelle organisée par le DHU FIRE, ni les colloques organisés en collaboration avec le LabEx Inflamex. (Annexe 18)

IV- LA GOUVERNANCE

1- Mise en place et organisation des divers comités

Le **Comité de Direction** du DHU est composé des coordinateurs des *Work Packages*. Il a pour rôle d'évaluer l'avancement des progrès du DHU et la gestion quotidienne. Il s'est réuni de façon bimensuelle les mercredis matins, rassemblant Bruno Crestani, Eric Daugas, Gabriel Steg, Marie-Pia d'Ortho et Ronan Roussel et la chargée de mission. Le Comité de coordination s'est à l'occasion réuni chez certains de ses partenaires. Le **Comité de Direction** a organisé deux réunions annuelles avec les coordonnateurs du Comité Scientifique, Renato Monteiro et Pierre Amarenco, notamment à l'occasion des jurys des programmes Emergence 1 et Emergence 2.

Le **Comité Stratégique (Strategy Advisory Board)** examine les progrès du DHU et donne des recommandations stratégiques au Comité de Direction. Il comprend les professeurs Peter Barnes (Imperial College London, UK), Gérard London (Paris) et Deepak.L Bhatt (Harvard Medical School, Boston, USA).
Le Comité de Direction du DHU a présenté le bilan d'activité du DHU à deux ans au Professeur Deepak Bhatt à l'occasion de son séjour à Paris en juin 2014 (invité du DHU FIRE). L'état d'avancement du DHU a par ailleurs été présenté de façon électronique à l'occasion d'une conférence téléphonique à Peter Barnes et Gérard London.
Le **Conseil du DHU** réunit au Comité de Direction 3 jeunes médecins (Louis Potier, Gregory Ducrocq et Raphaël Borie), 3 doctorants (Awen Menou, Ray Boustany et Claire Bouleti) et 3 infirmières (Sylvia Werner, Anne Vigneron et Caroline Albany). Le conseil se réunit deux fois par an et examine l'avancement des résultats, projets en cours ou émergents du DHU.
Enfin, la Fire Conférence annuelle est l'occasion de réunir tous les membres du DHU. Pendant la matinée, l'état d'avancement des projets du DHU est présenté et discuté avec les participants.

2- Utilisation des crédits APHP

Sur les 300 000€ de budget reçus par le DHU, 215 110 € ont été dépensés, soit un solde de 84 889 €.
Le DHU a lancé deux appels à projets Émergence (Émergence 1 en 2013 et Émergence 2 en 2014) offrant un crédit d'amorçage pour un projet transversal à un membre d'une des équipes du DHU Fire. Les projets portés par de jeunes investigateurs (étudiants en Thèse, Post-doctorants, CR, CCA et PHU) ont été particulièrement observés. Dans le cadre du premier appel à projets « Emergence » du DHU FIRE, après évaluation par deux rapporteurs, six projets ont été financés. Pour l'appel à projets Émergence 2, 19 projets ont été déposés et évalués par le Comité Scientifique du DHU, 5 projets ont été financés. Chacun a reçu un crédit de 15 000 euros.
Il a été décidé lors de la Fire Conférence du DHU le 4 septembre 2014 de lancer un appel à projet « Émergence 3 » pour l'année 2015.

Afin d'assurer la coordination des différents projets, l'organisation des Fire Conference ainsi que la communication, le DHU a engagé une chargée de mission à mi-temps depuis août 2013. Le complément a été utilisé pour l'organisation des conférences du DHU.
(Annexe 19 : Etat financier du DHU)
(Annexe 20 : Liste des projets Emergence 1 et 2)

3- Implication des autres partenaires institutionnels et privés

Le Doyen et la présidence de l'Université prennent en compte l'appartenance aux DHU pour le recrutement des personnels hospitalo-universitaires lors de la révision annuelle des effectifs, mais aussi pour l'affectation des locaux, des crédits et des personnels de recherche.
L'Hôpital Bichat fournit un bureau avec ordinateur et téléphone à la chargée de mission du DHU. La Faculté Bichat prête la Salle des Thèses pour l'organisation de la Conférence scientifique annuelle du DHU.
Des projets de recherche collaboratifs ont été proposés au conseil scientifique international du groupe Roche/Genentech et sont actuellement en cours d'évaluation. Une démarche identique est en cours avec d'autres partenaires industriels, notamment la société ResMed.
Néanmoins, à l'heure actuelle le DHU FIRE n'a pas contracté directement avec un industriel pour soutenir ses projets. C'est un point sur lequel nous ferons porter plus spécifiquement nos efforts dans la prochaine année.

Les partenaires du DHU ont cependant des interactions étroites avec ces partenaires industriels, tant pour la mise en place de projets de recherche communs que pour des essais thérapeutiques.

V- LA COMMUNICATION

1- Le site web

Le DHU dispose depuis sa création d'un site web (www.dhufire.org) dont l'interface a récemment été améliorée. Le site présente les partenaires, activités, actualités et newsletters du DHU. Il est supervisé par la chargée de mission du DHU et le Dr Antonino Nicoletti (U1148-DHU). Le Dr Martin Flamant (U1149-DHU) est le rédacteur en chef de la Newsletter du DHU qui est adressée de façon mensuelle aux membres du DHU.

2- L'organisation de séminaires spécifiques au DHU

➢ Fire Conférence

Le DHU organise une conférence annuelle la **Fire Conference** afin de réunir les membres du DHU et présenter les avancements des différents Work Packages et les activités du DHU (comme le projet Emergence). C'est aussi l'occasion d'inviter des orateurs extérieurs pour présenter des conférences sur les thématiques du DHU Fire. Le laboratoire Intermune a versé en 2013 et 2014 une subvention pour soutenir l'organisation de la Fire Conférence. Le programme des Fire Conference 2013 et 2014 figure en annexe. (Annexe 21 et 22)

➢ Conférences transversales organisées par le DHU

- *« Biomarkers in atherothrombosis »* le 1er Septembre 2011 (avant même la création « formelle » du DHU) à Paris, par **Marc Sabatine** (Harvard Medical School, Boston, MA, USA)
- *"New clinical advances in Idiopathic Pulmonary Fibrosis"* le 5 juin 2013 par **Harold Collard** (San Francisco, CA,, USA),
- *« An integrative view of lung fibrosis »* le 25 Septembre 2014 par **Moises Selman** (Mexico City, Mexico)
- *« IPF and Cancer »* le 13 janvier 2014 par **Carlo Vancheri** (Catane, Italie). Le professeur Vancheri est Professeur invité de l'Université Paris Diderot pour l'année 2014. Il est soutenu par le DHU FIRE.
- *«The future of renal denervation after SYMPLICITY 3 »* le 26 juin 2014, par **Deepak Bhatt**, directeur exécutif des programmes de cardiologie interventionnelle du Brigham and Women's Hospital of Boston et Professeur de Médecine à la Harvard Medical School .

VI- L'AVANCEMENT DU PROJET

1- W1: Fight Fibrosis – Bruno CRESTANI

Ce work-package propose un abord global de la fibrose comme une cible thérapeutique dans les maladies chroniques. Il s'articule autour de 6 grands axes qui ont progressé de façon significative depuis la création du DHU. Ce WP est essentiellement orienté vers la recherche avec une déclinaison vers les soins dès que possible. Ce work package a atteint ses délivrables comme prévu dans le projet initial du DHU FIRE.

1-Etude des liens entre inflammation et fibrose. Nous avons identifié de nouveaux acteurs de l'interface inflammation-coagulation-fibrose dans le poumon avec l'identification du rôle joué par la protease nexin-1, un inhibiteur de sérine protéases (François et al. Lab Invest, *2014)* et par la matriptase, une sérine protéase (Bardou et al. *soumis*). Le DHU soutient un projet émergent concernant le rôle des plaquettes dans le remodelage vasculaire (B Ho-Tin-Noé). La réactivation des voies du développement au cours de la fibrogénèse a été illustrée par l'identification du rôle de FOXF1 (Plantier, Am J Physiol Lung 2014) et de la voie Sonic Hedgehog (Cigna, Am J Pathol 2012 ; Moshai, Am J Respir Cell Mol Biol 2014) dans la fibrose pulmonaire. Le rôle antifibrosant potentiel des mastocytes dans la fibrose rénale a été étudié (Beghdadi, Kidney Int 2013 ; Madjene, Mol Immunol 2015, sous presse).

2-Hyperglycémie et fibrose. L'étude du rôle des kinines a été initiée (le DHU a apporté un soutien financier à Louis Potier pour ce projet dans le cadre de l'appel d'offres émergences).

3-Génétique de la fibrose. Le projet « génétique de la fibrose pulmonaire » soutenu par la Chancellerie des Universités et le PRES Sorbonne Paris Cité a permis d'identifier un nouveau gène impliqué dans les fibroses pulmonaires familiales, en collaboration avec l'institut IMAGINE (Kannengiesser et al. soumis). Le DHU a identifié en 2012 les mutations de TGFB2 à l'origine de formes familiales de dissections aortiques (Boileau Nat Genet 2012) et soutient un projet sur la génétique de la maladie de Marfan, un modèle de maladie du tissu conjonctif. Un réseau national pneumo/rhumato (TRANSLATE) portant sur la génétique de la fibrose pulmonaire eu cours de la PR a été initié par Ph. Dieudé dans le cadre du DHU.

4-Biomarqueurs et Fibrose. Différents travaux sont en cours ou finalisés, portant sur les fibrocytes dans la fibrose pulmonaire (Borie, Plos One 2013), la protéomique des fibroblastes pulmonaires (Plantier, soutien PRES SPC), cardiaque (Mebazaa, Eur Heart J 2012) et rénale. Le DHU soutient un projet concernant QSOX1 et fibrose cardiaque (N. Vodovar).

5-Imagerie de la fibrose. Ce WP est basé sur l'utilisation de l'imagerie multi-modalité (SPECT et IRM) pour la détection de l'inflammation et de la fibrose dans des modèles expérimentaux et chez l'homme, avec en particulier le développement de nano/microparticules polysaccharides, la détection de l'annexine A5, la détection d'organes lymphoïdes tertiaires dans des situations d'inflammation chronique/fibrose, le ciblage de l'activation endothéliale par la détection de la P-sélectine à l'aide d'un ligand naturel (fucoidan- Suzuki et al. Nanomedicine 2014).

6-Essais cliniques. L'essai multicentrique KEFI (traitement par KGF des exacerbations de fibrose pulmonaire) soutenu par le DHU débute en Novembre 2014. Le projet AsthmaTherm (Thermoplastie bronchique dans l'asthme sévère) conduit par Michel Aubier est finalisé. Les premiers résultats sont en cours de publication (Pretolani, AJRCCM, en révision).

Publications principales du WP :

Melboucy-Belkhir S, Pradère P, Tadbiri S, Habib S, Bacrot A, Brayer S, Mari B, Besnard V, Mailleux AA, Guenther A, Castier Y, Mal H, Crestani B, Plantier L. Forkhead Box F1 (FOXF1) represses cell growth, COL1 and ARPC2 expression in lung fibroblasts in vitro. Am J Physiol Lung Cell Mol Physiol. 2014 Sep 26. pii: ajplung.00012.2014. [Epub ahead of print]

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Mebazaa A, Vanpoucke G, Thomas G, Verleysen K, Cohen-Solal A, Vanderheyden M, Bartunek J, Mueller C, Launay JM, Van Landuyt N, D'Hondt F, Verschuere E, Vanhaute C, Tuytten R, Vanneste L, De Cremer K, Wuyts J, Davies H, Moerman P, Logeart D, Collet C, Lortat-Jacob B, Tavares M, Laroy W, Januzzi JL, Samuel JL, Kas K. Unbiased plasma proteomics for novel diagnostic biomarkers in cardiovascular disease: identification of quiescin Q6 as a candidate biomarker of acutely decompensated heart failure. Eur Heart J. 2012 Sep;33(18):2317-24.

Suzuki M, Bachelet-Violette L, Rouzet F, Beilvert A, Autret G, Maire M, Menager C, Louedec L, Choqueux C, Saboural P, Haddad O, Chauvierre C, Chaubet F, Michel JB, Serfaty JM, Letourneur D. Ultrasmall superparamagnetic iron oxide nanoparticles coated with fucoidan for molecular MRI of intraluminal thrombus. Nanomedicine (Lond). 2014 Jun 24:1-15.

2- WP2: Diabetes in chronic remodeling diseases- Ronan ROUSSEL

1 SOINS

Organisation des soins transversaux Cœur Vaisseau Diabète

Les services de diabétologie du DHU (Bichat et Lariboisière, ex-St Louis) ont entrepris de rendre systématique le dépistage des complications cardiovasculaires. Ainsi, le service de diabétologie de Lariboisière a organisé son soin ambulatoire dans le cadre du DHU, avec l'ouverture du CUDC (Centre Universitaire du Diabète et de ses Complications) en 2014 : il s'articule autour d'un Hôpital de Jour permettant d'hospitaliser jusqu'à 15 patients par jour, d'un secteur de consultations (notamment présence quotidienne de cardiologues des services des Pr Alain COHEN SOLAL et Patrick HENRY du DHU), d'une unité d'éducation thérapeutique et d'une unité de prise en charge ambulatoire des lésions des pieds. Réciproquement, le dépistage systématique des désordres métaboliques dans les services cliniques du DHU ont conduit à une augmentation importante des interventions diabétologiques directement au sein de ses services. Ainsi, pour l'hôpital Bichat, elles sont passées de 213 en 2012 à 525 en 2013 et 370 sur le premier semestre 2014. L'accélération de l'activité de soins "nutrition" à Bichat avec la nomination du Dr Hansel (voir ci-dessous Obésité-Boris Hansel) induit des développements connexes sur le plan du soin et de l'investigation clinique dans le DHU, développements ancrés pour leur partie recherche dans l'unité U1138 équipe 2 (Pr Roussel). Ainsi, l'exemple d'une expertise nouvelle et transversale est donné par la prise en charge des patients cumulant une obésité sévère, un diabète et une insuffisance rénale chronique, patients dont le pronostic est particulièrement sombre du fait du déclin extrêmement rapide de la fonction rénale et du recours à la dialyse précoce, sans espoir de greffe rénale du fait de l'obésité (contre-indication chirurgicale), et des complications vasculaires florides ; un essai randomisé évaluant la chirurgie bariatrique chez ces patients, en collaboration avec l'U1149 équipe 2 au sein du DHU (Pr Daugas) a été retenu par le PHRC (lettre d'intention, second tour d'évaluation en cours) a été initié sur la base du besoin clinique que cette activité transversale a révélé. (Annexe 23 : tableaux soins)

Protocoles communs

Les troubles respiratoires sont plus fréquents au cours du diabète, en particulier le syndrome d'apnées du sommeil dont la prévalence dépasse 50% dans la plupart des études. Sa présence augmente encore le risque de maladies cardiovasculaires, mais aussi de dégradation de la fonction rénale, risque déjà élevé dans le diabète. Le dépistage efficace et la prise en charge du syndrome d'apnées du sommeil est un challenge. Un protocole de dépistage très large des patients hospitalisés (toutes modalités d'hospitalisation) a été mis en place en collaboration entre le service de Diabétologie (DHU, Pr Marre) et l'unité d'exploration des troubles du sommeil (DHU, Pr d'Ortho) de l'hôpital Bichat avec un enregistrement d'oxymétrie et des flux respiratoires (Apnea Link) télétransmis quotidiennement à l'unité du Pr d'Ortho pour interprétation experte et décision d'orientation. Ce protocole est opérationnel depuis 2012 et est en cours d'extension au service de Diabétologie de l'hôpital Lariboisière (Pr Gautier) au sein du DHU.

Base de données

Le déménagement effectif du service de diabétologie de Saint Louis à Lariboisière et sa ré-organisation offre une opportunité de rapprochement entre les deux services de diabétologie du DHU (Lariboisière et Bichat), sur le plan du soin et de l'investigation clinique. En pratique, chaque entité développe actuellement une base de données destinée d'une part à son auto-évaluation propre, d'autre part qui permettra la définition d'indicateurs partagés, et qui facilitera la mise en commun des ressources pour l'investigation clinique.

2 RECHERCHE

Objectifs définis par le WP Diabète

- identification d'une nouvelle cible thérapeutique dans les complications du diabète (délivrable 2.1),
- Rôle du diabète dans les valvulopathies cardiaques : cohortes GENERAC/SOFRASA (délivrable 2.2)
- Insuffisance cardiaque diastolique, complication méconnue du diabète (délivrable 2.3)
- Épidémiologie et génétique des complications dégénératives du diabète (délivrable 2.4)

Etat d'avancement

La première partie du délivrable 2.1 porte sur l'évaluation pré-clinique de nouveaux agonistes des récepteurs B1 et B2 de la bradykinine, avec des résultats encourageants dans l'ischémie myocardique

(U1138, équipe 2, Potier et al., J Pharmacol Exp Ther. 2013 Jul;346(1):23). Cet axe de recherche se prolonge actuellement vers le remodelage cardiaque compliquant le diabète, en collaboration au sein du DHU qui a soutenu ce projet dans l'appel d'offres Émergence (délivrable 2.3).
Les analyses évaluant l'impact du diabète sur les caractéristiques et l'évolution des valvulopathies (cohortes GENERAC/SOFRASA) en collaboration entre l'équipe 2 U1138 et l'équipe 2 U1148 ont débuté. Les résultats sont programmés 1er semestre 2015.
La mise en évidence en 2013 d'un rôle prédictif majeur de la vasopressine et de la copeptine dans la néphropathie au cours du diabète de type 2 (Velho et al., Diabetes Care. 2013 Nov;36(11):3639) a été étendue au diabète de type 1 (Velho et al., manuscrit en préparation). Avec l'objectif principal d'étayer la causalité de cette association, des études d'épidémiologie génétique (type randomisation mendélienne) et un projet expérimental, destinés à identifier les récepteurs impliqués et le potentiel thérapeutique de leur blocage, ont été initiés.

Réorientations éventuelles

Le programme d'évaluation du potentiel thérapeutique des agonistes des récepteurs B1 et B2 de la bradykinine a été étendu à d'autres organes cibles des complications vasculaires du diabète, par des travaux sur la néphropathie (modèle de rongeurs diabétiques), et sur la vascularisation périphérique dans un modèle de récupération de perfusion après ligature de l'artère fémorale (Desposito, et al., en révision).
De nombreuses voies de signalisation impliquées dans les mécanismes de fibrose sont aussi essentielles au cours du développement embryonnaire. Sur ce constat, une collaboration entre des partenaires du DHU (JF Gautier, diabétologie Lariboisière, M. Marre, diabétologie Bichat, et U1138 équipe 2) a émergé afin d'identifier les locus génétiques différentiellement méthylés chez de jeunes adultes exposés ou non au glucose pendant la vie foetale (enfants de mères diabétiques), en associant ces différences de méthylation avec un marqueur de fonction rénale à l'âge adulte. Cette approche radicalement originale, en cours de réalisation, complètera le délivrable 2.4.

Perspectives

La création de l'unité U1138 équipe 2, au centre de recherches des Cordeliers, "Pathophysiology and therapeutics of vascular and renal diseases related to diabetes and nutrition" est extrêmement cohérente avec le projet du DHU et facilitera la mise en oeuvre des nombreux projets en lien avec le diabète. L'équipe a intégré le DHU FIRE.

3. ENSEIGNEMENT

DIU

Création en octobre 2012 d'un DIU de "suivi du patient diabétique" destiné aux médecins des spécialistes non diabétologues impliqués dans le dépistage et suivi des complications chroniques des patients diabétiques, en particulier cardiovasculaires et rénales. Ce DIU est une collaboration entre le DHU, Paris Diderot (R. Roussel) et Paris Descartes (E. Larger). Ce DIU est un succés (45 inscrits/an).

4. EXEMPLES DE PUBLICATIONS TRANSERVSALES DU WP2

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3- WP3: Chronic Graft Failure- Denis GLOTZ

La physiopathologie de la dysfonction chronique d'organe en allo-transplantation a récemment été reconsidérée, à la lumière de données nouvelles sur le rôle des anticorps dirigés contre le greffon (Donor Specific Antibody ou DSA). Ainsi, nous avons démontré que la progression des lésions vasculaires d'« artériosclérose » dans le rein transplanté était 4 fois plus rapide en cas de présence de tels DSA (1), et que ce phénomène se voyait également en transplantation cardiaque (2).

Nous avons étudié l'effet de tels anticorps sur l'interaction entre le système immunitaire et la cellule endothèliale dans un modèle in vitro mis au point dans notre laboratoire (3) et montré que l'existence de tels anticorps modifiait les interactions entre cellule endothéliale et lymphocytes en augmentant la génération de lymphocytes effecteurs TH17 et en diminuant la génération de lymphocytes régulateurs Treg (Taflin et al, soumis). De même, l'équipe U1148 étudie l'implication d'un autre type de lymphocytes, les T fh avec les cellules endothéliales.

L'étude d'une large cohorte de patients transplantés nous a permis de mettre en évidence un nouveau type de rejet, caractérisé par la présence de lesions vasculaires induites par ces DSA (4), et l'utilisation d'un nouveau test de détection de ces anticorps, explorant leur capacité à fixer le complément, nous a permis de mieux préciser le pronostic de ces greffes (5). Les anticorps fixant le complément dans ce test sont associés à une perte plus importante de greffon en analyse multivariée. Nous poursuivons ce travail en démontrant un phénotype lésionnel particulier chez les patients porteurs de tels anticorps, tant au niveau des lésions anatomopathologiques qu'au niveau moléculaire (Lefaucheur et al, en préparation).
Nous tentons maintenant (O Brugière) de démontrer le même effet de ces anticorps fixant le complément en transplantation pulmonaire en étudiant la fréquence du rejet humoral et de la dysfonction chronique d'allogreffe. L'étude d'une large cohorte de patients ayant bénéficié d'une transplantation pulmonaire (cohorte COLT) permettra de définir là aussi les marqueurs anatomopathologiques et moléculaires du rejet chronique (Thabut, U1152), en prêtant une attention particulière à l'expression d'une molécule du HLA : HLA-G (collaboration avec N Rouass-Freiss, CEA). Une de nos équipes a déjà pu montrer que l'expression de cette molécule HLA-G était associée à une protection significative du rejet chronique en transplantation pulmonaire (Brugière et al, AJT 2014 sous presse).

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4- WP4: Atherothrombosis- Gabriel STEG

1. Soins

- La prise en charge coordonnée Cardio-Neurologique comprend l'exploration systématique de l'athérothrombose coronaire chez les patients survivants d'un accident vasculaire cérébral. D'abord réalisée dans le cadre d'un protocole de recherche (étude AMISTAD), ceci a été intégré à la gestion clinique depuis 2012, et représente une cohorte d'environ 300 patients par an. De façon symétrique, les lésions athérothrombotiques sur les vaisseaux à destinée cérébrale sont systématiquement évaluées chez les patients coronariens. .

- De la même façon, stimulée par les perspectives de recherche clinique sur la dénervation rénale, le DHU a mis en place une prise en charge pluridisciplinaire des hypertensions artérielles résistantes ou sévères, faisant intervenir les différentes composantes cliniques du DHU. Cette activité est détaillée dans un document joint en annexe.
- Enfin, le DHU a permis une synergie de prise en charge des troubles « cardiométaboliques » avec une évaluation cardiologique systématique des patients diabétiques ou obèses prises en charge par le service de Diabétologie/endocrinologie/nutrition et également l'évaluation « diabétologique » des coronariens admis en Unité de Soins Intensifs Coronariens par le dépistage systématique du diabète chez ces patients (environ 350 patients/an)

2. Enseignement

Le DHU a permis d'aller vers une intégration des enseignements de premier, second et troisième cycle tournant autour du risque cardiovasculaire. En particulier, en PACES, création d'un séminaire commun « prévention et facteurs de risque cardiovasculaire », regroupant des enseignements jusqu'ici dispensés séparément. Au niveau du troisième cycle, l'enseignement au sein des DIU Urgences, USIC intègre au maximum les enseignements de cardiologie médico-chirurgicale, de neurologie vasculaire et de diabétologie/nutrition

3. Recherche. Elle est organisée autour de plusieurs thèmes correspondant au programme du WP

3.A. Interface Neuro-vasculaire/Cardiologie. La recherche dans ce domaine est organisée autour de 4 thèmes, et a permis des publications référencées ci-dessous

1. L'épidémiologie de l'interface coeur-cerveau : dès avant la création du DHU, une collaboration étroite entre les activités de recherche et les activités cliniques de Cardiologie et de Neurologie vasculaire s'intéressait à l'athérome de l'arche aortique[1,] à l'épidémiologie de l'athérothrombose [2-5] , et aux risques liés à l'utilisation des antithrombotiques chez les coronariens avec ATCD d'AVC/AIT [6]

2. La conception, l'organisation et l'analyse de grands registres ou essais cliniques multicentriques, internationaux qui s'intéressent à la prévention et au traitement des syndromes coronaires aigus et des accidents vasculaires cérébraux. Les équipes du DHU assurent ainsi le leadership mondial des essais SOCRATES [7] et OPTIC [8-10] (un essai pivot international et un registre international pour lesquels Pierre Amarenco préside le Comité de Pilotage) et l'essai pivot ODYSSEY-Outcomes [11] (18 000 Malades convalescents d'infarctus du myocarde, recrutés dans 44 pays) qui vise à tester l'effet d'un inhibiteur de PCSK9, l'alirocumab, sur la prévention des accidents cardio et cérébrovasculaires, qui est co-présidé par PG.Steg et G.Schwartz (Université de Denver CO, USA) et auquel Pierre Amarenco est également associé.

3. L'évaluation de l'efficacité et de la sécurité des thérapeutiques cardiovasculaires, qu'il s'agisse des antithrombotiques[6,12-16], des IEC/ARA II [16], ou des béta-bloquants [17-19]

4. L'Anémie et athérothrombose (REALITY: projet franco britannique d'essai comparatif de stratégies transfusionnelles dans l'infarctus aigu, préselectionné pour le PRME et déposé pour financement le 4/9/14)

Le projet pour 2015 dans ce domaine est la constitution d'un projet de réseau transatlantique de recherche sur l'interface cardio-Neurologique, centré sur la recherche translationnelle, l'imagerie et la théraoeutique, réunissant les équipes du DHU FIRE, l'équipe de Cardiologie et de Neurologie Vasculaire de Stanford University (GW.Albers & R.Harrington), de Harvard Medical School (DL.Bhatt) et de l'Université de Munich (M.Schwaiger), et qui serait soumis pour financement auprès de la Foncation Leducq, à l'appel d'Offres Fondation Leducq, fin 2015.

3.B. Interface Cœur/Poumons

L'activité du WP dans ce domaine est encore au niveau des projets de développement de recherche transversale sur les thèmes

- Asthme et cœur
- Fibrose Pulmonaire et Fibrose vasculaire

3. C. Imagerie et athérome

- Vulnérabilité des plaques d'athéromes coronaires, carotides et aortiques : un programme ambitieux d'imagerie invasive et non-invasive multimodalités (ultrasons, artériographie, échographie endovasculaire, tomographie par cohérence optique (OCT), et tomographie à émissions de positions) des plaques d'athérome coronaire chez l'homme, couplée à la mesure des biomarqueurs et à un

phénotypage détaillé des patients atteints d'athérome coronaire, carotide ou aortique est en cours au sein des études BIOCORE 1 et 2[20] et vise à déterminer les facteurs de vulnérabilité des plaques.

3.D. Interface Athérothrombose/Diabète (elle rejoint directement et chevauche l'activité du WP2). Elle est centrée sur les 4 thèmes suivants et a donné lieu à des publications référencées

1. l'épidémiologie des complications cardiovasculaires du diabète [21]
2. La tolérance cardiovasculaire des traitements hypoglycémiants [22,23]
3. L'aggrégabilité plaquettaire spécifique à la maladie coronaire du diabète (SPACE) [24]
4. Les essais thérapeutiques prospectifs (THEMIS)[25]. Là aussi, les équipes du DHU assurent le leadership d'un essai randomisé prospectif multicentrique international, intéressant plus de 17,000 patients, portant sur la prévention des accidents cardiovasculaires chez les diabétiques coronariens stables (PG.Steg & DL.Bhatt sont co-présidents du Comité de Pilotage)

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5- WP5: Syndrome cardio-renal- Eric DAUGAS

Le syndrome cardio-rénal regroupe les intrications cliniques des maladies cardiaques et rénales. Il est un facteur de gravité pour les patients atteints d'insuffisance cardiaque et les patients atteints d'insuffisance rénale, il augmente les coûts de leur prise en charge. Il concerne un quart des patients hospitalisés pour une décompensation cardiaque et l'insuffisance cardiaque est la première co-morbidité des patients atteints d'insuffisance rénale (20% des dialysés). Le projet FIRE a d'emblée été une opportunité pour le développement des soins et de la recherche sur le syndrome cardio-rénal (figure).

Soins

Les unités de cardiologie et de néphrologie de FIRE ont pu développer des axes de soins adaptés dès 2012 pour les patients hospitalisés et en ambulatoire **(deliverable 5.5. Timeline 2012) :** des procédures conjointes spécifiques des patients atteints de syndrome cardio-rénal, consultations mixtes mais surtout un parcours de soins facilité des patients entre les deux disciplines, un accès à la dialyse pour le traitement de l'insuffisance cardiaque réfractaire, le recours à la transplantation cardiaque et/ou rénale. L'offre de soins est donc élargie quantitativement et qualitativement.
Plus spécifiquement, une filière de prise en charge hautement spécialisée de l'insuffisance cardiaque réfractaire par les techniques de dialyse (dialyse péritonéale et hémodialyse) a pu être initiée (F. Vrtovsnik, G Jondeau, D. Logeart).
Perspectives : Augmenter l'activité cardio-néphrologique avec une simplification de l'accès à la filière de soins cardio-rénale, dans toute l'aire géographique de FIRE. Mise en place d'une RCP cardio-néphrologique. Augmenter l'activité de prise en charge spécialisée de l'insuffisance cardiaque réfractaire par dialyse (activité de type centre de référence).

Recherche clinique

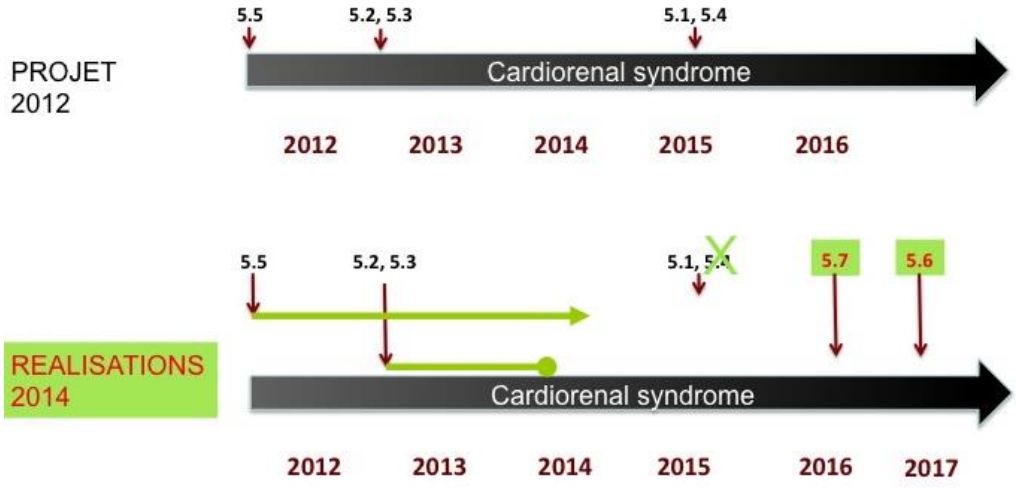
L'important recrutement des patients atteints de syndrome cardio-rénal (25% des 600 patients hospitalisés chaque année pour décompensation cardiaque) a permis de développer des projets spécifiques.
Une cohorte prospective des patients admis pour insuffisance cardiaque est constituée sur les sites Lariboisière et Bichat avec une biothèque systématique à Lariboisière (Alain Cohen-Solal).
L'étude VOLEMIC (G. Jondeau, E Daugas) a évalué l'impédancemètrie pour mieux quantifier l'hyperhydratation des patients hospitalisés pour insuffisance cardiaque et y adapter leur traitement, et ainsi prévenir (ou contenir) le syndrome cardio-rénal (**deliverables 5.2 and 5.3. Timeline 2013**). Le résultat est négatif : individuellement, l'impédancemètrie ne permet pas de mesurer plus précisément l'état d'hydratation que les données cliniques, échographiques cardiaques, voire biologiques. Le projet VOLEMIC II qui prévoyait l'évaluation de l'ajustement des soins par l'impédancemètrie (**deliverable 5.4. Timeline 2015**) est donc abandonné.
Perspectives : L'investigation clinique sera cependant poursuivie avec :

- Le projet IRAPICA (G. Jondeau, E Daugas, A. Cohen-Solal) est une étude prospective dont l'objectif primaire est de déterminer si une stratégie de traitement de l'insuffisance cardiaque tolérant l'insuffisance rénale aigüe est supérieure à la stratégie usuelle limitant la déplétion hydrosodée en cas d'insuffisance rénale aigüe (**new deliverable 5.6. Timeline 2017**).
- Un travail collaboratif entre les équipes de néphrologie et de cardiologie du DHU (F. Vrtovsnik, G Jondeau, D. Logeart) doit déterminer l'adaptation à l'insuffisance cardiaque réfractaire des modalités de traitement usuellement destinées à l'insuffisance rénale, l'hémodialyse et la

dialyse péritonéale. Une cohorte de près de 100 patients a été constituée en lien avec le RDPLF. Son évaluation doit déboucher sur la construction d'un essai multicentrique (**new deliverable 5.7. Timeline 2016**).

Recherche translationnelle et fondamentale

La recherche au laboratoire, est le projet qui doit encore être le plus structuré (**deliverable 5.1. Timeline 2015**). Le projet initial entre l'U1149 (E. Daugas et U. Blank) l'U1148 (G. Jondeau et J-J Mercadier) intégrera l'U942 (A. Cohen-Solal) afin d'exploiter son expertise des modèles animaux d'insuffisance cardiaque pour développer un modèle d'étude du syndrome cardiorénal.



6- WP6: Sleep disordered breathing and tissue remodeling- Marie-Pia d'ORTHO

Le syndrome d'apnées du sommeil (SAS) pose un problème de santé publique en raison à sa prévalence élevée et des complications qui lui sont liées : HTA, pathologies cérébro- et cardio-vasculaires, pathologies métaboliques. Ces pathologies font le cœur du DHU FIRE à travers le socle physiopathologique commun représenté par le remodelage tissulaire et l'inflammation, intimement lié au SAS à travers l'hypoxie intermittente que ce dernier provoque et per se l'inflammation systémique.

1. Soins

Grâce à un soutien hospitalier et universitaire fort, un centre de sommeil a été créé en 2009 dans le Groupe Hospitalier HUPNVS – site Bichat, labélisé par la Société de Médecine et de Recherche du Sommeil en 2011, associé centre maladies rares "hypersomnies" en 2012, recensé par l'European Sleep Research Society en 2014. Dans le cadre du DHU, le centre du sommeil prend en charge les cas complexes [SAS chez l'insuffisant cardiaque, association BPCO et SAS, obésités avec hypoventilation alvéolaire …], avec 2 grands objectifs : la prise en charge transdisciplinaire des co-morbidités et l'optimisation de la ventilation nocturne, déterminants majeurs de leur pronostic.

2. Recherche Clinique

Rôle *du SAS dans la physiopathologie et le pronostic des pathologies métaboliques, cardiovasculaires et inflammatoires:*

Bilan des projets énoncés lors de la soumission du DHU (2011)

Le DHU suit de nombreuses cohortes, dont certaines font l'objet d'études ancillaires concernant le ***prévalence*** et ***l'impact pronostique*** du SAS sur leur évolution ou certains de leurs ***traits phénotypiques***, ainsi

- NEPHROTEST (Pr Vtrovsnik, Dr Flamant) cohorte ouverte créée en 2000, dont le but est d'identifier les déterminants et les biomarqueurs pronostiques et thérapeutiques de l'IR. Le dépistage du SAS y est devenu systématique depuis 2012, et le dépistage est maintenant intégré dans les soins courants.

- COBRA est une cohorte nationale de 1000 patients asthmatiques. Nous avons exploré les asthmatiques sévères de façon systématique (Dr Taillé) et avons montré une prévalence élevée (40%) de SAS, avec des profils d'inflammation des voies aériennes différents entre asthmatiques avec ou sans SAS (résultats présentés dans des congrès internationaux (2013, 2014), un article sous presse, un second en révision).
- COFI, cohorte de patients porteurs de fibrose pulmonaire, une prévalence élevée de SAS y a été montrée, l'article est en cours de rédaction. Les liens physiopathologiques restent à explorer.
- Prévalence du SAS chez les patients diabétiques (voir WP2 Diabète)

Des études observationnelles physio-pathologiques portent sur le rôle du SAS dans le contrôle glycémique de patients diabétiques de type 1 (promotion industrielle) et dans leur dysautonomie (PHRC 2012).

Des études interventionnelles randomisées et des études de cohorte sont en cours, dont la réalisation a été rendue possible en partie grâce au rôle structurant fort du DHU, ainsi

- SERVE HF (internationale multicentrique financement industriel) Le recrutement est terminé (n = 1253, dont un tiers en France), le suivi se poursuit jusqu'en 2015. Le « design paper » est publié (Cowie, Eur Heart J,2013).
- FACE, suivi de cohorte complémentaire de SERVE-HF (Pr d'Ortho, IP, comité scientifique), multicentrique français (financement industriel). Les patients seront suivis deux ans, une étude ancillaire se donne l'objectif d'identifier les facteurs associés à l'observance au traitement (soumission au CPP sept. 2014). Le « design paper » est soumis.
- Le PHRC P071227 évalue l'impact d'un traitement optimal de l'œdème maculaire diabétique, incluant la prise en charge du SAS (Pr d'Ortho comité scientifique). L'étude est terminée, les données sont en cours d'analyse.

<u>Projets ayant émergé depuis 2011</u>

- Le rôle du SAS dans la récidive de la fibrillation atriale après ablation : projet complet soumis au PHRC (septembre 2014)
- Traitement du SAS par orthèse d'avancée mandibulaire :, suivi pendant 5 ans d'une cohorte française (Pr d'Ortho, comité scientifique). Le recrutement des patients est terminé (2013). Les résultats intermédiaires montrent l'efficacité sur le SAS, la très bonne observance et le peu d'effets indésirables, ainsi qu'un effet significatif sur les chiffres tensionnels (communication orale, ERS 2014, article soumis).

3. Recherche fondamentale : le SAS de la femme enceinte intervient-il dans programmation péri-natale des pathologies adultes ?

La programmation périnatale de certaines pathologies adultes (hypertension artérielle, insulino-résistance) est démontrée, les études ont identifié le stress oxydatif comme élément déclencheur. Nous avons développé un modèle d'exposition de souris gestantes à l'hypoxie intermittente et étudions la descendance à différents âges post-nataux. L'exploration des souriceaux jusqu'au 30ème jour post-natal est conduite dans l'unité INSERM U1141 (Université Denis Diderot, DHU Protect, Pr P. Gressens, http://www.u141.inserm.fr/page.asp?page=3786), les animaux adultes sont explorés au Centre d'Explorations Fonctionnelles du petit animal (Collaboration Dr B. Escoubet).

4. Enseignements

4.A. Internat

Un poste d'interne a été créé en pneumologie pour être partagé avec le service de physiologie (2013), et depuis 2014 le même principe permet l'accueil d'un interne de neuro-vasculaire.

4.B. DIU

L'UFR de médecine de l'université Denis Diderot est très impliquée dans le DIU « le sommeil et sa pathologie », qui forme chaque année 70 médecins, issus de spécialités très variées (pneumologues, neurologies, cardiologues, internistes). L'enseignement théorique est centralisé à Bichat.

4.C. Création d'un master de médecine du sommeil

Une spécialité de master « Biologie, Physiologie et pharmacologie de la Respiration » existe depuis 2000. A l'occasion du nouveau contrat quinquennal (2014-2019) un parcours médecine du sommeil est ajouté. Ce master s'appuie sur une architecture définie par la Société Européenne de Sommeil, et l'objectif à terme est la création d'un master européen.

Publications principales du WP6 :

1- Philippe C., Boussadia Y., Pruliere-Escabasse V., Papon J. F., Clerici C., Isabey D., Coste A., Escudier E. and d'Ortho M. P. Airway cell involvement in intermittent hypoxia-induced airway inflammation. *Sleep & breathing = Schlaf & Atmung* 2014.
2- Roche-Campo F., Thille A. W., Drouot X., Galia F., Margarit L., Cordoba-Izquierdo A., Mancebo J., d'Ortho M. P. and Brochard L. Comparison of sleep quality with mechanical versus spontaneous ventilation during weaning of critically III tracheostomized patients. *Critical Care Medicine* 2013, 41: 1637-1644.
3- Dauvilliers Y., Arnulf I., Lecendreux M., Monaca Charley C., Franco P., Drouot X., d'Ortho M. P., Launois S., Lignot S., Bourgin P., Nogues B., Rey M., Bayard S., Scholz S., Lavault S., Tubert-Bitter P., Saussier C. and Pariente A. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. *Brain : a journal of neurology* 2013, 136: 2486-2496.
4- Cowie M. R., Woehrle H., Wegscheider K., Angermann C., d'Ortho M. P., Erdmann E., Levy P., Simonds A., Somers V. K., Zannad F. and Teschler H. Rationale and design of the SERVE-HF study: treatment of sleep-disordered breathing with predominant central sleep apnoea with adaptive servo-ventilation in patients with chronic heart failure. *European journal of heart failure* 2013, 15: 937-943.
5- Drouot X., Roche-Campo F., Thille A. W., Cabello B., Galia F., Margarit L., d'Ortho M. P. and Brochard L. A new classification for sleep analysis in critically ill patients. *Sleep medicine* 2012, 13: 7-14.
6- Damy T., Margarit L., Noroc A., Bodez D., Guendouz S., Boyer L., Drouot X., Lamine A., Paulino A., Rappeneau S., Stoica M. H., Dubois-Rande J. L., Adnot S., Hittinger L. and d'Ortho M. P. Prognostic impact of sleep-disordered breathing and its treatment with nocturnal ventilation for chronic heart failure. *European journal of heart failure* 2012, 14: 1009-1019.

CONCLUSION GENERALE DE L'AUTOEVALUATION

A mi-mandat, nous considérons que la création du DHU est un succès pour plusieurs raisons:

- **Revendication par les équipes de l'appartenance au DHU**
- **Développement de l'interaction entre les équipes des différents sites du DHU**
- **Meilleure intégration clinique-recherche**
- **Meilleure cohésion des équipes intra-DHU autour de projets communs**
- **Investissement sur les jeunes chercheurs et cliniciens dans le cadre des projets « Émergence »**
- **Excellence de la production scientifique**

Le DHU a certaines faiblesses qui sont autant d'opportunités pour les deux années à venir :

- **Concrétisation des projets de recherche avec les industriels**
- **Meilleure utilisation des cohortes de patients**
- **Développement des projets Cœur-Poumon et Cœur-Rein**