Call for proposal « Fédération Hospitalo-Universitaire »

Aquitaine's Care and Research OrganisatioN for inflammatory and Immune-Mediated diseases

Project Lead:

Pr Patrick Blanco, MD, PhD

August 2015

Table of contents:

LIST OF ABBREVIATIONS

To the members of the jury: We apologize because some of the institutional support letters are in French and because some of the abbreviations in the main text are directly from the French language. However, translations are provided for most, if not all, of the abbreviations.

AHU: Assistant Hospitalo-Universitaire / Assistant Professor
CCA: Chef de Clinique Assistant / Assistant Professor
CNRS: Centre National de la Recherche Scientifique / National Institute for Scientific Research
CNS: Central Nervous System
COPD: Chronic Obstructive Pulmonary Disease
CR: Chargé de Recherche / Research Investigator
DR: Directeur de Recherche / Principal Investigator
FHU: Fédération Hospitalo-Universitaire / University and Hospital Federation
GP: General Practitioner
GWAS: Genome Wide Association Study
ID: Inflammatory Disease
INSERM: Institut National de la santé et de la recherche médicale / National Institute for Medical Research
MCF: Maître de Conférence / Associate Professor
MCU: Maître de conférence des Universités / Associate Professor
MCU-PH: Maître de conférence des Universités/ Praticien Hospitalier / Associate Professor in Medicine
MS : Multiple Sclerosis
PU: Professeur des Universités / Professor
PU-PH: Professeur des Universités/Praticien Hospitalier / Professor of medicine
SLE: Systemic lupus erythematosus
SSc: Systemic sclerosis
Th: T-helper cells

1. Designation of the coordinator and deputy coordinator	
Scientific coordinator – Project lead	
	**Pr Patrick Blanco**, PU-PH Laboratoire d'Immunologie et Immunogénétique. Hôpital Pellegrin. CHU de Bordeaux patrick.blanco@chu-bordeaux.fr Tel : +33 6 88 18 12 24 Fax : +33 5 56 79 60 79
Medical coordinators – Deputy coordinators	
	**Pr Jean-Luc Pellegrin**, PU-PH Service de Médecine Interne et Maladies Infectieuses Hôpital Du Haut Lévêque. CHU de Bordeaux jean-luc.pellegrin@u-bordeaux.fr Tel : +33 6 01 17 68 28 Fax : +33 5 57 65 60 86
	**Pr Thierry Schaeverbeke**, PU-PH Service de Rhumatologie Hôpital Pellegrin. CHU de Bordeaux. thierry.schaeverbeke@chu-bordeaux.fr Tel : +33 6 80 27 19 75 Fax : +33 5 56 79 60 84

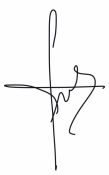
CVs of the coordinators are provided in Annex 1 (p 50).

2. Title and thematic of the FHU	
Title	**A**quitaine's **C**are and Research **O**rganisatio**N** for inflammatory and **I**mmune-**M**ediated diseases (ACRONIM)
Thematic	Chonic Inflammatory Diseases

August 2015, the 4th

Patrick Blanco

Thierry Schaeverbeke



Jean-Luc Pellegrin

3. Objectives of the FHU

Chronic inflammatory diseases (IDs) are the third cause of death in developed countries, after cancer and cardiovascular disorders, and their prevalence is growing at an alarming rate in westernized countries. These diseases constitute a heterogeneous group of illnesses, including rheumatic diseases (e.g., rheumatoid arthritis), autoimmune systemic diseases (e.g., lupus and vasculitis), organ-specific auto-immune diseases (e.g., type 1 diabetes and multiple sclerosis), inflammatory bowel diseases, respiratory diseases (e.g., asthma and COPD), and cutaneous diseases (e.g., psoriasis and vitiligo). Although their phenotypes are quite different, characterization of their pathogenesis has shown that they share genetic factors (GWAS has identified a striking overlap of genetic loci across IDs), common environmental factors (e.g., smoking), prominent cytokine roles (e.g., IL-1 in auto-inflammatory disease, gout, and Still's disease) or cell type (e.g., TH17 lymphocytes in Crohn's disease, psoriasis, and multiple sclerosis), suggesting a pathophysiological continuum between all IDs.

The pathophysiological mechanisms involved in IDs are increasingly being characterized, which has allowed the development of many biodrugs that target pro-inflammatory cytokines or specific cells. These treatments, although extremely effective, do not cure the patients, thus leading to long-term exposure of patients to these drugs. This exposure has two primary consequences: prolonged exposure to therapeutic risks for the patient and considerable societal cost.

Thus, the major "issues" in IDs could be located elsewhere, and the extremely early stages of IDs appear extremely attractive. Indeed, from a therapeutic point of view, the early introduction of an appropriate treatment after the onset of the first clinical manifestations of the disease clearly can have a major impact on the long-term course of the disease. This observation is classically defined under the concept of "windows of opportunity" for treatments. From a pathogenic point of view, observing similar genotypes that lead to clear phenotypically distinct diseases is puzzling; concordance studies conducted in dizygotic and monozygotic twins have shown that the importance of genetics is rather limited in IDs (with the exception of early-onset paediatric disorders). This observation emphases the important potential role of other contributing factors such as environmental, dietary, micro-environmental (in particular, the microbiota), epigenetic and stochastic factors. Nevertheless, their respective implications remain largely unknown, particularly in extremely early stages or preclinical stages of IDs. However, a better understanding of these factors is of significant importance because they could constitute key novel therapeutic targets and eventually pave the way for preventive actions in IDs.

In addition, chronic IDs share another peculiarity: the long-term development of diseases called comorbidities, which seem to be the consequence of metabolic and immune disorders promoted by chronic low-grade inflammation. These comorbidities, including cardiovascular diseases, infections, bone loss and cancer, are the cause of the increased mortality observed in IDs. Thus, these comorbidities represent not only an important issue in the care of IDs but also a key scientific interest because they can be viewed as a dynamic model of accelerated ageing, justifying the term "inflammageing". Therefore, all of the key findings from examining this topic could obviously benefit other medical fields.

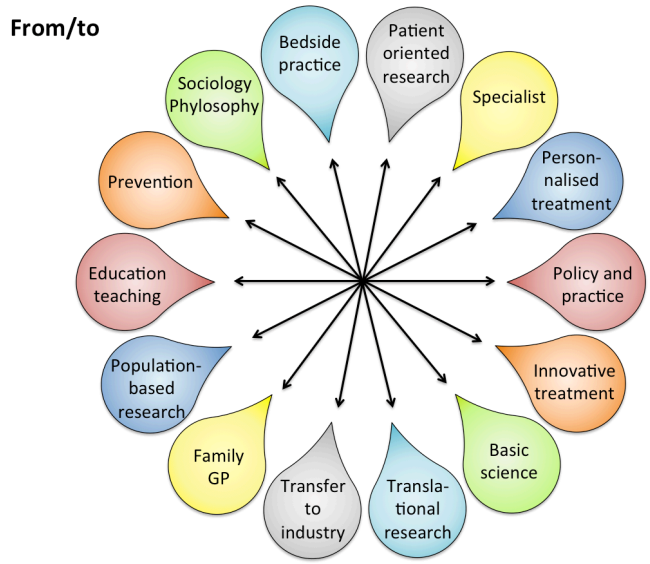
Based on these observations, we should focus our efforts on the following goals to improve future ID care:

- improving our knowledge regarding the implications of environmental, diet and other determining factors
- identifying at-risk subjects
- studying early stages of IDs
- identifying biomarkers predictive of the transition from symptom-free to clinical stages of disease
- developing preventive strategies for at-risk subjects
- developing new therapeutic strategies for early stages of IDs, assuming that this "window of opportunity" is the most appropriate to induce long-term remission
- studying the factors underlying comorbidities and accelerated ageing associated with IDs

Although these avenues of study may appear very ambitious at first glance, we consider that they constitute the key future questions to be addressed regarding ID; therefore, they constitute the core theme of the ACRONIM FHU project. The specific focus on the early stages of IDs will offer an original investigative approach for clinical, epidemiological and translational research. Investigating pathogenesis across all IDs will allow the cross-field coordination of projects independent of the phenotype of the disease. The constitution of a database and collection of samples from patients with early ID will allow us to build a unique foundation for identifying biomarkers predictive of the risk of developing a specific disorder, and that will eventually be shared across different diseases.

To reach our goals, we decided to remove barriers between specialists (and their respective approaches, particularly in the University Hospital) to refocus care and investigation of IDs around a dominant duo represented by the patient and the general practitioner. This original aspect of the project justifies several actions: 1) a close collaboration with the Department of General Medicine of the University of Bordeaux, 2) the investment of the Health Regional Agency (ARS) in the care organization, 3) an economic evaluation by health insurance and 4) the transfer to a regional company involved in medical devices or e-health. All these aspects are more precisely developed within the WP2.

In the same manner, we wanted to remove barriers between researchers, and individuals with different expertise, including immunologists, philosophers, chemists, cell biologists, bioinformaticians, and biostatisticians, have embarked on this project. While we consider this complementary group an asset to reconsider the "ID problem" from many different new and original perspectives, these individuals share the same eagerness to work together in close connection to solve human health problems.



ACRONIM's multidimensional approach to inflammatory diseases

4. Detailed list of the entities of the FHU

Within the scope of the present FHU project, 14 medical teams (10 clinical and 4 paraclinical), 11 research teams, the Department of General Practitioners, and the peripheral hospitals within the Aquitaine region will share and combine their expertise.

4.1. List of clinical partners from the University Hospital of Bordeaux

The table hereafter summarize all of the people involved within the FHU, their performance in term of publication based on their SIGAPS score. Only people involved in ID care are listed in the table.

NAME	People involved	Numbers of publication / Numbers of A and B publications (2012-2015)	SIGAPS (2012-2015)/ SIGREC score/
Department of Rheumatology	Pr Schaeverbeke Thierry Pr Richez Christophe Dr Truchetet Marie Elise Dr Thomas Barnetche	55 A : 18 B : 14	685 / 24
Department of Internal Medecine	Pr Pellegrin Jean-Luc Pr Viallard Jean-François Dr Lazaro Estibaliz Pr Morlat Philippe Pr Bonnet Fabrice Dr Marianne Vandenhende	286 A : 93 B : 65	2506 / 28

	Pr Mercié Patrick Dr Duffau Pierre Dr Ribeiro Emmanuel		
Department of Gastroenterology	Pr De-Ledinghen Victor Pr Zerbib Franck Pr Laharie David	166 A : 90 B : 27	2225 / 91
Department of Vascular Disease	Pr Constans Joel Dr Skopinski Sophie Dr Boulon Carine	19 A : 3 B : 8	176 / 2
Department of Dermatology	Pr Taieb Alain Dr Seneschal Julien Pr Doutre Marie Sylvie Pr Beylot-Barry Marie	212 A : 77 B : 69	3326 / 78
Department of Diabetology/ Nutrition	Pr Rigalleau Vincent Dr Blanco-Baillet Laurence	96 A : 33 B : 16	962 / 3
Department of Pneumology	Pr Tunon de Lara Manuel Pr Raherisson Chantal Dr Blanchard Elodie	49 A : 9 B : 2	424 / 2
Department of Paediatrics	Pr Lamireau Thierry Dr Pascal Pillet Dr Labrèze Christine Pr Boralevi Franck Dr Harambat Jérôme Dr Llanas Brigitte Dr Aladjidi Nathalie	179 A : 39 B : 53	1795 / 108
Department of Obstetrics	Pr Dallay Dominique Pr Brun Jean-Luc Dr Chabanié Pierre Dr Brun Stéphanie Dr Coatleven Frédéric	38 A : 1 B : 3	322 /47
Department of Nephrology	Pr Combe Christian Pr Merville Pierre Dr Couzi Lionel Dr Rigothier Claire	121 A : 41 B : 32	1365 / 66

4.2. List of clinical partners from the hospitals in the Aquitaine region

To fulfil our primary objective, i.e., to improve the care of patients throughout the southwest part of France, people from different hospitals that are involved in the FHU are listed hereafter.

LOCATION OF THE HOSPITAL (department)	People involved	Size of the Hospital (number of beds)
PAU (64)	Dr Lequen Laurence Dr Delbrel Xavier	779

BAYONNE (64)	Dr Oui Benoit Dr Monnier Agnès	1263
DAX (40)	Dr Lifferman François Dr Shipley Emilie	1010
AGEN (47)	Dr Rispal Patrick	692
LIBOURNE (33)	Dr Vergnes Jean-Philippe Dr Caubet Olivier Dr Meunier Vincent	580
PERIGUEUX (24)	Dr Lastaste Philippe Dr Jarnier- Loussouarn Dominique	1269

4.3. List of the paraclinical partners from the University Hospital of Bordeaux

The departments listed in the table hereafter are of tremendous importance, as they constitute relevant expertise for the FHU in pharmacology (biotherapy monitoring), immunology, and radiology. In addition, the Laboratory of Immunology hosts the "Groupe de Recherche Clinique en Immunologie Clinique" (GRIC, Immunology Clinical Research Group), which is a research laboratory with 2 people dedicated to clinical immune research in ID, cancer, and allergies. This group is accustomed to working in close connection with bona fide research labs and with the "Centre de Ressource Biologique" and constitutes an important connection for many translational projects. Of note, GRIC and Centre de Ressource Biologique (CRB/Biobank) are directed by the same person (Dr Pellegrin Isabelle).

NAME	People involved	Numbers of publication / Numbers of A and B publication (2012-2015)	SIGAPS (2012-2015)/ SIGREC score
Laboratory of Immunology	Pr Blanco Patrick Pr Moreau Jean-François Dr Bordes Cécile Dr Visentin Jonathan	60 A: 20 B: 19	710 / 0
Laboratory of Bacteriology	Pr Bébear Cécile Pr Mégraud Francis Pr Dubois Véronique Dr de Barbeyrac Bertille Dr Pereyre Sabine Dr Lehours Philippe Dr Bessède Emilie Dr Peuchant Olivia	92 A : 18 B : 21	1228 / 5
Department of Neuroradiology	Pr Dousset Vincent Dr Tourdias Vincent	79 A : 29 B : 18	916 / 18
Laboratory of Pharmacology	Pr Breilh Dominique Dr Djabarouti Sarah	185 A : 41 B : 36	2503 / 0

4.4. The Department of General Practitioners.

The following are the missions of this department:

• Organizing the training and education of general practice studies

• Managing and monitoring educational general practice students of Bordeaux University

• Teaching towards the specialized study diploma of general practice

• Developing clinical research in primary care in close collaboration with the research centre INSERM U 897

From a functional point of view, this department is based on the presence of senior general practitioners (called "Maître de stage" in French) who are allowed to work with fellows in general practice throughout the southwest part of France. Senior doctors are present in each department (187 in Gironde, 50 in Dordogne, 33 in Lot et Garonne, 58 in Landes, and 79 in Pyrénnées-Atlantiques) constituting the Aquitaine region. Fellows in general practice will be involved directly in the different projects, particularly in the WP2. A complete description of this department is provided in Annex 2 (p 57). This department constitutes a key partner of the project, as it will allow the linkage of our early ID detection programme to the general practitioners throughout the Aquitaine region. Moreover, this department will allow important primary care research programmes, in addition to scientific and clinical research programmes. **We consider this department an asset for the feasibility of our project.**

4.5. Research Sstructures associated with the FHU.

Hereafter is the list of the research partners involved directly in the FHU ACRONIM. Due to the heterogeneity of the unit involved in the project, in Annex 3 (p 59), we decided to provide a detailed description of the research projects, primary publications, and people involved for each structure, as well as a small chapter explaining how they envision their roles within the FHU.

NAME	Director	Theme	People involved	HCERES evaluation
UMR/CNRS 5164 (CIRID)	Pr Moreau JF	Immunology Systemic autoimmune disease Philosophy of science	Pr Blanco P (PU-PH) Dr Merville J (DR) Pr Moreau JF (PU-PH) Dr Capone M (CR) Pr Richez C (PU-PH) Dr Bordes C (MCU-PH) Dr Pradeu T (CR) Dr Truchetet ME (AHU) Dr Lazaro E (MCU-PH) Dr Duffau P (MCU-PH) Dr Faustin B (post-doc) Dr Duluc D (MCF) Dr Larmonier N (PU)	Excellent
INSERM U1045	Pr Marthan R	Team 1 : Lung inflammation Asthma Bronchial	Pr Berger P (PU-PH) Dr Choukroun ML (MCU-PH) Dr Dournes G (CCA)	Excellent

		remodelling <u>Team2:</u> TGF-beta / endothelial cells	Dr Dupin I (MCF) Pr Fayon M (PU-PH) Dr Girodet PO (MCU-PH) Pr Hilbert G (PU-PH) Pr Laurent F (PU-PH) Dr Macey J (PH) Pr Marthan R (PU-PH) Pr Montaudon M (PU-PH) Dr Thumerel M (PH) Dr Trian T (MCF) Pr Vargas F (PU-PH) Elisabeth Génot (DR), IJsbrand Kramer (PU) Isabelle Fremaux (AI-INSERM)	
UMR/CNRS 5116 (Centre Emile Durkheim)	Dr Smith Andy	Sociology Psychology	Bossy T (MCU) Guigner S (MCU) Jacques B (MCU) Langlois E (MCU) Ragouet P (PU) Zaffran J (PU)	Excellent
ATIP-AVENIR	Pr Taieb A	Skin Inflammation Vitiligo	Dr Seneschal J (MCU-PH) Dr Boniface K (MCF)	NA
ATIP-AVENIR UMR/CNRS 5164	Pr Moreau JF	Brain inflammation Multiple sclerosis	Dr Schmitt Nathalie	NA
INSERM U869	Dr Mergny JL	Aptamers	Dr Toulme J J (DR) Dr Azema L (MCU)	Excellent
UMR/CNRS 5800 LABRI	Dr Weil P	Genomics Image analysis omics	Pr Desbarats P (PU) Pr Domenger JP (PU) Dr Baldacci F (MCF) Dr Vialard A (MCF) Dr Coupé P (CR) Dr Nikolski M (DR) Pr Blin G (PU), Dr Uricaru R (MCU)	Excellent
INRIA/ SISTM	Pr Thiebaut R	System biology	Pr Thiebaut R(PU-PH)	Excellent
INSERM U897	Pr Tzourio C	Environmental factors	Pr Brochard Patrick (PU-PH)	Excellent
UMR5248 CNRS/UB/ INP CBMN	Dr Dufourc E	Institute of Chemistry & Biology of	<u>Team1</u>: « Extracellular Vesicles and Membrane Repair »: Pr. Brisson A	Excellent

		Membranes & Nanoobjects	(PU), Dr. Bouter A(MCU), Dr. Arraud N(Post-doc) Team2: « Tissue Engineering » : Dr. Durrieu MC (DR INSERM), Dr. Plawinski L (IR CNRS)	
USC INRA EA3671	Pr Bébéar C (PU-PH)	Mycoplasmal and chlamydial infections in humans Host-pathogen interaction	Pr Bébéar C (PU-PH) Pr Schaeverbeke T (PU-PH) Dr de Barbeyrac Bertille Dr Pereyre Sabine Dr Peuchant Olivia (MCU-PH)	Very good

4.6. Support for clinical research.

The following key transverse structures are necessary for the development of translational research projects.

1) Bordeaux Biothèques Santé CHU de Bordeaux (BBS) (Medical Director: Dr Pellegrin Isabelle): BBS is a biobank that stores biological samples for medical or scientific use. This biobank provides a confidential, secure and qualitative short-, medium- or long-term preservation. These samples are linked to demographic, biological or clinical data concerning the patient along with data specific to the sample and its traceability. A more detailed presentation is provided in Annex 5 (p 131).

2) Unité de Soutien Méthodologique et Recherche (Methodological unit) (Medical Director: Pr Rodolphe Thiebaut**):** This clinical trial unit is composed of 25 people, has been ISO 9001 compliant since 11/2014, and is a member of EUCLID (EUropean CLInical trials & Development). This unit has a strong expertise in clinical trials (151 ongoing trials).

4.7. Overview of the FHU partners

1) Metrics

	Number	Comment
Clinical department	15	11 clinical / 4 para-clinical
Research department	11	
Publications (2012-2015) IF>20	9	Within the scope of the FHU
Overall estimation of SIGAPS score (2012-15)	19170	
HDR	Approximately 60	
National PHRC	15	
Regional PHRC	20	
Patents	19	Licensed: 3
ANR	16	

ERC	4	
ATIP-AVENIR	2	
Visiting professor	1	
Reference center (clinics)	2	
Competence center (clinics)	10	
LAbEx directly involved	2	One CLU
Start-up	3	
SIGREC	472	

2/ Already established collaborations

The FHU is already based on long-lasting collaborations between all the partners as illustrated in the table hereafter. The cross sign indicates ongoing and/or past collaborations between partners within the FHU. By collaboration, we mean established studies with already published papers 1) combining at least two departments **and** 2) based on the theme "inflammatory disorder".

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Rheumatology (1)	0	x	x		x	x	x	x			x	x		
Internal Medicine (2)	X	0	x	x	x		x	x	x	x	x		x	x
Gastroenterology (3)	X	x	0		x	x		x			x	x	x	
Vascular disease (4)		x		0	x					x	x			
Dermatology (5)	X	x	x	x	0			x			x			
Diabetology/ nutrition (6)	X		x			0		x	x	x				
Pneumology (7)	X	x					0	x				x		
Paediatrics (8)	X	x	x		x	x	x	0	x	x	x			
Obstetrics (9)		x				x		x	0	x	x			
Nephrology (10)		x		x		x		x	x	0	x		x	
Immunology (11)	x	x	x	x	x				x	x	0			x
Bacteriology (12)	x		x				x					0		
Pharmacology (13)		x	x							X			0	
Neuroradiology (14)		x									x			0

5. Description and objectives of the FHU

5.1. Context justifying the structure of the future FHU

5.1.1. Scientific background justifying the FHU:

The past decade has witnessed a revolution in our understanding of the immune system and in our ability to develop safer and more effective immunotherapies for IDs. Currently, our society needs to be prepared to face the up-coming challenges of IDs and the questions that remain to be addressed. Interestingly, although IDs encompass a wide array of clinical phenotypes, many of the remaining questions are shared by different disorders. This observation emphasizes the need to change our current view of and/or approach towards these diseases. Until now, those complex diseases have been considered homogeneous entities defined by combinations of symptomatology, bedside observations, macroscopic imaging, and classical biochemical and histopathological measurements. Recent progress in genomics, molecular immunology and biotechnology, coupled with an increasing focus on translational research, is modifying our current way of thinking and bringing hope for the so-called precision medicine, which should be considered a first step of the current concept of personalized medicine. However, to reach these goals, several barriers must be removed. For example, asthma, inflammatory bowel diseases, rheumatoid arthritis, multiple sclerosis, and psoriasis should not be viewed as individual diseases managed by individual doctors from different sub-specialities (each having their own language) but rather as products of tissue inflammation. Thus, we consider that a transdisciplinary approach for IDs will be the cornerstone of future medical treatments for IDs. Central to this new approach for considering the ID problem will be a long-term, longitudinal view of research partners including, importantly, the patient.

5.1.2. Bordeaux: A long-lasting collaboration between several teams from clinical care to translational research regarding IDs:

Over the past 15 years, the Departments of Internal Medicine (Pr Pellegrin JL), Rheumatology (Pr Schaeverbeke T) and Immunology (Pr Blanco P) have established robust connections. Indeed, initial collaborations around the theme “lupus” has allowed the discovery of key pathways in human SLE pathogenesis, including the implication of type I interferon, CD8+ T lymphocytes, platelets and, more recently, the OX40/OX40L axis. Moreover, due to the systemic nature of lupus, different specialties, including nephrology and dermatology, have been implicated in these research projects. This group, which is composed primarily of physicians/scientists, has grown year after year and extended its area of expertise through the creation of a group working on IDs within the CNRS/UMR5164, the awarding of 2 ATIP/AVENIR teams (skin inflammatory disorders and immunology of multiple sclerosis), and the extension of original research to new models of IDs (i.e., scleroderma, vitiligo, and multiple sclerosis). By working primarily on human samples, the primary goal of this group is to relate the work as close as possible to human beings, and several already published basic works have been translated into clinical trials. In parallel, patient care culminated with the establishment of trans-disciplinary consultations for patients with some IDs and with the development of common educational programmes. However, we believe that this slowly growing process has reached its limits. Indeed, as mentioned in the first section of this chapter,

IDs should not be viewed as individual diseases but rather as a consequence of a common process, namely, tissue inflammation. Therefore, inflammation in other tissue should be incorporated in new research programmes. In addition, to be competitive at an international level, research regarding IDs needs to involve people with new expertise in biological and fundamental aspects of inflammation and immunology, as well as in bioinformatics or in system biology. One could also imagine reconsidering some of the scientific and medical questions from a philosophical point of view.
To illustrate our previous commitments on working on all of the aspects (from clinical trials to clinical research and basic research) of IDs, in Annex 6 (p 133), we provide a selection of key achievements (i.e., publications) conducted by the members of the FHU regarding IDs over the past 15 years.

5.1.3. The FHU: An approach to reaching the next level

The FHU will strengthen the existing connections while stimulating new collaborations and cross-field coordination within an integrated structure dedicated to a common medico-scientific objective: better management of patients with IDs starting at their very early stages in close connection with family doctors. This approach will be conducted in close connection with translational and basic research programmes while proposing high-level teaching and training activity. To do so, the clinical perimeter of the FHU covers almost the entire spectrum of IDs, and the selected research structures include groups specifically involved in the understanding of systemic, skin, lung, or neurological inflammation as examples combined with transverse structures including bioinformaticians and biostatisticians. Moreover, the University Department of General Practitioners is directly involved in the FHU to treat the early stages of the disease, assuming that they constitute a window of opportunity for specific treatments to allow long-term remission and a fertile ground for basic research programmes.

5.1.4. Coherence with the strategies of the hospital, the university and the "EPST"

The ACRONIM project is consistent with many objectives of our hospital and university.

For the hospital:

Four key strategic orientations were defined in the last hospital project:

- To reorganize itself to better respond to population needs
- To maintain excellence and a high-quality service level
- To emphasize its position as a referral hospital
- To strengthen cooperation and partnership with the territory (i.e., the Aquitaine region)

ACRONIM is definitely consistent with these key orientations:

- The health care organization proposed is defined to improve the coverage of population needs and the care of patients with chronic IDs.
- This project emphasizes the central position of the University Hospital of Bordeaux and of referral hospitals of the Aquitaine region regarding chronic IDs.
- The coordination of a large portfolio of medical specialities in terms of clinical research, partnership with university research units, and organization of medical education, provides the basis to maintain and strengthen excellence in clinical immunology and chronic inflammation.

- ACRONIM, developed in close cooperation/connection with the Health Regional Agency of Aquitaine and the Aquitaine region, has been built to 1) answer to health care organizations throughout the entire territory; 2) develop cooperation with young regional companies, particularly those supported by "Aquitaine Science Transfert investment committee", such as Novaptech or Aesia; and 3) to integrate the telemedicine regional project.
- ACRONIM will also correspond with the next hospital project, i.e., the development of out-of-hospital medical management, optimization of the territory hospital community, and complementarity between community medicine and the hospital.

For the University of Bordeaux:

Previously, the University of Bordeaux developed three primary domains of excellence in medicine: neuroscience, cardiology and public health. The recent creation of the SIRIC-BRIO (integrated structure dedicated to cancer research) is the first step in structuring cancerology. ACRONIM represents a unique opportunity to involve a significant number of individuals (from clinicians to basic researchers) in a translational research programme dedicated to IDs. ACRONIM will allow the following actions:

- To federate many medical specialities from the University Hospital of Bordeaux around a single mobilizing project, which focuses on research, care, organization and teaching regarding inflammatory and immune- mediated diseases. Approximately fifteen clinical specialities and eleven research units are directly involved in a single project.
- To develop a new cluster of research excellence at the University of Bordeaux. Many of the units involved in this project are well recognized in their own speciality at national and international levels. Their federation within the ACRONIM FHU will definitely emphasize their national and international visibility beyond each medical speciality. Such structure will allow participation in international grant proposals/programmes.
- To develop a true primary care research programme in close connection with the Department of General Medicine. These aspects, although of importance, are missing in many integrated structures. Nevertheless, providing our young collaborators in general practice access to MD/PhD programmes (a clear underdeveloped situation in France compared to other countries) is crucial.
- To develop unusual new collaborations within different components of the new Bordeaux University. These components include computer research (LABRI, INR), psychosociology, philosophy of science, immunology, medical imaging and medical units.
- To propose a high standard of education in inflammation by considering all aspects of this process. Inflammation involves studies of immunology, bacteriology, cell biology, and molecular biology.

For the Public Scientific and Technical Research Establishment (EPST):

Usually, translational research applies findings from basic science to enhance human health and well-being, as illustrated by the classical formulation "from bench to bedside". However, research is moving rapidly, and the development of many recent

targeted immunotherapies has demonstrated that major discoveries result, in fact, from close collaboration between scientist and clinician from "bench to bedside" and from "bedside to bench". The discoveries of auto-inflammatory diseases, inflammasomes, IL-1-dependent diseases and IL-1 inhibitors are most likely some of the best illustrations of the crucial importance of ad-hoc clinical observations to strengthen genetic and basic research programmes.
ACRONIM is structured to promote clinical and translational research and will provide a real opportunity to develop an ambitious translational research programme based on well-characterized cohorts of patients and collections of biological samples. The special interest in the early stages of IDs is certainly a major driving force to develop innovative studies from many points of view.

***For the regional institutions*:**
Aquitaine is a vast territory (41,300 km^2 or 15,949 sq mi) composed of five departments (Dordogne, Lot et Garonne, Pyrénées-Atlantiques, Landes and Gironde), and consisting of 3.3 million inhabitants.
Although the density of physicians is superior to the French average at the regional level, important discrepancies exist between the five departments. Important concentrations of physicians and hospital capacities are located in Gironde and Pyrénées-Atlantiques compared with the other three departments, where the medical capacities are extremely low and few GP and specialists are present. Thus, important challenges faced by the regional health authorities are having equivalent access to health care across the territory and limiting the cost of transportation.
The primary orientations of ACRONIM are consistent with a territory-based structure of health care, the study of environmental factors, and the possibility of preventive actions. These orientations are perfectly in line with the primary objectives of the Aquitaine region and the Health Regional Agency of Aquitaine (ARS). Conversely, the health care organization/design proposed in the context of the FHU ACRONIM has the benefit of close collaboration with the ARS and the Aquitaine region. This aspect is corroborated by the support letters written by Alain Rousset, president of Aquitaine, and Michel Laforcade, General Director of the ARS Aquitaine, provided in Annex 7 (p 135).

5.1.5. Articulation with the local invests programmes.
Several local investment programmes constitute a strength for the DHU. Six aspects are listed hereafter.

1) The i-Share cohort:
The Internet-based Students HeAlth Research Enterprise cohort (i-Share) is a cohort of 30,000 students in France (Bordeaux, Paris-Versailles Saint Quentin, and Nice) recruited over a period of 5 years and followed during 10 years. This cohort has been funded through the French Investment for the Future programme. The aim of this cohort is to study the well-being of the students and the factors associated with diseases. The students will be included once they have filed a first electronic case report form (eCRF). The following year, an appointment will be taken for clinical (blood pressure and body mass index measurements) and neuropsychological examinations. Extremely relevant information for the present project is already included in the baseline questionnaire; this information includes smoking habits, alcohol consumption, exercise, nutrition,

infectious disease history, family medical disease history, and stress. The cohort will constitute a unique useful tool to assess normal persons at risk of developing IDs (see WP1).

2) The LabEx TRAIL and BRAIN:
Nathalie Schmitt was recently awarded an ATIP/AVENIR grant for a project based on a study of effector T cell subsets in patients with multiple sclerosis. To examine whether the alteration of specific CD4 T cell subset is associated with specific types of CNS lesions in MS patients, she will established a collaboration with Pr Vincent Dousset (Neurocentre Magendie, Bordeaux University and LabEx TRAIL) and Pr Bruno Brochet (Neurological Department and LabEx Brain), who have extensive expertise in MRI in MS patients. MS activity can be assessed non-invasively with advanced MRI that is able to provide a much more detailed phenotype compared to the three-class clinical phenotype and sensitively quantifies the alteration of the blood-brain barrier that is associated with the inflammatory component of the disease. Furthermore, Pr Dousset is currently validating a more advanced MRI method called diffusion tensor imaging (DTI), which can provide indirect quantitative data reflecting tissue organization and microstructures such as ectopic germinal centre formation. By applying these most advanced MRI technologies in neuroscience, we expect to assess the CNS lesions of MS patients in unprecedented detail and to determine the correlation between the phenotype and function of the CD4 T cells and the type of CNS lesion. Moreover, the Bordeaux Neurocampus will constitute a unique place to interconnect the immunological disorders found in MS patients and their potential consequences from a purely neurophysiological aspect. In addition, Nathalie obtained funding through the IdEx Junior Chair Programme.

3) The Euskampus International Programme:
The Euskampus project is an Initiative of Excellence of the University of Bordeaux aimed at promoting international collaborations (i.e., Basque University and Bordeaux University). Patrick Blanco (Bordeaux) and Guillermo Ruiz Irastorza (Bilbao) are two leaders in lupus research in Europe. Therefore, these researchers decided to join their efforts to promote the emergence of projects with high benefits. Thus far, these researchers organized the first Basque lupus meeting held in Bayonne on the 5th of June 2015, and a French medical fellow is working on a medical thesis with patients from both cohorts. Soon, these researchers are planning to exchange students, collaborate on common projects, evaluate best practices in autoimmune diseases, and apply for European and international grants on behalf of Euskampus.

4) The LaBRI, Cluster of Excellence:
Advances in "-omics", imaging, and other advanced biomedical technologies in recent years have resulted in the exponential growth of biomedical data and have started the era of "Big Data" in health and biomedicine. The general goal of our research team is to develop methods to improve the acquisition, analysis, modelling, synthesis, and interaction with these data. The data manipulated by this team represent a wide spectrum from genetic data to 2D or 3D images and video. This team will be a transverse support for many of the research projects from the clinic to basic science.

5) **Aquitaine Science Transfert:**
This company is dedicated to the Society for the Acceleration of Technology Transfer in the Aquitaine Region (SATT Aquitaine). Created with the Programme of Future Investments, its objective is the valorisation of academic research and improvement of the process of technology transfer to companies. This company acts on behalf of the University of Bordeaux, Montaigne Bordeaux University, Sciences Po Bordeaux (Institute of Political Studies), Bordeaux INP, Bordeaux Science Agro, CHU of Bordeaux, Bergonié Institute, ESTIA (Superior School of Advanced Industrial Technologies), UPPA (University of Pau and Adour), CNRS and INSERM. Aquitaine Science Transfert is the interlocutor of the researchers for protection, maturation and valorisation of research results and helps companies to meet their requirements of innovative solution development in an efficient way. Aquitaine Science Transfert contributes to increasing the competitiveness of French companies and promotes job creation and wealth in the region. As mentioned later, several aspects of projects have been conducted in close collaboration with Aquitaine Science Transfert. To illustrate this collaboration, a support letter (for one project) is provided in Annex 7 (p 135).

6) The LabEx Vaccine Research Institute (Director: Pr Yves Levy):
Through the Biostatistics/Bioinformatics Division led by Pr Rodolphe Thiébaut, this institute is devoted to the development of vaccines specifically against HIV and Ebola. From the projects performed in this LabEx, methods for the integration of high-dimensional data generated through microarray, NGS, CYTOF have been developed or are under development. Furthermore, the study of the inflammatory response to the vaccines and the impact of the inflammatory status on the vaccine response are topics that will fit within the FHU project.

5.1.6. Access to source materials (clinical data and biological resources):

Clinical data:

- **For the out-of-hospital patients:**

As will be explained later in the WP2, the organization of the FHU will involve a structure named "territorial support platforms", where patients identified by any general practitioner from Aquitaine that is collaborating with the FHU will be notified if they present an ID. The territorial support platforms will create a medical record for each of the patients; this record will be integrated (with the authorization of the patient) into the database of the FHU. This medical record will contain demographic information, mail exchanged by GPs and specialists, and eventually data entered by clinical research assistants if appropriate.

- **For the patients currently followed in the University Hospital:**

Specific electronic records have been developed within the computerized medical system of the hospital. These records allow the creation of a complete database for in-patients and out-patients followed at the CHU. As an example, a database of more than 1000 rheumatoid arthritis patients and more than 700 spondyloarthritis patients is already available, including a complete medical history record and disease activity scores at each visit. Similar databases are currently being developed for systemic lupus erythematosus, systemic sclerosis (250 systemic sclerosis patients followed at the CHU

of Bordeaux) and several other IDs. These databases will be transferred to the FHU and extended to all IDs.

Biological resources:
A biobank (Centre de Ressource Biologique) was created by the Hospital of Bordeaux a couple of years ago (Annex 5, p 131). Different pre-existing collections of samples (stored in different areas) have been moved to the CRB of the CHU of Bordeaux. All collections developed in the context of the FHU will be stored in this unit.
For the out-of-hospital patients, access to biological resources will depend on the nature of the specimen. Blood specimens will be collected via the closest hospital.

Legal, ethical and privacy considerations:
The biomedical research project, data management and storage conditions, anonymization method, information notes, consent forms and biological sampling for research declaration will be addressed to the University Hospital of Bordeaux for sponsoring and submission to specific authorities, namely, the ethical committee (Comité de Protection des Personnes Sud-Ouest et Outremer) and CNIL (Commission Nationale de l'Informatique et des Libertés).

5.1.7. Academic and private partnerships:

Existing partnerships:

Academic partnerships:
- Aquitaine region
- Health Regional Agency of Aquitaine (ARS)
- University of Bordeaux
- University Hospital of Bordeaux

Public-private partnerships:
1) Local start-ups
- Novaptech: development of aptamer-based tools for analytical and diagnostic applications
- Cellomet: development of proteomic and metabolomics
- Aesia: on-line video game publisher based in Bordeaux and previously involved in the development of serious games for addiction prevention and treatment

2) Pharmaceutical laboratories involved in ID research
As a non-exhaustive list, we can cite Abbvie, Biogaran, BMS, Hospira, MSD, Novartis, Pfizer, Roche, and UCB.

Partnerships to be established:

Academic partnership:
- Aquitaine Health Insurance System (Caisse Régionale d'Assurance Maladie d'Aquitaine): The goal of this system is to work on medical data regarding

patients suffering from chronic inflammatory diseases, for instance, to evaluate adherence to treatment by reimbursement of the drug.

Public-private partnership:

- AXA-prévention: Prevention of disease and early detection are major goals for an insurance company. We will develop a partnership with AXA to not only obtain funding from the AXA foundation but also develop our health care organization model and implement prevention actions.
- ESCEN (Ecole Supérieure de Commerce et d'Économie Numérique/Web Business School – Bordeaux): ESCEN is a web business school based in several cities in not only France but also London, Montreal, San Francisco and Singapore. ESCEN is involved in all aspects of e-commerce and includes an e-health department. We will develop collaboration with this school to offer practical training for their students.
- Safisis (Souston, Landes, France): This biotechnological company specializes in the development of natural ingredients using microbiological methods, yeasts and bacteria. Some of the partners of the FHU are in close contact with this company to develop prebiotics and probiotics.

5.2. Development potential of the FHU

5.2.1. Medico-scientific background

The natural course of an ID can be divided into 5 phases:
Genetic predisposition: Over the past decades, genetic factors have been extensively studied in most IDs due to the emergence of new technologies for genotyping. Many genetic factors are shared by different IDs. Some factors are highly prevalent in the general population, such as MHC class II alleles associated with rheumatoid arthritis. Therefore, studying at-risk populations that are genetically or epidemiologically predisposed (i.e., first-degree relatives of patients) is crucial for understanding the determinants of disease development in at-risk patients.
Preclinical stages of the disease: For several IDs, if not all, biological auto-immunity (auto-antibodies specific for the disease) precedes the occurrence of the first clinical manifestations for months or years, depending on the disease. Intriguingly, not all subjects presenting with such biological abnormalities develop the clinical disease. These two first points illustrate the fact that the exposure of genetically predisposed subjects to an environmental factor can lead to an immunological conflict several years before the occurrence of the disease, indicating that a second hit is necessary to induce the clinical stage of the disease. This aspect underscores the facts that 1) a preclinical screening is feasible if at-risk subjects can be identified (first-degree relatives of patients or subjects exposed to an identified environmental factor as examples) and 2) preventive measures may be set-up before disease onset. However, a body of work needs to be conducted to understand the mechanisms involved in the very early stages of the diseases and particularly how genetic predisposing factors (single-nucleotide polymorphisms as an example) would modify the immunological response towards environmental factors including various pathogens. This aspect constitutes the core of

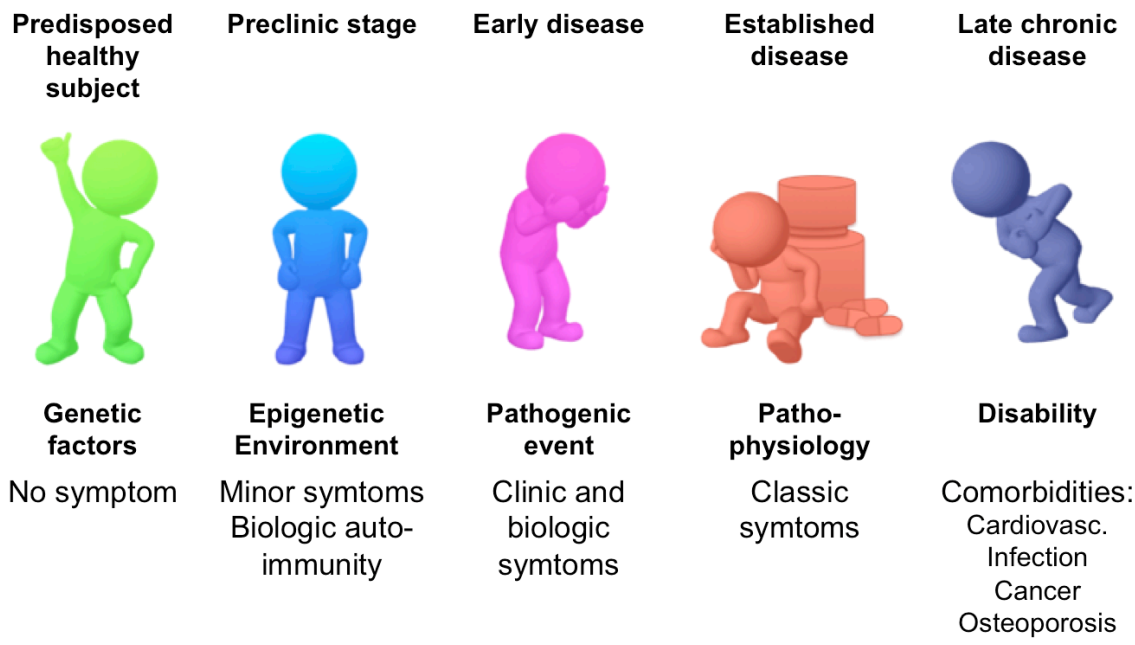
the WP1 by conducting studies in symptom-free individuals having a biological autoimmune trait.

Early stages of the disease: A genetically predisposed individual exposed to a specific environmental factor will eventually develop symptoms that characterize the very early stage of a chronic ID. Remarkably, many studies (independent of the phenotype of the ID) have shown that early initiation of an optimal treatment strategy can limit the impact of the evolution of the ID and keep patients at work. Therefore, having access to early stages of the IDs appears of tremendous importance for therapeutic purposes and for translational research. The ability to work on early stages of IDs requires a reorganization of our health care system and constitutes one of the aspects addressed by our FHU in close collaboration with the Regional Agency of Health, the Department of General Practitioners, and the Regional Council of Aquitaine (WP2).

Established disease: The disease is fully established and evolved to chronicity in the final period. This period remains a challenge for clinicians, although many new treatments have been discovered over the past 15 years. Several challenges of this stage include improving the efficacy and tolerance of the treatment by accurate drug monitoring, improving treatment adherence of the patient, adherence to recommendations from the doctor, predicting flare-ups of the disease and improving rapid access to specialists in cases of disease flare-ups, considering the complexity of systemic diseases through interdisciplinary consultations, limiting the social cost of IDs, and finding new therapeutic options and targets. All these aspects will be addressed in WP3.

Long-term complications: Finally, chronic inflammatory diseases share the emergence of late complications collectively grouped under the name “comorbidities”. These complications include cardiovascular disorders, infectious complications, osteoporosis and cancer and are responsible for the increased mortality observed in IDs. Understanding the pathogenic pathways that promote/enhance these disorders represents a major challenge as it could permit the proposal of appropriate drugs that can block/slow the development of ID-associated long-term complications. This aspect will be addressed through the study of implications of newly described metabolites and microparticles in the perpetuation of chronic low-grade inflammation (WP4).

The cartoon below depicts the different steps in the development of an ID and constitutes the streamline for the description of the FHU.



5.2.2. Care, research and teaching projects

The entire project is divided into 5 different WPs described hereafter. For each WP, a brief rationale is provided to fully provide the context and to highlight the project.

WP 1	The preclinical stage of the disease	WP teams:
		Epidemiology (ISPED) Dpt General Medicine (DMG) Clinician specialists LABRI / INRIA Philosophists

Rationale:

Increasing evidence suggests that many IDs, including systemic and organ-specific ID have a "preclinical" period of development. During that stage, disease-related biomarkers, particularly autoantibodies, develop and evolve, initially in the absence of or with mild clinical signs and symptoms of tissue injury. Therefore, individuals who develop IDs have an initial preclinical stage of biological benign autoimmunity that will evolve later on into clinically apparent disease and tissue inflammation. However, not all individuals with a biological autoimmune trait develop a disease, and the reason is unknown. A genetically predisposed patient, develops preclinical characteristics (such as specific auto-antibodies), when exposed to an environmental stimulus, but a second "hit" seems to be necessary to trigger the clinical phase. Understanding this observation appears to be of tremendous importance as it could pave the way towards preventive treatments of ID. This aspect constitutes one important question that will be addressed by the FHU, and that will be studied through a work within the I-share cohort and through a close collaboration with the obstetrics department, which follows many pregnant women with biological autoimmune traits but without any established disease. In addition, Thomas Pradeu, a philosopher of sciences, will be associated with this project to analyse conceptual questions addressed by the management of the preclinical stage of the diseases.

Aim 1: Projects within the I-Share cohort

Our goal is to investigate whether individuals at increased risk of developing IDs (ie patients with a biological autoimmune trait, and familial history of ID) are characterized by variations of their immune response against different stimuli that are considered to reproduce environmental factors, and/or characterized by a different microbiota signature compared to normal individuals. We hypothesize that we will observe differences between the two populations in terms of immune responses and/or microbiota signature and that this variation could differ from individual to individual for the same stimuli, and differ between individuals with different biological autoimmune traits. Finally our long-term follow-up will allow us to work on the identification of biological and/or microbiota signature that will be predictive of the evolution of a biological autoimmune-positive trait into a bona fide clinical disease. This aspect constitutes the groundwork to explore the relative contributions of genes and their environment to immunological processes. (Description of a more detailed project can be provided upon request).

Aim 2: Projects in connection with the obstetric department

Pregnancy has both short-term effects and long-term consequences for women who have an ID or only autoimmune biological abnormalities. We plan to focus on the role of environmental factors in the development of these pregnancy-associated disorders, including miscarriages. Half of miscarriages are caused by chromosomal or structural abnormalities. Other known causes of miscarriage include infections, immune system abnormalities and hormonal irregularities with a likely high impact of interactions of

both environmental and genetic risk factors. Interestingly, based on our long-term collaboration with the obstetric department, we have noticed that a significant proportion of pregnant women who develop recurrent miscarriages are characterized by the presence of circulating autoantibodies (primarily anti-nuclear antibodies with or without specificity, and anti-thyroid antibodies). This population of patients in combination with the I-Share cohort will be of tremendous help to build research programmes to: 1) establish the effect of the environment on the development of these unresolved issues, 2) establish a link between autoimmune biological abnormalities and recurrent miscarriages, and 3/ characterize the mechanisms involved in such observations through additional fundamental studies.

Aim 3: Philosophical considerations

The definition of illness and health is a crucial question, for philosophers and medical doctors. Classically, illness has been defined as the opposite of health.However, when considering at-risk subjects, or the preclinical stage of the disease (biological abnormalities without clinical expression), should one talk about disease?

When does a disease start? Is a therapeutic intervention (with possible iatrogenic risks) acceptable in the preclinical stage? With leading immunologist Eric Vivier, Thomas Pradeu has suggested the “discontinuity theory”, which states that effector immune responses are due to sudden modifications in the body. On that basis, we will collectively aim at determining whether significant phenotypic changes in the lives of individuals (e.g., puberty, pregnancy) might constitute important early steps in the onset of autoimmune diseases but remains physiological in a majority of cases. Do we need to wait for a substantial phenotypic change to speak about illness? Where is the cursor position? Does it depend on the level of risk represented by the potential severity of the disease, or its probability, or the risk of the preventive medical strategy?

Addressing such questions in a manner that articulates medicine, biology, and the humanities will constitute another major originality of the ACRONIM project.

WP 2	The early stage of the disease	WP teams:
		DMG + Clinician Specialists. + ARS LABRI / INRIA / INSERM U897 UMR/CNRS 5164 / INSERM U1045 ATIP/AVENIR –INSERM U1035 USC EA 3671

Rationale:

The backbone of the DHU is to focus on early stages of inflammatory diseases to: 1) improve the management of the early stages, considering the fact that early proper management will have positive impact on the long-term outcome, and 2) investigate the early pathogenic events governing the appearance of the diseases.

Until now, the standard for the management of inflammatory disorders, independent of the phenotype, is the involvement of the general practitioner primarily in disease detection based on symptoms described by the patients. Then, the patient is often referred to a specialist for diagnostic confirmation, prognosis assessment and first treatment prescription. The most severe forms of diseases are referred to the hospital. Depending of the availabilities of the specialists in private practice or at the hospital, this first step between the first symptom, the formal diagnosis, and the first specific therapy can take up to 6 months. Interestingly, several IDs in their early stages offer a phase called the “window of opportunity” where appropriate treatments can induce long-term remission easily compared to established diseases.

As an example, in rheumatoid arthritis, several groups have shown that a close relationship exists between the chance to achieve and to maintain remission with the first line drug and the time lapse between the first symptoms and the treatment onset. In the French cohort ESPOIR, the time to access a rheumatologist is the primary obstacle to apply the international guidelines in newly diagnosed RA. This time can be viewed as a lost chance for the patient to have access to an early effective treatment. This aspect will affect not only the course of the disease but also the societal cost.

The early stage of IDs is thus a key period to set up the treatment and the follow up and is a key period for both clinical and translational research to evaluate new therapeutic strategies and to investigate environmental factors or prognostic biomarkers. Finally, the Aquitaine region offers a large diversity of environments (large cities, and rural areas with vineyards, farming, forests, seaside, and mountain) that provide a unique opportunity to investigate environmental factors.

Aim1: Design a new health-care organization framework

In close collaboration with the ARS (Health Regional Agency) of the Aquitaine region, we have designed a new organization to facilitate the access of general practitioners to current recommendations and referral specialists according to the symptoms presented by the patients.

Efforts will be focused on a few breaking points:

- Disease onset
- Loss of efficacy of therapeutic in established disease
- Rapid access to University Hospital of severe forms of disease

This aim implies the following goals:

- To improve the identification of ”red flags” that justify the rapid requirement of a specialist
- To provide rapid and simplified access, either physical access or remote access

via telemedicine tools, to specialized structures.

The structure of this organization, as summarized in figure 1, will be composed of the following members:
1) Territorial support platforms (already created)
2) A regional coordination unit (to be created)

Territorial support platforms:
Distributed throughout the Aquitaine region (one or two for each department), these platforms will be managed by general practitioners and health professionals trained in health coordination. These platforms will answer promptly to any claim of general practitioners in the case of suspicion of relevant IDs. In the case of an easy problem that could be resolved by the application of a simple recommendation, a reference framework will be given to the practitioner. If specialized advice is mandated, then the platform team will propose to the practitioner to organize a prompt appointment with a referent specialist. With patient permission, a medical record will be created, facilitating the follow up of the patient, and ensuring that the submitted problem has been solved. This medical record will collect mails and relevant information related to the event.
The territorial support platforms will also identify patients corresponding to inclusion criteria for ongoing research projects. The patients will be informed and a clinical research assistant will be connected to each qualifying patient. Three types of studies will be conducted: epidemiological studies, translational research and clinical trials.

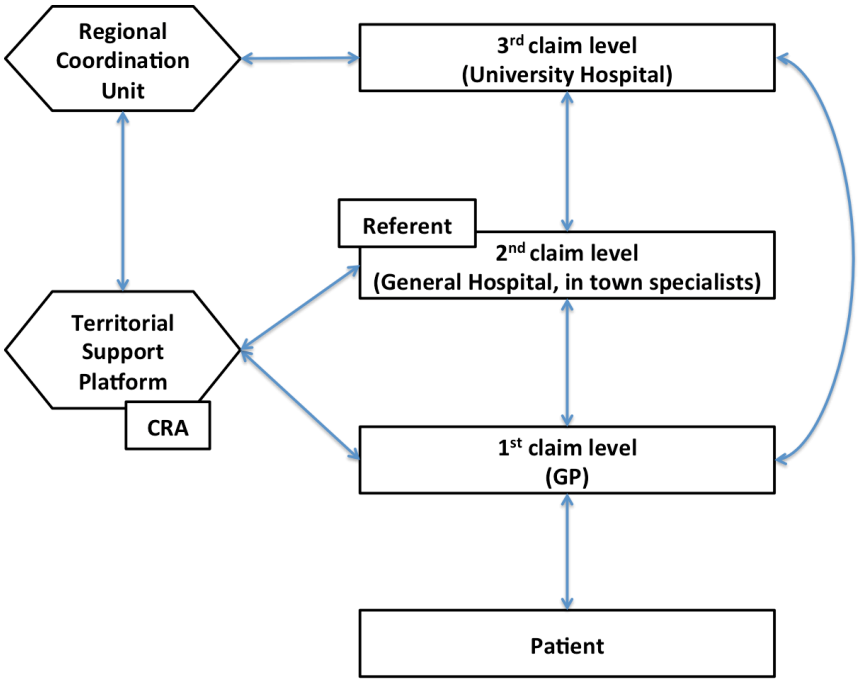
Regional coordination unit:
This unit will include a medical practitioner and a secretary. This unit will have the following responsibilities:

- General coordination of the project
- Establishing referent frameworks and providing recommendations
- Transmitting referent frameworks to territorial supply plateforms
- Formation of resource persons in territorial support platforms
- Making the link with the 3rd claim level
- Making the link with the clinical research and translational research project within the DHU

This organization is a central aspect of the project, and can be considered as:

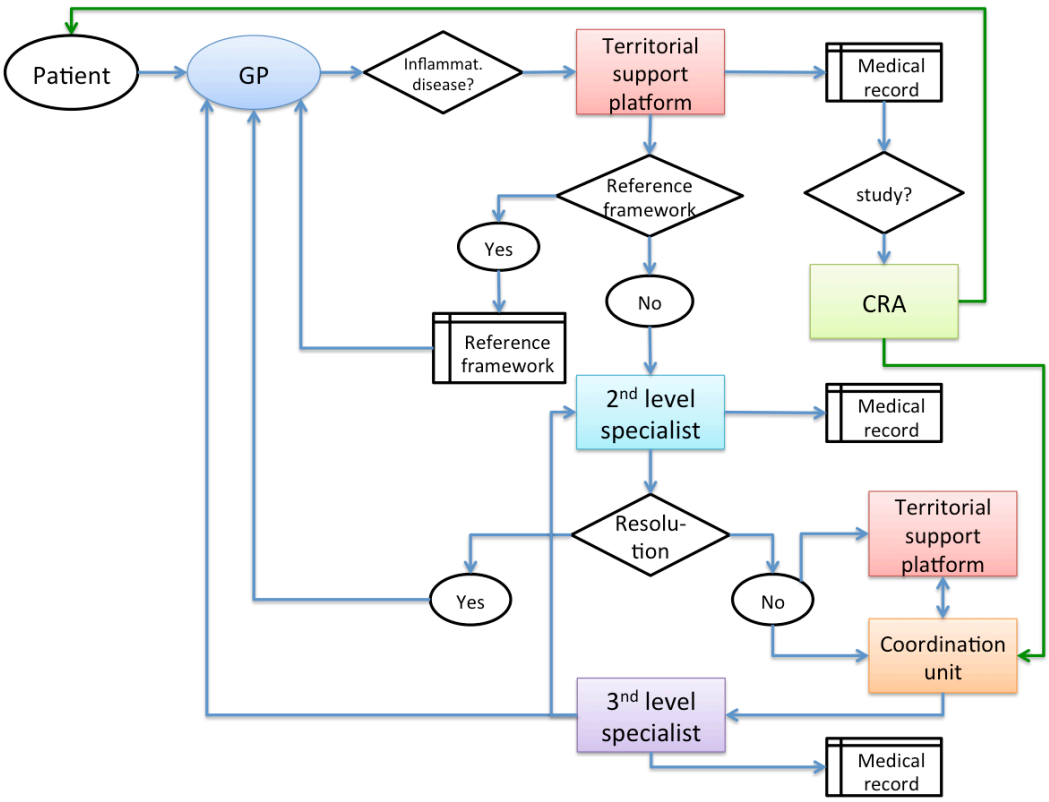
- A tool to facilitate access to care at a territory level and to improve quality of care
- A tool designed to act as a support and to allow the alliance between the patient and the GP to be the core of the health-care system
- A permanent interlinking and overlapping of care, research and training, to facilitate clinical and translational research, and ameliorate patient health
- A new health care organization model, that will be evaluated by the Health Regional Agency in term of efficacy and cost-efficiency
- A new model of the relationship between patients and the health-care system, GP and specialists, and specialists and other specialists, that will be evaluated from a sociological point of view.

Figure 1: Health organization within the DHU



(GP: general practitioner; CRA: clinical research assistant)

Figure 2: Itinerary of a patient within the DHU



(GP: general practitioner; CRA: clinical research assistant)

Aim2: Screening and follow up of patients at risk of developing an ID
For different IDs, the following framework will be set up:

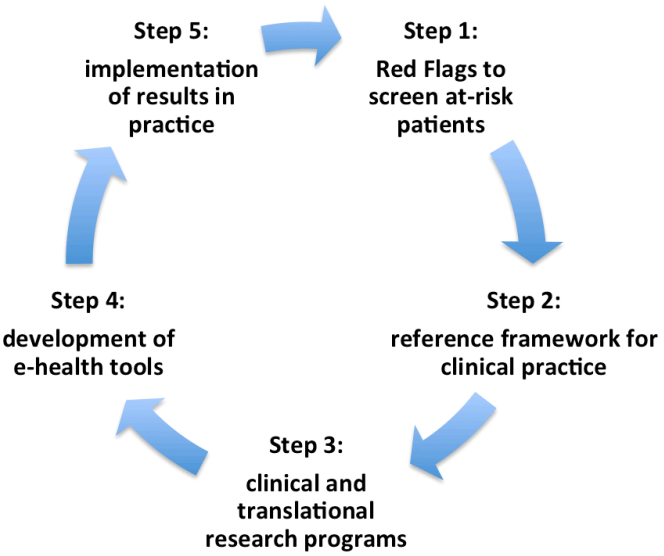
Step 1: Identification of "red flags"
A core set of clinical and/or biological symptoms suggestive of early ID manifestation will be defined with each subspecialty and GP as so-called "red flags" to identify at risk patients easily in daily practice.

Step 2: Establishment of reference frameworks
Reference frameworks will be established by specialists and reference GP to define the check-up list to be performed by the GP, and to propose of typical follow-ups to be scheduled according to the clinical situation. A specific medical record will also be designed, and biobanking of blood samples will be performed for further investigations.

Step 3: Design of clinical and translational studies
For each ID of interest, the scientific committee will be in charge of defining a research program: epidemiological studies, clinical and translational studies, clinical trials…

Step 4: Brainstorming regarding e-health tools development to promote home follow-up of patients
The conventional follow-up of patients with chronic IDs has many limitations. The consultations with specialists are usually scheduled in advance, and the specialists most often miss the period of disease activity. In the case of disease flare-up, treatment adaptation is often delayed for many reasons e.g., time for the patient to request and to obtain a consultation or, discordance between patient complaints and clinician findings at the time of the consultation. We will work with different partners (such as Novaptech) to create user-friendly devices with automatic transmission by smartphones or mail to follow biological parameters at home.

Step 5: Implementation of results in daily practice
Any results obtained from these studies will be later transferred into practice using the teaching organization of the FHU.



To illustrate this aspect, we will use early systemic sclerosis as the model. A similar work is in process for type 1 diabetes screening (Pr Vincent Rigalleau) but is not detailed here. However, this project is available upon request.

Taskforce 1: Screening and follow up of patients at risk of systemic sclerosis (Leaders: Marie-Elise Truchetet, Joël Constans)

Clinical screening: Late Raynaud's phenomenon as a "red flag"
While Raynaud's phenomenon is an extremely common and benign symptom in young girls after exposure to cold, late onset Raynaud's phenomenon is less frequent and strongly associated with the risk of developing systemic sclerosis within few years. Patients with late onset Raynaud's phenomenon, auto-antibodies and/or capillaroscopic abnormalities have a risk of developing definite systemic sclerosis of approximately 25% at one year, 50% at two years, and 90% at five years.
Thus, the identification of patients complaining of Raynaud's phenomenon that started after the age of 30, will be proposed to general practitioners.

Fine characterization and follow up:
These patients will be addressed to a referent to undergo the following procedures:

- A fine clinical examination to look for minor symptoms suggestive of scleroderma (i.e. digital ulcers or scars, puffy fingers, telangiectasia, short breath, and dysphagia or heartburn…)
- A blood screening for auto-antibodies and biobanking for further investigations
- A capillaroscopy.

Other tests could be performed depending on the results of the physical examination.
Preventive measures will be given to the patients.
An annual survey will be organized.

Screening for environmental factors:
A Clinical Research Assistant will interview the patient regarding environmental exposure to nutritional, housing, occupational and professional factors (such as silica, fine particles, solvents, pesticides, and cold exposure to cold). The same interview will be performed with controls matched for sex, age, and housing area). This aspect will be performed in close collaboration with the INSERM unit U605

Clinical trial:
Considering the high proportion of severe forms of systemic sclerosis and the lack of efficient treatments in established systemic sclerosis, the development of preventive treatments could be a major objective. Because a platelet-induced endothelial dysfunction has been identified (manuscript in prepararion) in early systemic sclerosis, we will propose that the patient is included in a placebo-controlled clinical trial to investigate the potential preventive effect of a platelet anti-aggregant (clopidogrel). This trial, named PSSIT, is currently being reviewed as a regional PHRC.

Translational research for biomarkers of risk to develop systemic sclerosis and specific biomarkers for specific organ's damages (lung, kidney, pulmonary hypertension…):
At inclusion and during the annual follow-up, blood specimens will be collected for

subsequent tests for biomarkers (e.g. fine specificity antibodies, circulating microparticles, and cytokines (TGF-beta)).
Patients included in the studies will be followed annually and at least one annual consultation will be scheduled by the territorial support platform, in charge of the specific medical record.
The data will be analysed by bioinformaticians, who will combine clinical data, environmental data, biological data, and biomarkers.

Aim3: Microbiota and inflammatory diseases

Rationale:
Metagenomics consists of describing the genetic biodiversity of an environment by sequencing all the genetic material it contains. This type of analysis is particularly valuable for circumventing the limitations of conventional culture-based microbiological methods, which identify only those organisms amenable to culturing. Metagenomic analysis is indeed crucial to the investigation of the gut microbiota, as over 80% of DNA sequences identified in faeces are from uncultured anaerobic bacteria.
In addition to its long-established role in digestion, the gut microbiota plays a major role in educating the immune system. Axenic animals (germfree animals raised in a completely sterile environment) have smaller Peyer's patches, fewer mesenteric lymph nodes and fewer CD4+ T cells, γδ T cells, and dendritic cells compared to animals harbouring normal gut microbiota. The spleens of germfree animals also contain fewer CD4+ T cells and have fewer and smaller germinal centres, indicating that the gut immune system affects the development of the entire immune system. In germfree animals, gut colonization by filamentous bacteria partially restores the T- cell population, suggesting that these bacteria may be required for immune system maturation.
Gnotobiotic animals are germ-free animals exposed only to those bacteria that are under study. Investigations of the immune responses of gnotobiotic animals have shown that the gut microbiota exerts a direct influence on the orientation of the adaptive immune response. Some bacteria (such as *Faecalibacterium prausnitzii*,) can induce FoxP3 expression by naive T cells, which then differentiate into regulatory T cells (Tregs), promoting immunological tolerance. Gnotobiotic animals harbouring these tolerogenic bacteria are particularly vulnerable to the introduction of enteropathogenic bacteria into their food but exhibit spontaneous resistance to the induction of ID such as experimental arthritis or experimental autoimmune encephalitis (EAE). In contrast, filamentous bacteria promote the differentiation of CD4+ T cells and Th17 cells. Gnotobiotic mice harbouring filamentous bacteria are resistant to enteropathogens but highly susceptible to experimental arthritis and EAE. Thus, the normal gut microbiota contains both tolerogenic bacteria and proinflammatory bacteria. Thus, a simple gut microbiota imbalance involving a decrease in the tolerogenic flora or an increase in the proinflammatory flora, may promote the development of an ID.
Most of the metagenomic studies performed for medical purposes have focused on describing the bacterial flora (or microbiota) of the gut in both healthy individuals and patients with various diseases. Interestingly, dysbiosis (abnormal microbiota

composition or abnormal amounts of some of the bacterial species) has been documented in patients with Crohn's disease and ulcerative colitis. In addition, dysbiosis is characterized by a lack of microbiota diversity, due to the disappearance of some bacterial species.

Taskforce 1: Gut Microbiota in early ID

Thus far, most of the studies examining gut microbiota under pathological conditions have been conducted in chronic stages of diseases. Therefore determining the potential pathogenic role of the dysbiosis is impossible.

Our aim is to evaluate the gut microbiota composition in early stages of Crohn's disease and ankylosing spondylitis, before any immunosuppressive treatment and to re-evaluate this microbiota after 3 months of different treatments (conventional immunosuppressive treatments such as azathioprine or methotrexate or biologics such as TNF-inhibitors), to assess whether a microbiotal signature of these disorders exists before any treatment and to analyse the exact impact of the treatment on the microbiota.

Tasforce 2: Pulmonary microbiota in ID

Cystic fibrosis (CF; OMIM 219700) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance gene (CFTR); this disorder affects the exocrine glands of the respiratory, digestive and reproductive systems. Cystic fibrosis is responsible for abnormal mucus secretions on different mucosal surfaces, primarily on the respiratory and digestive tracts. The consequences are recurrent lung infections (most often due to *Staphylococcus aureus* or *Pseudomonas aeruginosa*), leading to progressive respiratory deficiency, pancreatitis, hepatitis and gut obstruction, with a lethality ranging from the first year of life to the third or fourth decades.

Low-grade chronic inflammation has been observed, as well as a dysbiosis affecting both the airway and the gut microbiotas, characterized by a decrease in the bacterial diversity. Our hypothesis is that antibiotic treatments given during recurrent episodes of respiratory infection contribute to dysbiosis worsening, promoting infectious risk and leading to a vicious circle of infection and treatment.

We aim to follow the airway and faecal microbiota simultaneously in a cohort of young children followed for cystic fibrosis in the paediatric department of the University Hospital of Bordeaux and to correlate dysbiosis to the number of instances of antibiotic exposure of these children.

Taskforce 3: Self and non-self-revisited from a microbiota point of view

The knowledge of the gut microbiota also addresses some philosophical questions. If we consider that our "self" is limited to our own eukaryotic cells, then we are organisms composed of approximately 10^{13} cells, with a genome composed of approximately 25,000 genes (no more than an helminth). However, our gut microbiota contains 10^{14} bacteria (thus, according to some accounts, 10 times more prokaryotic cells than all our own eukaryotic cells), and the sum of different genes contained in these symbiotic or commensal bacteria represent about 350,000 gene, 150 times the number of genes exhibited by our own genome… Many of these genes are essential for our metabolism, producing vitamins, essential amino-acids or lipids… This information demonstrates the close symbiotic relationship between our microbiota and us.

However, in addition to these metabolic functions, we observed previously the crucial role for the gut microbiota in the education and orientation of the immune system. This observation has led to the “microbial self” concept. Our gut microbiota and our immune system may result from a process of adaptive co-evolution: our immune system (Toll- and NOD-like receptors, HLA system) restricts our microbiota, which represents a first obstacle to colonization by enteropathogens and participates in the differentiation and activation of our immune responses. This possibility led to the idea that we are supra-organisms, our “self” being the superposition of our eukaryotic component and our microbiota.

WP 3	The established disease	WP teams:
		DMG, Clincian Spe., ARS LABRI / INRIA / ISPED LABRI / INRIA / INSERM U897 UMR/CNRS 5164 / INSERM U1045 ATIP/AVENIR –INSERM U1035 USC EA 3671

Rationale:

More than 80 IDs have now been identified. GWAS has identified a striking overlap of genetic loci across IDs. In this context, distinct diseases from a phenotypic point of view appear to share common pathogenic key events. Therefore, classification of diseases according to their biological underpinnings will guide more precise targeting of new therapies, and molecular characterization of therapeutic responses will allow a clearer understanding of human biology and provide direction for therapy improvement. Moreover, with regard to drug development, an additional practical consideration is the immunogenicity of biologic agents, exacerbated with intermittent administration, which reduces efficacy and increases adverse side effects. Although not yet achieving consensus approval, the monitoring of biotherapy could be of tremendous help to better assess the therapy response and to reduce the costs of treatments.

Aim1: Better patient care through an interdisciplinary approach, and a unique combination of expertise

Taskforce 1: Interdisciplinary consultation

Most, if not all of IDs are complex multisystemic disorders, that may require a multidisciplinary approach to address all medical aspects of the patients and to fully optimize their care. In the context of the health care organizational framework proposed within the FHU, the third level of specialized consultation is the care in Bordeaux University Hospital. Since 2013, we have developed a multidisciplinary care team dedicated to SLE, where patients with complex SLE cases are evaluated by a ”lupus clinic” composed of different specialists including nephrologists, dermatologists, rheumatologists and internal medicine physicians. All team members are specialized in IDs. This multidisciplinary team provides the full range of health care services needed for optimal and global treatment for SLE aspects, and offers both consultative services and long-term management.

Our objective is to extend this approach to develop an ID clinic where the patient could be evaluated the same-day by different specialist providers with expertise in IDs, such as ophthalmologists, gastroenterologists, gynaecologists, neurologists or nutritionists. The principal interest of this clinic will be to ensure convenience for consultation addressing all aspects patient conditions. Moreover, the ID clinic can provide care that goes beyond diagnosis, focusing on special needs that are tailored by individual disease complexity. For instance, patients could be offered cardiovascular risk factors, osteoporosis prevention, or vaccination. During pregnancy, a multidisciplinary approach will offer a superior chance of improved pregnancy outcome. In addition to providing direct medical care when needed, members of the ID clinic health care team will also encourage patients to learn about their disease and disease management. This focus on educational programmes and patient self-management will help patients to

better understand their ID, how the disease changes over time and how to adapt to these changes, to improve their quality of life. Additionally, the ID clinic could offer the opportunity to enrol patients in a registry and to provide easy access to clinical trials and translational research facilitated by on-site clinical research coordinators. The overall idea of a multidisciplinary approach for ID offers the opportunity to provide the most comprehensive treatment plan for our patients. We anticipate that this approach could reduce the overall number of consultations and therefore the societal cost.

***Taskforce 2*: Child/adult transition consultation**

Adolescents with chronic conditions must be prepared for transitioning from the paediatric to the adult health-care system. Ideally, the transition should be a purposeful, organized, and coordinated process involving the youth, family and the health-care team, with the goal of optimizing health, avoiding morbidity and facilitating personal development. This process of transition is becoming increasingly recognized as an important area for clinicians, researchers, and policy-makers to address. In an effort to improve the transition process and ultimately the outcome of young adults with childhood-onset chronic diseases, over the past few years in Bordeaux, we have developed an organization dedicated to facilitating this step. Most of the time, management of the teenagers and young adults is first discussed between paediatric and adult health care clinicians, and common (or shared, mutual or joint) medical examinations are organized. When patients are feeling confident with the adult team, a definitive transfer is scheduled, with additional visit in the paediatric department sometimes occurring a few weeks later. However, we believe that this process has still room for improvement. We identified a few problems to address:

- medication adherence, notably with effects of chronic prednisone use on their body image;
- missed appointments;
- common concerns of young people, such as smoking, alcohol, drugs consumption and sexual health;
- loss of information during the transfer.

Our ability to improve the transition process is constrained by the number of times the adult health care clinicians are able to attend a combined clinic at the paediatric hospital. Indeed, this process must often occur in the setting of limited staff, time, and resources. We believe that the reorganization of our health care system proposed in the current project could offer the opportunity to improve this transition. We plan to dedicate a specific clinician in each specialty to the process of transition and more importantly to involve transition-specialized nurses and primary care providers. Nurses may be the most appropriate health-care providers for improving the 4 points enumerated above. General practitioners could also be interesting partners in the management and transition of youth with special health care needs. Indeed, patients and their families often have to travel long distances for specialty visits in academic centres and paediatric rheumatologists, neurologists, nephrologists, pneumologists rely on primary care providers for their knowledge of local community resources, such as physical and occupational therapists, as well as adult clinician who will continue to follow patients over time.

Taskforce 3/ Adherence, compliance and medical inertia: major concern in the treatment of chronic inflammatory diseases

In 2003, the World Health Organization considered that "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments". Many studies have demonstrated that non-adherence is associated with increased frequency of disease flare-ups and increased disability caused by e.g. rheumatoid arthritis, systemic lupus, psoriasis, and inflammatory bowel diseases, and that improving adherence may increase treatment efficacy and safety.

Surprisingly enough, patient non-adherence is not the only source of flawed disease management. Medical inertia, most likely, has identical consequences. Medical inertia may be assimilated to a non-adherence of practitioners to recommendations, despite the facts that recommendations do exist, are well known and are theoretically applicable. However for unclear reasons, the recommendations are not followed by the clinician.

Emmanuel Langlois, a sociologist from the "Centre Emile Durkeim", a partner of ACRONIM, will be in charge of studying these two phenomena and of developing strategies to limit their impact.

Taskforce 4/ Monitoring of biologics:

Biological agents, particularly TNF inhibitors, have been a major advancement in the management of ID (especifically in rheumatoid arthritis and ankylosing spondylitis) and inflammatory bowel diseases. However, not all patients respond well to these treatments: registries estimate that approximately 20 to 30% of RA patients fail to respond to the first TNF inhibitor and that more than 20% of patients who initially responded experience a loss of efficacy within the first two years of treatment.

Interestingly, in cases of loss of efficacy, the clinical response can be restored by switching from the first TNF inhibitor to another, suggesting that loss of efficacy could be related to the immunogenicity of the medication. Indeed, biological agents are large molecules that are potentially immunogenic, such immunogenicity being attested by the development of anti-drug antibodies (ADAbs).

Many studies have shown that ADAbs can be detected in up to one-third of patients receiving biological agents, particularly anti-TNF monoclonal antibodies. These antibodies are associated with low trough drug levels and loss of clinical efficacy. ADAbs occur early, primarily in the first weeks after treatment onset, and in combination with methotrexate or other immunosuppressive agents decrease the risk of ADAb production.

Many factors have been shown to be associated with low c-trough levels of anti-TNF: the presence of ADAb, high level of inflammation at treatment onset, lack of combination with synthetic immunomodulator, and obesity.

Conversely, some patients have been shown to have extremely high c-trough levels of the biodrug, with such overtreatments potentially responsible for an increased risk of adverse events, primatily infections, and an unwarranted extra cost.

The **monitoring** of biodrugs will be conducted in close collaboration with the pharmaceutical departments (Pr Breilh Dominique) and new methods of monitoring biodrugs will be tested.

Aim2: Research program: to continue the existing projects, to bring new areas of investigation, and to interconnect the research teams.

We plan to continue all of the ongoing projects that are in direct line with previously published and/or unpublished observations for each team. The constitution of the FHU will allow the cross-field coordination, and interconnection between projects and/or teams. New expertise should also allow specific questions regarding IDs to be addressed by using up-to-date technologies

Taskforce 1: To find new pathogenic pathways in systemic autoimmune diseases: systemic lupus erythematosus (SLE, and systemic sclerosis (SSc) (Patrick Blanco, Cécile Bordes, Christophe Richez, Estibaliz Lazaro, Marie Elise Truchetet, Patrick Berger). (UMR/CNRS5164)

SLE: Previously the study of SLE pathogenesis has been an intense area of investigation, nd we have been able to implicate the following key players: Type I interferon, dendritic cells (Science, 2001), platelets (Science Translational Medicine, 2010), CD8+ T-lymphocytes (Arthritis Rheumatology, 2008) and more recently the OX40/OX40L pathway (Immunity, 2015). We are planning to continue our project programme and to incorporate specific projects on cutaneous lupus in close collaboration with ATIP/Avenir directed by Julien Seneschal. One of the primary goals that will be pursued by the group is to implicate the dysfunction of the recently described follicular regulatory T cell population in lupus pathogenesis.

SSc: **SSc:** Fibrosis, vasculopathy and dysimmunity are the primary hallmarks of the rare but severe autoimmune disease systemic sclerosis (SSc). Nevertheless, the precise nature of the mechanisms leading to fibrosis is unknown. Recent studies have identified interleukin (IL)13 as a key downstream mediator in the development of fibrosis. The source of IL13 is thought to be Th2 cells, although the evidence remains indirect. Recently identified, activated type 2 innate lymphoid cells (ILC2) are able to produce rapidly large amounts of IL13 and are involved in hepatic and pulmonary fibrosis in mouse. Our preliminary data show that ILC2 levels decrease in SSc patients and correlate inversely to the extent of skin fibrosis. Moreover, in SSc patients, we identified dermal microvascular endothelial cells as an important source of thymic stromal lymphopoietin, an inducer of IL13 production by ILC2. **Thus, the aim of this project is to implicate ILC2 in human SSc fibrosis and to decipher how the cells of the microenvironment (i.e., endothelial cells and fibroblasts) could affect their recruitment and their activation.** This objective will be pursued through extensive phenotyping of ILC2 in whole blood and skin samples from SSc patients with correlation to disease activity and clinical parameters. Two ILC2-depleted mouse models of scleroderma and *in vitro* analysis will help to decipher the mechanisms leading to ILC2 accumulation and activation in fibrotic tissues and, notably, the roles of endothelial cell- and fibroblast-derived factors. Finally, we will analyse the consequences of ILC2 activation on the fibrotic process through (i) the release of pro-fibrotic factors such as amphiregulin and IL13 by ILC2 and (ii) the local modulation of adaptive immunity towards a Th2 phenotype. From a clinical point of view, this project aims to identify novel biomarkers to predict scleroderma severity and fibrosis extent. This project could also lead to the development of innovative therapeutic strategies to block ILC2 recruitment and/or activation. We believe that our approach will have a broader impact on diverse diseases, including hepatitis, pathological scarring, and idiopathic pulmonary fibrosis.

Taskforce 2: To find new pathogenic pathways in multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory and neurodegenerative disease that results from the autoimmune destruction of myelin and associated collateral tissue damage within the central nervous system (CNS). MS affects approximately 2.5 million people worldwide. The prevalence of MS varies considerably around the world, likely reflecting a combination of genetic and environmental influences on the pathogenesis. Although usually non-fatal, MS often progresses over time and substantially affects patient quality of life. While several treatment options are currently available, no treatment completely stops disease progression. Furthermore, responses to treatments largely differ among patients, and no patient stratification strategy is currently available for treatment options. Therefore, a deeper understanding of the pathogenesis of MS is necessary to develop more efficient treatment strategies. Our long-term goal is to develop a novel therapeutic approach for MS, which aims at inhibiting the generation and/or functions of pathogenic CD4 T cells. Undoubtedly, mouse studies using the experimental autoimmune encephalitis (EAE) model have contributed substantially to the understanding of MS pathogenesis. However, the human immune system is not identical to the mouse immune system, and the findings in EAE models do not always apply to human MS. Furthermore, our recent studies regarding the developmental mechanism of T follicular helper cells, a CD4 T cell subset specialized for the provision of help to B cells, have also identified multiple differences between mouse and human MS. Therefore, we believe that analysing samples obtained from patients is essential for determining the nature of pathogenic CD4 T cells in MS. The goal of this study is to determine the types of pathogenic CD4+ T cells in MS patients, together with the factors associated with their development and/or functions. An ATIP/AVENIR grant was obtained by Nathalie Schmitt for this project.

Taskforce 3: To find new pathways in inflammatory cutaneous diseases (Julien Seneschal and Katia Boniface)

Analysing inflammatory cutaneous diseases and cutaneous signs of systemic diseases could be an interesting approach to better understanding the pathogenesis of IDs. Indeed, skin represents a reliable and accessible non-lymphoid organ to better explore the response of the immune system in a specific disease. This group is currently working on the pathogenesis of vitiligo, which is the most frequent depigmenting disorder affecting approximately 1% of the general population. Vitiligo involves complex combinatorial pathogenic effects, multiple susceptibility genes, and unknown environmental triggers similar to many autoimmune disorders. This group is involved in the extensive characterization of skin-homing autoreactive CD4+ T lymphocytes from patients with vitiligo. This group has developed all of the necessary tools, from the sampling of patients with skin disorders to the work at the bench (3D skin culture as an example), to develop translational projects.

Taskforce 4: To find new pathways in inflammatory pulmonary disorders (Patrick Berger)

Asthma and chronic obstructive pulmonary disease (COPD) are extremely frequent airway diseases (i.e., 5 and 4 million patients in France, respectively). Although asthma mortality has dramatically decreased within the last 20 years, uncontrolled asthma still has major consequences on morbidity, quality of life, and economic burden. Severe asthmatics represent 5 to 10% of all asthmatics and generate a large proportion of

resource expenditure. By contrast, the mortality of COPD continues to increase. COPD is now the 4th cause of death worldwide, and projections predict that COPD will reach the 3rd cause of death in 2030. Various phenotypes have been described in both diseases. For instance, frequent exacerbations can predominate not only in a subgroup of severe asthmatic patients with fixed airflow obstruction but also in COPD patients. Moreover, these patients present a higher rate of lung function decline over time.

Both asthma and COPD are inflammatory diseases that are characterized by different patterns of bronchial remodelling. In asthma in particular, the mass of the bronchial smooth muscle (BSM) increases within the entire bronchial tree, which is related to a decrease in lung function. For instance, during the previous contract, we demonstrated the key role of mitochondrial biogenesis in the BSM remodelling of severe asthmatics. In COPD, the increased mass of the BSM appears less important compared to peribronchial fibrosis, both of which are limited to the distal airways. Bronchial remodelling was initially thought to be the consequence of an incomplete repair process following inflammation. However, the early onset of this process suggests that remodelling, and particularly BSM remodelling in asthma, may be the cause and not the consequence of chronic inflammation. Nevertheless, the pathophysiology of bronchial remodelling of both asthma and COPD remains largely unknown. In addition, the effects of exacerbations in both diseases on bronchial remodelling have yet to be described and understood. The primary cause of these exacerbations is viral infection of the bronchial epithelial layer. Indeed, viruses are found in approximately 80% of wheezing episodes in school-aged children and in 50 to 75% in adults. Human rhinovirus is the most common virus found during an exacerbation. However, only symptomatic drugs are available today for the treatment of both diseases and their exacerbations. Therefore, new treatments able to modify the natural history of these diseases are urgently needed. Our hypothesis is that bronchial remodelling should be a primary target of these innovative treatments.

In addition to inflammatory cells, bronchial epithelial cells can play a key role in asthmatic bronchial inflammation. Indeed, epithelial cells can produce a variety of cytokines such as TSLP or IL-33. Human samples from both asthmatic and non-asthmatic patients will be collected using on-site running cohorts. We will evaluate the effects of epithelial cell-derived cytokines on smooth muscle cells, particularly on cell proliferation, extracellular matrix production and cell migration, all of which are crucial in asthmatic bronchial remodelling. Moreover, smooth muscle cells can produce various cytokines such as IL-33, TGF-beta1. We will evaluate the effects of smooth muscle-derived cytokines on epithelial cells. We will then co-culture both cell types together to elucidate the complex relationships between epithelium and smooth muscle.

The mechanisms of peribronchial fibrosis in COPD are largely unknown. Recent findings from the team demonstrated the recruitment of blood fibrocytes during an acute exacerbation of COPD. The mechanisms of fibrocyte recruitment from the blood to the lung need to be explored in vitro, ex vivo and in vivo. Because COPD also involves systemic inflammation, we will evaluate the effects of fibrocytes obtained from COPD or controls on T cell polarization.

Taskforce 5: To interconnect research projects

Project 1: Patrick Berger/Cécile Contin-Bordes

Dendritic, epithelial and smooth muscle cell interactions in asthma remodelling following rhinoviral exacerbations. This project is based on the collaboration between 2

teams (i.e., INSERM U1045 [Team 2 "bronchial remodelling"] and UMR CNRS 5164). The role of monocyte-derived dendritic cells will be evaluated in the complex relationship between epithelium and smooth muscle specifically during a rhinoviral infection. For instance, the possibility of smooth muscle or epithelial cells from asthmatics to drive an inflammatory phenotype in dendritic cells will be assessed. This project will associate both in vitro and in vivo experiments with a translational point of view including both "bed to bench" and "bench to bed" approaches. This collaborative project will allow us to identify new therapeutic targets against BSM remodelling in asthma, which is the primary unmet need of this frequent disease.

Project 2: Marie Elise Truchetet/Julien Seneschal

SSc project. SSc is one example of an immune disorder where a close collaboration between different specialities is important in both clinic and research. Despite severe skin induration development during the progression of the disease, patients often suffer from skin pigmentation abnormalities. Based on the Bordeaux SSc cohort (VISS cohort; PI, Dr M.E. Truchetet), we have identified patients with and without skin pigmentation disorders and will explore mechanisms regulating skin pigmentation in the context of SSc inflammation. Skin pigmentation is due to melanin production by epidermal melanocytes. In preliminary results, we showed that melanocytes belong to a melanisation dermo-epidermal unit in which the key members apart from melanocytes are fibroblasts and keratinocytes. We observed that collagen production by skin fibroblasts is linked to hypo- or a hyper-epidermal pigmentation in some cases. On the one hand, we showed *in vitro* and *in vivo* that we were able to modulate the skin pigmentation from a Caucasoid to a Negroid type depending on the number of fibroblasts. On the other hand, we observed that CCN3/NOV expression was highly modulated in pigmentation abnormalities. Notably, CCN3 has an anti-fibrotic role in SSc. An increase in CCN2, of which CCN3 is the negative regulator, has been described in SSc. Using a transverse approach, we would like to establish a link between pigmentation regulation and fibrosis by focusing on the role of CCN molecules in SSc. This research could be of prognostic interest and provide a proof of concept for new therapeutic options to treat a disease without any current treatments for its fibrotic aspect in humans. This project will be handled by a PhD student (fellow in Rheumatology, INSERM School) directed by MET and JS starting in November 2015.

Aim3: To test new therapeutic options in ID (All clinical teams)

All clinical partners of the FHU have developed an academic research on clinical trials (new treatment strategies, PHRC) or in term of industrial research (clinical development of new drugs by pharmaceutical companies), as illustrated by the number of SIGREC points.

This activity will be developed within the FHU. The cooperation of different specialties will encourage transfer of treatment strategies from one specialty to another, and will also allow mutualizing resources, including patients, research assistants, and nurses.

Aim 4: Telemedicine/e-health

We believe that telemedicine could play a major role in the new health care organization framework that we proposed in ACRONIM. Because telemedicine permits the exchange of medical information from one site to another via electronic communications, this service will help to structure health care organization and therefore to improve patient health. In the past few years, the use of telemedicine in Bordeaux has spread rapidly and is now becoming integrated into the ongoing

operations of various specialties such as neurology with stroke centres and geriatric care facilities.

What services could be provided by telemedicine in ACRONIM?

1) Inflammatory disorder specialists from secondary or tertiary care hospitals and clinics may assist the primary care physician or allied health professional in determining a diagnosis. This assistance may involve the use of live interactive video or the use of stored and forwarded transmission of diagnostic images, clinical signs and/or video clips along with patient data for later review. This service has multiple advantages: i) allows an early diagnosis and provides rapid management; ii) improves the identification of red flags that justify the rapid requirement of a specialist; iii) provides rapid and simplified access to specialized structures, either physical access or remote access via telemedicine tools; iv) emphasizes the position of our hospital as a referral hospital; and v) strengthens cooperation and partnerships between community medicine and hospitals.

2) Remote patient monitoring, including home telehealth, uses devices to remotely collect and send data to a physician involved in ACRONIM for interpretation. Such applications might include specific clinical signs (e.g., swollen joints, painful joints, and fever) or a variety of indicators for homebound patients. Such services can be used to supplement the use of visiting nurses and to detect co-morbidities. This service could support the development of out-of-hospital medical management and therefore could give equivalent access to health care in the entire territory, limiting the cost of transportation.

3) On-line multi-disciplinary concertation meetings (so-called Réunion de Concertation Pluridisciplinaire in French).

4) Medical education provides continuing medical education credits for health professionals and special medical education seminars for targeted groups in remote locations.

What could be the benefits of telemedicine for ACRONIM?

1) Improving doctor access to patients and providing ACRONIM project specialists to expand their reach beyond their own department

2) Improving cost efficiencies through better management of chronic diseases, shared health professional staffing, reduced travel times, and fewer or shorter hospital stays

3) Decreasing patient stress by reducing travel time and related stresses for the patient and by offering patients access to providers that might not be available otherwise and access to medical services without the need to travel long distances

4) Facilitating a transdisciplinary approach for treating IDs, including transdisciplinary e-consultations for patients with IDs and common educational programmes

As an example of device conception, we have chosen the following ongoing project examining pulmonary IDs.

Asthma exacerbations represent an acute or sub-acute worsening in symptoms and lung function compared to the patient's usual status. Early detection of exacerbations is a major public health issue. In clinic, asthma management involves asthma control questionnaires and pulmonary function tests (FEV1, FeNO). At home, the peak expiratory flow rate (PEFR) measured by the peak flow metre is an aid to monitor asthma; however, its ability to predict asthma exacerbations remains controversial. Anharmonic morphological analysis of the respiratory signals (AMARS) is a new

morpho-mathematic biomarker that produces objective and accurate measures of the shape of the ventilatory flow. The current study aims at monitoring the resting spontaneous breathing at home using a portable device for telemonitoring in asthmatics. Changes in AMARS may be a predictor of early symptoms of asthma exacerbations.

WP 4	The late chronic disease phase and the long-term comorbidities of ID	WP teams:
		DMG, Clinician Specialists, ARS

Rationale:

IDs are characterized by the long-term occurrence of different complications including cancer, cardiovascular diseases, osteoporosis, and infectious diseases at a higher prevalence compared to the general population. These complications, collectively named comorbidity, represent the leading causes of mortality among such patients. Regarding cardiovascular disorder (CVD) associated with ID, although such effects are partly explained by a higher prevalence of traditional CV risk factors, many studies have indicated that such factors do not fully explain the enhanced CV risk in these patients. In addition, risk stratification algorithms based on traditional CV risk factors are not as predictive for autoimmune diseases as for the general population. For these reasons, the timely and accurate assessment of CV risk in these high-risk populations remains an unmet clinical need. Enhanced contributions of different inflammatory components of the immune response and autoimmune elements (e.g., autoantibodies, autoantigens, and cellular response) have been proposed to underlie the incremental CV risk observed in these populations. However, this aspect only partly explains the full spectrum of CVD in inflammatory disorders, and novel explanations need to be found to be able to propose appropriate drugs that can block/slow the development of atherosclerosis. We have decided to focus on this aspect by addressing the three following aspects.

Aim 1: The establishment of a comorbidity consultation regardless of the ID

Annual reviews dedicated to comorbidities evaluation are yet organized for patients with long-standing rheumatoid arthritis in the day-hospital unit of the rheumatology department. These annual reviews comprise a check-up of all infectious events that occurred during the past year, an update of vaccinations, a survey of cancer risk (chest X-ray, mammography, cervical smear, colonoscopy when appropriate), a physical examination, an electrocardiogram and a biological control of lipids, glucose, renal function… These annual reviews will be extended to other ID.

Aim 2: To study the roles of metabolites in chronic low-grade inflammation in different chronic inflammatory disorders (Benjamin Faustin and Pierre Duffau)

Chronic low-grade inflammation is associated with the normal process of ageing in humans and with the progression of various major pathological conditions including CVD and metabolic syndromes (obesity, type 2 diabetes and gout). The identification of sterile DAMPS has begun to emerge partly due to the initiation phase of these diseases, which can trigger the production of proinflammatory cytokines including IL-1β, IL-18 and Type-I IFN. These inflammatory components may amplify the deleterious clinical outcome of CVD and metabolic syndrome. All sterile DAMPS identified thus far have been characterized as small molecule metabolites derived from dysregulated metabolic pathways (cholesterol, uric acid crystals, palmitate, and ceramide), and these DAMPS can be sensed by host innate immune machineries that control the production of potent inflammatory mediators. We have identified new circulating DAMPS that accumulate in the blood in the elderly; these molecules participate in low-grade chronic inflammation

observed during ageing in humans and are associated with worse clinical CVD parameters including increases in hypertension and arterial stiffness. Therefore, we have established the concepts that the innate immune system can sense systemic metabolic stress in the form of accumulated circulating metabolites and that these metabolites are associated with comorbidities including CVD. We plan to study the accumulation of specific metabolites in ID patient blood samples that may be associated with comorbidities. These small molecules from blood may be conveniently used as biomarkers to predict disease progression and thereby to stratify patients at risk. In addition, these small molecules will be instrumental in identifying new inflammatory mechanisms that might be targeted to block the progression of inflammation-associated common illnesses.

Aim 3: To establish the role of microparticles in long-term comorbidities (Alain Brisson, Christophe Richez, Vincent Rigalleau, Laurent Plawinski, Marie Christine Durrieu) and to identify innovative physicochemical surface functionalization for IDs (e.g., diabetes) ***(Laurent Plawinski, Marie-Christine Durrieu, Vincent Rigalleau)***

Microvesicles are phosphatidylserine-positive membrane fragments shed by cells that are activated by a variety of stimuli including inflammatory cytokines, growth factors, serine proteases, and stress inducers. Microvesicles originating from platelets, leukocytes, endothelial cells, and erythrocytes are found in circulating blood at relative concentrations determined by the pathophysiological context. The procoagulant activity of microvesicles is their most characterized property and is a determinant of thrombosis in various vascular and systemic diseases including myocardial infarction and diabetes. These microvesicles have been described as reliable hallmarks of cell damage in various cellular models and in different pathological conditions. An increase in circulating microvesicles has also been associated with autoimmune systemic diseases (e.g., systemic lupus erythematosus), rheumatic diseases (e.g., osteoarthritis, rheumatoid arthritis, and juvenile idiopathic arthritis), and organ-specific diseases (e.g., type 1 diabetes and multiple sclerosis). Microvesicles are also produced from complications of these diseases (e.g., cardiovascular disease and ischaemic cerebrovascular accidents). Recent data indicate that in addition to their procoagulant components and identity antigens, microvesicles bear a number of bioactive effectors that can be disseminated, exchanged, and transferred via microvesicle-cell interactions. Furthermore, as activated parenchymal cells may also shed microvesicles carrying identity antigens and biomolecules, microvesicles are now emerging as new messengers/biomarkers from the specific tissue undergoing activation or damage. Thus, the detection of microvesicles in biological fluids of patients with inflammatory chronic disease would not only improve our comprehension of this pathophysiology but also constitute a powerful tool as a biomarker in disease prediction, diagnosis, prognosis, and follow-up.

The novelty of the technology we propose is that we have identified a unique synthetic compound (dinuclear zinc complexes) that selectively recognizes phosphatidylserine, the primary phospholipid characteristically exposed at the membrane of microvesicles. A high density of these complexes is grafted onto the surface of a material to ensure that the microvesicles are captured. This inexpensive and easy to use synthetic compound does not present the complications encountered with the use of annexin A5 by flow cytometry and prothrombinase capture assay. Our synthetic compound ensures

specific signal detection upon selective capture, identification of cellular origin and **functional analysis** of microvesicles. This approach is a major breakthrough as no technological procedure is currently available that may allow this versatility: the detection of a broad range of microvesicles sizes with the use of different antibodies and reagents on target microvesicles.

Aim 4: To understand the mechanisms of long-term occurrence of lymphoma in patients with IDs (Dorothé Duluc and Nicolas Larmonier)

Patients with particular autoimmune disorders and inflammatory conditions have an increased risk of developing specific lymphomas. Generally, the link between autoimmune diseases and developing lymphoma is correlative; however, a subset of autoimmune diseases exists for which the risk of subsequent lymphoma development is strong. Chronic antigenic stimulation and inflammation define the immunological environment of autoimmunity and are factors that can precipitate the onset of lymphoma. However, the molecular pathways and cells from the immune system that are directly involved in lymphomagenesis remain unclear. This project will focus on the potential implication of the Th9 and Tfh subsets in lymphomagenesis linked to IDs. This work will be conducted in close collaboration with the SYRIC-BRIO.

WP5	Teaching and dissemination	WP Teams:
		All teams

Rationale:
Scientific and medical students must be prepared for new jobs and careers that will be created from the needs of translating system biology to clinical practice. In addition, current professionals must be cross-trained regularly. Finally, patient education is certainly a major issue in the care of chronic IDs. The participants in this FHU are heavily committed to educational activities at the graduate and post-graduate level. All participants are involved in PhD programmes. Many nurses in our clinical departments are involved in therapeutic education programmes. The goals are to not only continue the existing education programmes but also create specific teaching related to the FHU.

Aim 1: The ACRONIM conference
These conferences (6-8/year) will aim to attract senior international speakers and will be based on translational topics. The programme will be established yearly by the scientific committee of the FHU. In addition to this programme, the FHU will organize a one-day thematic conference on a yearly basis where young scientists and clinicians will present their ongoing projects and/or published observations. One or two selected speakers will also be included.

Aim 2: The ACRONIM masters programme
A specific master programme will be developed that focuses on the pathophysiology of inflammatory and immune mediated diseases and that is dedicated to young medical doctors and scientists.
The theoretical part of the programme will proposed a series of training courses combining one pathology with one technique of investigation as follows:

- Pathophysiology of Crohn's disease – investigating intestinal microbiota
- Pathophysiology of rheumatoid arthritis –exploring genetic factors
- Pathophysiology of systemic lupus – investigating humoral immune response

The practical part of the masters programme will consist of a stage proposed within the research team involved in the FHU.

Aim 3: The ACRONIM teaching programme for GP residents
The organization of teaching for GP residents is the primary mission of the Department of General Medicine. This teaching programme will be a unique opportunity to explain the functioning of the territory organization for IDs.
This teaching programme will be composed of the principle of early ID screening and diagnosis, the primary red flags for ID suspicion, the ID follow up guidelines and current recommendations.

Aim 4: The ACRONIM continuous training programme and effective use of territory organization
Dedicated to both specialists and GPs, this programme will highlight the newest developments in IDs and recommendation updates.
This programme will also promote the health care organization proposed within the FHU.
This programme will be integrated into an official "DPC" programme (personal

continuous training), which will be available as both an on-line and face-to-face course.
Aim 5: Improving ID primary training for medical students An e-learning programme will be proposed to the University of Bordeaux to be integrated in the teaching modules of the second cycle of medical studies to improve not only student knowledge of IDs but also the understanding of what living with a chronic disease is like. This programme will include professors in medicine, sociologists, nurses and patients.
Aim 6: Training health workers in ID care A specific programme for health workers will be set up in close collaboration with nurses, physiotherapists, psychologists, nutritionists and medical doctors of clinical teams involved with the FHU.
Aim 7: Therapeutic education and information for patients and families Existing therapeutic education programmes developed by the clinical teams participating in the project will be integrated into a unified program, which will be developed in close collaboration with health professionals and patient associations.

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6. Governance of the FHU.

The creation of the FHU ACRONIM results from a partnership of four institutions called the "parties": CHU de Bordeaux (Bordeaux University Hospital), the University of Bordeaux, the CNRS (National Centre for Scientific Research), the INSERM (National Institute of Health and Medical Research)

The FHU is made up of several clinical units and research units from these parties; these units are called "teams".

The first coordinator of the FHU ACRONIM will be Patrick Blanco, MD, PhD, Professor of Immunology at the University of Bordeaux.

The governance of the FHU has three different levels:

1) **The executive committee** of the FHU includes a representative from each of the parties (CHU, UB, CNRS, and INSERM), a representative of each clinical team and research team. Outside personalities will be representative of the Regional Health Agency, the Aquitaine Regional Council and patient associations.

The full council will meet at least twice a year and review advancements of the FHU including results of ongoing projects, emerging projects, financial and logistic issues, and educational programmes.

The council includes three sub-committees: clinical, educational, and translational research; each subcommittee is led by two coordinators (one from a clinical team and one from a research team).

2) **The steering committee** is composed of the sub-committee coordinators and the coordinator of the DHU. Patrick Blanco has been nominated by FHU participants to assume this task for the first four years. The direction committee will meet monthly to evaluate the general progress of the FHU and to address day-to-day issues.

3) **The WP leaders and co-leaders** are responsible for monitoring day-to-day operations in their WP, organizing WP internal meetings and work groups, proposing

WP scientific and budget priorities, and providing a progress report with budget requests to the direction committee every 6 months.

A **strategic advisory board** will review FHU's progress and provide strategic recommendations to the direction committee. This board will be composed of internationally recognized key opinion leaders in the field of ID. The board will visit the FHU yearly at the time of its annual scientific meeting.

You will be provided with a more detailed governance in French in Annex 8 (p 142).

7. Economic and societal value

7.1. Economic model

The economic model of the FHU will be built on five components:

1. Partnership with the Health Regional Agency for health care organization implementation
2. Submissions to the calls for proposals for research studies
3. Support from the pharmaceutical industry
4. Partnership with companies involved in the project
5. Creation of a foundation with the University of Bordeaux

Finally, we will participate in the RHU call for proposals in collaboration with the other FHU of Bordeaux. Two options are being explored: either collaboration with a FHU TALISMENT, proposed by a consortium of neurologists, on the topic of neuro-inflammation or a partnership with a FHU devoted to small vessels, as there are many correlations between small vessels and inflammatory diseases.

7.2. Economical partnerships

Economical partnerships will include the following partnerships:

Partnerships with pharmaceutical laboratories involved in ID research:

- Production of clinical data
- Collaborations in clinical trials
- Translational research to improve the understanding of drug effects

Partnerships with industries involved in medical devices, diagnostic tools, telemedicine and e-health, with special attention given to regional industries

Partnerships with medical insurance companies:

- Development of a health care model
- Implementation and evaluation of prevention actions

7.3. Valorisation of the FHU

The partners of the FHU have excellent records of accomplishment in terms of publications and patents, with 19 patents issued in the past 10 years, and in obtaining public or private funding for translational or clinical trials. Collaboration with pharmaceutical companies or devices companies is extremely active. These contacts are based on patient cohorts and innovative research on IDs for mechanistic and pharmacological investigations. Some of the partners are involved in biotech companies based on their exploitable patents. The FHU network will promote collaboration and productivity. The collaboration with the different LabEx participants is an excellent approach, and the multiple sclerosis programme is one of the best examples where we will create a unique environment to work on this disease through the interaction of the LabEx Trail, Brain, and the recently obtained ATIP AVENIR programme by Nathalie Schmitt.
We propose the following criteria for a successful FHU:

(1) Number of submitted grants with two or more partners of the FHU
(2) Original articles signed by two or more partners of the FHU
(3) Patents submitted involving two or more partners of the FHU
(4) Effective organization of an annual scientific workshop on the topic of IDs
(4) Attraction of one or more scientific or clinical groups along the general theme of the DHU to our hospital or laboratories
(5) Numbers of clinicians, physician/scientists, and researchers, recruited to the FHU during the 5-year mandate

Conclusion:

Annex 1: Curriculum vitae of the coordinators of the project

CURRICULUM VITAE : BLANCO Patrick

PERSONAL INFORMATIONS

BLANCO Patrick
Date of Birth: 08/291970. Married, 2 children.
Web site: http://www.umr5164.u-bordeaux2.fr/

EDUCATION

- 01/10/1998: University of Bordeaux, France, MD.
- 10/1/2002: University of Bordeaux, Qualification in Internal Medicine
- 16/12/2004: University of Bordeaux, France, PhD, Immunology.

CURRENT POSITIONS

Professor: Head of the Department of Immunology, CHU de Bordeaux. France.
Principal Investigator: CNRS/UMR5164, University of Bordeaux. France.

Co-director: CNRS/UMR5164, University of Bordeaux. France.

Coordinator of the center of competence for systemic autoimmune diseases (Aquitaine Region)
Consultant: Baylor Institute for Immunology Research. Autoimmune Center of Excellence, directed by Dr Virginia Pascual. Dallas. Tx. USA

PREVIOUS POSITIONS

Medical field:

From 2009-2014: **Professor**, Department of Immunology, University Hospital of Bordeaux. France.
01/09/2002 – 01/09/2009: Associate Professor, Department of Immunology, University Hospital of Bordeaux. France.
01/11/1994 -01/11/2002*:* Residency in different medical departments. University Hospital of Bordeaux. France.

Research field:

From 01/09/2012 to 01/09/2014: Principal Investigator (2 sabbatical years):
Baylor Institute for Immunology Research. Dallas. Texas. USA.

From 01/09/2007: Principal Investigator: UMR-CNRS 5164 CIRID. University of Bordeaux. France.

01/021999-01/03/2001: **Post-doctoral position**: Baylor Institute for Immunology Research. Dallas. Texas. USA

COMMITTEE AND ADVISORY BOARD

- Reviewer for different journals: Arthritis Rheumatism, Annals of Rheumatic diseases, Journal of Immunology, PNAS.
- Member of the scientific board of the University of Bordeaux2 (2008-2012)
- Member of the French Society of Immunology, Rheumatology and Internal Medicine.

MAIN PUBLICATIONS : 2010-2015

Duffau P, Seneschal J, Nicco C, Richez C, Lazaro E, Douchet I, Bordes C, Viallard JF, Goulvestre C, Pellegrin JL, Weil B, Moreau JF, Batteux F**, Blanco P**. Platelet CD154 Potentiates Interferon-{alpha} Secretion by Plasmacytoid Dendritic Cells in Systemic Lupus Erythematosus**. Sci Transl Med**. 2010 Sep 1;2(47):47ra63.

Contin-Bordes C, Lazaro E, Richez C, Jacquemin C, Caubet O, Douchet I, Viallard JF, Moreau JF, Pellegrin JL, **Blanco P**. Expansion of myelin autoreactive CD8+ T lymphocytes in patients with neuropsychiatric systemic lupus erythematosus. **Ann Rheum Dis.** 2010 Dec 27.

Tauzin S, Chaigne-Delalande B, Selva E, Khadra N, Daburon S, Contin-Bordes C, **Blanco P**, Le Seyec J, Ducret T, Counillon L, Moreau JF, Hofman P, Vacher P, Legembre P. The naturally processed CD95L elicits a c-yes/calcium/PI3K-driven cell migration pathway. **PLoS Biol.** 2011 Jun;9(6):e1001090

Eric Boilard, Patrick Blanco and Peter A. Nigrovic. Platelets: Active players in the pathogenesis of arthritis and systemic lupus erythematosus. Nat Rev Rhumatol. 2012 Aug 7;8(9):534-42.

Raffray L, Douchet I, Augusto JF, Youssef J, Contin-Bordes C, Richez C, Duffau P, Truchetet ME, Moreau JF, Cazanave C, Leroux L, Mourrissoux G, Camou F, Clouzeau B, Jeannin P, Delneste Y, Gabinski C, Guisset O, Lazaro E, Blanco P. Septic Shock Sera Containing Circulating Histones Induce Dendritic Cell-Regulated Necrosis in Fatal Septic Shock Patients. Crit Care Med. 2015 Apr;43(4):e107-16.

Clément Jacquemin, Nathalie Schmitt, Cécile Contin-Bordes, Yang Liu, Priya Narayanan, Julien Seneschal, Typhanie Maurouard, David Dougall, Emily Spence Davizon, Hélène Dumortier, Isabelle Douchet, Loïc Raffray, Christophe Richez, Estibaliz Lazaro, Pierre Duffau, Marie-Elise Truchetet, Liliane Khoryati, Patrick Mercié, Lionel Couzi, Pierre Merville, Thierry Schaeverbeke, Jean-François Viallard, Jean-Luc Pellegrin, Jean-François Moreau, Sylviane Muller, Sandy Zurawski, Robert L. Coffman, Virginia Pascual, Hideki Ueno and **Patrick Blanco**. OX40 Ligand contributes to the pathogenesis of autoimmunity by promoting T follicular helper response. **Immunity.** 2015 Jun 16;42(6):1159-7.

Hideki Ueno, and **Patrick Blanco**. OX40/OX40L axis: not a friend in autoimmunity. **Oncotarget**. In press.

Pierre Duffau, Linda Wittkop, Estibaliz Lazaro, Fabien Le Marec, Céline Cognet, **Patrick Blanco,** Jean-François Moreau, Frédéric-Antoine Dauchy, Charles Cazanave, Marie-Anne Vandenhende, Fabrice Bonnet, Rodolphe Thiebaut, Isabelle Pellegrin. Association of Immune-activation and -senescence Markers With non AIDS defining Comorbidities in HIV suppressed patients. **AIDS**. In Press.

PATENTS

Methods of treating autoimmune diseases in a subject and in vitro diagnostic assays. Patent Application n°10/042, 644.

Use of allogeneic cell lines to load antigen-presenting cells to elicit or eliminate immune responses. Patent application n°10/110, 553.

«METHODS AND PHARMACEUTICAL COMPOSITION FOR NEUTRALISING THE CYTOTOXIC ACTIVITY OF EXTRACELLULAR HISTONE PROTEINS». Patent number: 14 306 445.9.

ANTAGONISTIC ANTI-OX40L ANTIBODY TO BLOCK INFLAMMATORY EFFECTOR T CELLS. In Process

CURRICULUM VITAE – Jean-Luc PELLEGRIN

Name: Jean-Luc PELLEGRIN
Date and place of birth: October 31th, 1956 in Cauderan, France
Nationality: Français
Marital status: married, three children (1990, 1993, 1993)
Personal address: 278 boulevard Wilson, 33000 Bordeaux
Tel : 33 5 56 12 25 28
Professional address: Service de Médecine Interne et Maladies Infectieuses
Hôpital Haut-Lévêque, 5 avenue de Magellan, 33600 PESSAC
Tel: 33 6 01 17 68 28
Fax:05. 57.65.64.84
e mail : jean-luc.pellegrin@u-bordeaux.fr;

National medical board number 33/07980

Education and Academic functions

Since 2014 Director of the college of health sciences, University of Bordeaux
2009-2014 Dean, faculty of medicine, University of Bordeaux
1993- Professor of internal medicine, University of Bordeaux2 and University hospital of Bordeaux
1993- HDR (Habilitation in medicine), University of Bordeaux2
1990-1993 Assistant professor – University hospital of Bordeaux
1989-1990: Research-Fellow , New-England Medical Center Hospitals-Tufts University School of Medicine.
Boston, USA. (Infectious diseases and geographic medicine Pr. M.E.A. Pereira)
1989- Certified board in internal medicine
1987- Master in biology (microbiology), University of Bordeaux2
1985-1989 Clinical fellow, University of Bordeaux2 and University hospital of Bordeaux
1985- MD, University of Bordeaux2
1984- Certified board in Hematology (biology), University of Bordeaux2
1983: Certified in tropical medicine, University of Bordeaux2
1980-198 Resident in internal medicine - University hospital of Bordeaux

Hospital positions

Since 1997 Head internal medicine department, Haut-Lévêque hospital, University hospital of Bordeaux
1993: Professor of internal medicine
1990-1993: Assistant professor – University hospital of Bordeaux
1985-1989: Clinical fellow, University hospital of Bordeaux
1980-1985: Resident in internal medicine - University hospital of Bordeaux

Publications

The 10 more recent publications

Myocarditis in Patients With Antisynthetase Syndrome: Prevalence, Presentation, and Outcomes. Dieval C, Deligny C, Meyer A, Cluzel P, Champtiaux N, Lefevre G, Saadoun D, Sibilia J, **Pellegrin JL**, Hachulla E, Benveniste O, Hervier B.

Medicine (Baltimore). 2015 Jul;94(26):e798.

Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. Leroux M, Desveaux C, Parcevaux M, Julliac B, Gouyon JB, Dallay D, **Pellegrin JL,** Boukerrou M, Blanco P, Lazaro E.
Lupus. 2015 Jun 16. pii: 0961203315591027. [Epub ahead of print]

OX40 Ligand Contributes to Human Lupus Pathogenesis by Promoting T Follicular Helper Response. Jacquemin C, Schmitt N, Contin-Bordes C, Liu Y, Narayanan P, Seneschal J, Maurouard T, Dougall D, Davizon ES, Dumortier H, Douchet I, Raffray L, Richez C, Lazaro E, Duffau P, Truchetet ME, Khoryati L, Mercié P, Couzi L, Merville P, Schaeverbeke T, Viallard JF, **Pellegrin JL**, Moreau JF, Muller S, Zurawski S, Coffman RL, Pascual V, Ueno H, Blanco P.
Immunity. 2015 Jun 16;42(6):1159-70.

Intrinsically impaired platelet production in some patients with persistent or chronic immune thrombocytopenia. Rivière É, Viallard JF, Guy A, Kilani B, Vieira-Dias J, Pons AC, Couffinhal T, **Pellegrin JL**, James C.
Br J Haematol. 2015 Aug;170(3):408-15.

Severe morbidity according to sex in the era of combined antiretroviral therapy: the ANRS CO3 Aquitaine Cohort. Hessamfar M, Colin C, Bruyand M, Decoin M, Bonnet F, Mercié P, Neau D, Cazanave C, **Pellegrin JL**, Dabis F, Morlat P, Chêne G; GECSA study group.
PLoS One. 2014 Jul 30;9(7):e102671.

Pre-dose plasma concentration monitoring of mycophenolate mofetil in patients with autoimmune diseases. Streicher C, Djabarouti S, Xuereb F, Lazaro E, Legeron R, Bouchet S, Greib C, Breilh D, **Pellegrin JL**, Viallard JF.
Br J Clin Pharmacol. 2014 Dec;78(6):1419-25

Efficacy of bortezomib, cyclophosphamide and dexamethasone in treatment-naïve patients with high-risk cardiac AL amyloidosis (Mayo Clinic stage III). Jaccard A, Comenzo RL, Hari P, Hawkins PN, Roussel M, Morel P, Macro M, **Pellegrin JL**, Lazaro E, Mohty D, Mercie P, Decaux O, Gillmore J, Lavergne D, Bridoux F, Wechalekar AD, Venner CP.
Haematologica. 2014 Sep;99(9):1479-85.

Effect of cytomegalovirus-induced immune response, self antigen-induced immune response, and microbial translocation on chronic immune activation in successfully treated HIV type 1-infected patients: the ANRS CO3 Aquitaine Cohort. Wittkop L, Bitard J, Lazaro E, Neau D, Bonnet F, Mercie P, Dupon M, Hessamfar M, Ventura M, Malvy D, Dabis F, **Pellegrin JL**, Moreau JF, Thiébaut R, Pellegrin I; Groupe d'Epidémiologie Clinique du SIDA en Aquitaine.
J Infect Dis. 2013 Feb 15;207(4):622-7.

Granulomatosis-associated common variable immunodeficiency disorder: a case-control study versus sarcoidosis. Bouvry D, Mouthon L, Brillet PY, Kambouchner M, Ducroix JP, Cottin V, Haroche J, Viallard JF, Lazor R, Lebargy F, Tazi A, Wallaert B, Smail A, **Pellegrin JL**, Nunes H, Amoura Z, Cordier JF, Valeyre D, Naccache JM; Groupe Sarcoïdose Francophone.
Eur Respir J. 2013 Jan;41(1):115-22.

Lower 12-hour trough concentrations of mycophenolic acid in patients with active systemic vasculitides taking mycophenolate mofetil. Djabarouti S, Lazaro E, Breilh D, **Pellegrin JL**, Viallard JF.
J Rheumatol. 2012 Nov;39(11):2222-3.

Thierry Schaeverbeke, MD, PhD

Date of birth: 8 june 1960
Family status: maried, 3 children born in1988, 1991 and 1994
Address : 28, rue Pasteur 33200 Bordeaux
t.schaeverbeke@me.com

Professionnal contact informations:

Department: Rhumatologie
Address: Hôpital Pellegrin 33076 Bordeaux cedex
Tel: 33 (0)5 56 79 55 56 **Fax**: 33(0)5 56 79 60 84
E-Mail: thierry.schaeverbeke@chu-bordeaux.fr
University: Unité sous Contrat, Infections à Mycoplasmes et à Chlamydia chez l'Homme, University of Bordeaux

Education and qualifications:

Bac: 1978
PCEM: 1979
"Concours de l'Internat de Spécialités Médicales": 1984
Rheumatologist: 1989
Doctor of Medicine: 1989
Assistant professor: 1989 - 1993
Postgraduate Degree: 1993
University Hospital Practitioner: 1993 - 1997
PhD: 1997
"Habilitation à Diriger des Recherches": 1997
University Professor and Hospital Practitioner: 1998

Activities and service:

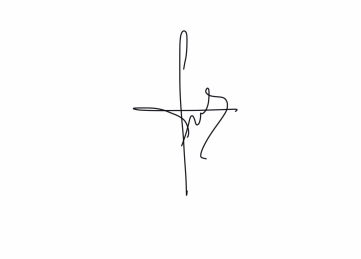
Head of the department of Rheumatology
Member of the Federation of Medicine of Pellegrin Hospital
Member of National Council of Universities from 2006 to 2012
Member of "Conseil National du Concours de l'Internat" from 2003
Member of Council of Medical Dpt of the University of Bordeaux from 2001 to 2009
Vice-president of the "Congrès Français de Rhumatologie" 2012 - 2013
President of the "Congrès Français de Rhumatologie" since 2014

Membre de Sociétés Savantes :
Member of the French Society for Rheumatology
Member of the American College of Rheumatology

H index: 33

Main recent publications:

1. Immunogenicity of biological agents in rheumatoid arthritis patients: lessons for clinical practice. Thierry Schaeverbeke, Marie-Elise Truchetet, Marie Kostine, Thomas Barnetche, Bernard Bannwarth, Christophe Richez. Rheumatology. In press
2. OX40 Ligand contributes to the pathogenesis of autoimmunity by promoting T follicular helper response. Jacquemin C, Schmitt N, Contin-Bordes C, Liu Y, Narayanan P, Seneschal J, Maurouard T, Dougall D, Spence Davizon E, Dumortier H, Douchet I, Raffray L, Richez C, Lazaro E, Duffau P, Truchetet ME, Khoryati L, Mercié P, Couzi P, Merville P, Schaeverbeke T, Viallard JF, Pellegrin JL, Moreau JF, Muller S, Zurawski S, Coffman R.L., Pascual V, Ueno H and Blanco P. Immunity. In press.
3. Predictive risk factors of serious infections in patients with rheumatoid arthritis treated with abatacept in common practice: results from the Orencia and Rheumatoid Arthritis (ORA) registry. Salmon JH, Gottenberg JE, Ravaud P, Cantagrel A, Combe B, Flipo RM, Schaeverbeke T, Houvenagel E, Gaudin P, Loeuille D, Rist S, Dougados M, Sibilia J, Le Loët X, Meyer O, Solau-Gervais E, Marcelli C, Bardin T, Pane I, Baron G, Perrodeau E, Mariette X; all the investigators of the ORA registry and the French Society of Rheumatology. Ann Rheum Dis. 2015 (IF: 10.4).
4. Gut metagenome and spondyloarthritis. **Schaeverbeke T**, Truchetet ME, Richez C. Joint Bone Spine. 2013 Jul;80(4):349-52.
5. Epistatic interaction between BANK1 and BLK in rheumatoid arthritis: results from a large trans-ethnic meta-analysis. Génin E, Coustet B, Allanore Y, Ito I, Teruel M, Constantin A, **Schaeverbeke T**, Ruyssen-Witrand A, Tohma S, Cantagrel A, Vittecoq O, Barnetche T, Le Loët X, Fardellone P, Furukawa H, Meyer O, Fernández-Gutiérrez B, Balsa A, González-Gay MA, Chiocchia G, Tsuchiya N, Martin J, Dieudé P. PLoS One. 2013 Apr 30;8(4):e61044.
6. When and where does rheumatoid arthritis begin? **Schaeverbeke T**, Truchetet MÉ, Richez C. Joint Bone Spine. 2012 Dec;79(6):550-4.
7. Sources of information on lymphoma associated with anti-tumour necrosis factor agents: comparison of published case reports and cases reported to the French pharmacovigilance system. Théophile H, **Schaeverbeke T**, Miremont-Salamé G, Abouelfath A, Kahn V, Haramburu F, Bégaud B. Drug Saf. 2011 Jul 1;34(7):577-85.
8. Myeloid dendritic cells correlate with clinical response whereas plasmacytoid dendritic cells impact autoantibody development in rheumatoid arthritis patients treated with infliximab. Richez C, **Schaeverbeke T**, Dumoulin C, Dehais J, Moreau JF, Blanco P. Arthritis Res Ther. 2009;11(3):R100.
9. Should we eradicate Helicobacter pylori before prescribing an NSAID? Result of a placebo-controlled study. **Schaeverbeke T**, Broutet N, Zerbib F, Combe B, Bertin P, Lamouliatte H, Perié F, Joubert-Collin M, Mégraud F. Am J Gastroenterol. 2005 Dec;100(12):2637-43.
10. Potential role of Mycoplasma hominis in interleukin (IL)-17-producing CD4+ T-cell generation via induction of IL-23 secretion by human dendritic cells. Truchetet ME, Beven L, Renaudin H, Douchet I, Férandon C, Charron A, Blanco P, **Schaeverbeke T**, Contin-Bordes C, Bébéar C. J Infect Dis. 2011 Dec 1;204(11):1796-805.



Le 12/07/2015 Thierry Schaeverbeke

Annex 2: Description of the Department of General Practitioner

Department of general practice
College of Health Sciences – Bordeaux University

1 – Department missions :
• Organization of the training and education of general practice studies
• Management and monitoring of educational general practice students of Bordeaux University
• Lessons for the specialized study diploma of general practice (lessons in pedagogical local commissions, practical placements)
• Lessons in first and second cycle of medical studies (teaching in the units of 2nd cycle, optional certificates, training)
• Development of clinical research in primary care with the research center INSERM U 897 and CIC 07 EC.

2 - Activity 2014/2015 :
• Education:
- 2nd cycle: 326 hours
- 3rd cycle: 2314 hours

• Internships:
- 2nd cycle: 177 Internships for 7 weeks in DC3 and 31 Internships for 4 weeks in DC4
- 3rd cycle: 1200 Internships for 6 months (including 931 in hospitals and 17 + 252 in the community)

3 – Number of students in general practice 3rd cycle from Bordeaux subdivision (2014/2015): 688 IMG registered
- TCEM1: 211 including 9 military sudents
- TCEM2: 213, including 10 military students
- TCEM3: 264 IMG including 5military students

4 - Structure of the department:
● Management, project development and deliberation of the department in the University:
o One council
o Three standing committees:
- Educational committee
- Research committee
- Theses committee

o Ten local educational committees (LEC): decentralized on a hospital site or group of hospitals located in Aquitaine; coordinated by a university lecturer of the department; composed of hospital doctors, GPs teachers and tutors; responsible for the implementation of provisions adopted by the department of the council, on a proposal of the commissions.

5 - Resources of the department:

• Teachers:
o 1 Professor, director of the department: Professor Bernard GAY.
o 1 emeritus Professor, deputy director: Professor Jean-Louis DEMEAUX.
o 3 associated Professors: Prof. G. DUCOS, Prof. W. DURIEUX, Pr JP. JOSEPH (regional coordinator of general practice diploma specialized for the subdivision of Bordeaux)
o 5 associated masters conferences: Drs C. ADAM, Ph. CASTERA, S. DUHAMEL, L. MAGOT and F. PETREGNE.
o 3 heads clinic: Dr. Sh KINOUANI, Dr. M. Afonso, Dr. William CONORT.
o 77 charged teachers ; 23 attached teachers.
o 442 university internships supervisors
• Administrative staff:
1 administrative officer (Mrs. BONNIN) and 5 assistants.
• budgetary resources:
- Overall operating
- Additional course hours
• Premises
- 85 m²: 2 offices (Management, Administrative Management), 2 secretariats, 1 technical room.

6 - Department contact Information:

Website: www.dmg.u-bordeaux.fr
University of Bordeaux, DMG 146 rue Léo Saignat - 33076 Bordeaux cedex -
Tel. (33)5.57.57.13.11 - Fax: (33)5.57.57.14.13 - Email: directeur.medecine-generale-3@u-bordeaux.fr

Annex 3: Description of the clinical partners.

Partner : Hospital unit, Dermatology and Paediatric Dermatology

Localization : Saint André and Pellegrin Hospitals | **Institution** : University of Bordeaux

Head : Pr. Alain Taieb

Key personnal : Julien Seneschal, PU-PH, auto-immune and inflammatory skin disorders, Marie-Beylot Barry, PU-PH; inflammatory skin disorders, skin cancers, Marie-Sylvie Doutre PU-PH, Auto-immune skin disorder, vasculitis, collagenosis, Franck Boralevi, PU-PH, Atopic Dermatitis, Brigitte Milpied PH, allergology and Cutaneous Adverse Drugs Reactions.

Field of expertise: Auto-immune and Inflammatory skin disorders, Vitiligo, Psoriasis, Hidradenitis suppurativa, Atopic Dermatitis, Systemic Lupus, systemic sclerosis and Skin features of rare inflammatory diseases, auto-immune bullous dermatosis, cutaneous and systemic vasculitis

Cutaneous skin reactions to therapies used in inflammatory skin diseases.

Previous contributions : Epidemiology in Vitiligo : VITGENE consortium : international genome wide association studies in vitiligo : identification of genes associated with vitiligo disease. Patients from our unit are currently invited to participate in translational research : blood collection and skin biopsies samples)**.** Psoriasis: investigators in national clinical and biological studies from the GRPso (Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie) and from the RePso (French Network for Research on Psoriasis). Investigators (and member of the Scientific Council MBB) of the national cohort of psoriasis on systemic treatments (PSOBIOTEQ). Auto-immune bullous diseases : Investigators in national studies from the Groupe Bulles de la Société Française de Dermatologie. Vasculitis : participation to national studies of French Vasculitis Study group

Recognized Resources: National Reference Center for Rare Skin Diseases**,** VITGENE consortium**,** National Psoriasis cohort: PSOBIOTEQ (150 patients)**,** VISS (Vasculopathie, Inflammation et Sclérodermie Systémique) cohort (…patients)**,** Competence Center for Toxic Bullous Skin Disorders, REGISCAR : European Registry of Severe Cutaneous Adverse Reactions. Competence Center for auto-immune bullous dermatosis**.** Hidradenitis suppurativa: on-going establishment of multicentric cohort associated with translational research.

Expected contribution to the BIRD DHU: Cohort development with expertise in skin manifestations of systemic disorders to better improve early diagnosis ; patient databases with skin samples ; Phenotype and care of patients developing Cutaneous Adverse Skin Reactions induced by targeted therapies used in inflammatory and auto-immune diseases. Study of the relationship between cutaneous and systemic inflammatory diseases (psoriasis and hidradenitis), therapeutic approaches and pathophysiological models

Main grants since 2009: PHRC-N, Société Française de Dermatologie, Industrial grants

Relevant publications and patents in the field since 2001:

V. Eleftheriadou, K. Thomas, N. van Geel, I Hamzavi, H. Lim, T. Suzuki, I. Katayama, T. Anbar, M. Abdallah, L. Benzekri, Y. Gauthier, J. Harris, C.C. Silva de Castro, A. Pandya, B.K. Goh, C.C. Lan, N. Oiso, A. Al Issa, S. Esmat, C. Le Poole, A.Y. Lee, D. Parsad, A. Taieb, M. Picardo, K. Ezzedine; Vitiligo Global Issues Consensus Group (VGICG). Developing core outcome set for vitiligo trials: international e-Delphi consensus.**Pigment Cell Melanoma Res.** 2015; 28: 363-9

M.Jachiet, B.Flageul, A.Deroux, A.Le Quellec, F.Maurier, F.Cordolani, P.Godmer, C.Abascq, L.Belenotti, D.Bessis, A.Bigot, M.S.Doutre, M.Ebbo,I.Guichard, E.Hachulla,E.Heron, G.Jeudy,N.Jourde-Chiche,D.Jullien, C.Lavigne,L.Machet M.A.Marchet,C.Martet, S.Belkhir, C.Morice, A.Petit, B.Simorre, T.Zenone, L.Bouillet, M.Bagot, V.Bacchi-fremeaux ,L.Guillevin, L.Mouthon, N.Dupin, S.Aractingi, B.Terrier French Vasculitis Study group. The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a french nationwide study of fifty-seven patients **Arthritis Rheum** 2015;67:527-34

Y. Jin, S.A. Birlea , P.R. Fain, K. T.M. Ferrara, S. Ben, S.L. Riccardi, J.B. Cole, K. Gowan, P.J. Holland, D.C. Bennett, R.M. Luiten, A. Wolkerstorfer, J.P. van de Veen, A. Hartmann, S. Eichner, G. Schuler, N. Van Geel, J. Lambert, E.H. Kemp, D.J. Gawkrodeger, A.P. Weetman, A. Taieb, T. Jouary, K. Ezzedine, W.T. McCormack, M. Picardo, G. Leone, A. Overbeck, N.B. Silverberg, R.A. Spritz. Genome-wide association analyses identify 13 new susceptibility loci for generalized vitiligo. **Nat Genet**; 2014 42: 676-80.

F. Boralevi, M. Saint Aroman, A. Delarue, H. Raudsepp, A. Kaszuba, M. Bylaite, G.S. Tiplica . Long-term emollient therapy improves xerosis in children with atopic dermatitis. **J Eur Acad Dermatol Venereol** 2014;28:1456-62.

E. Mahé, A. Beauchet, C. Bodemer, A. Phan, A.C. Bursztejn, F. Boralevi, A.L. Souillet, C. Chiaverini, E. Bourrat, J. Miquel, P. Vabres, S. Barbarot, D. Bessis, C. Eschard, S. Hadj-Rabia; Groupe de Recherche de la Société Française de Dermatologie Pédiatrique. Psoriasis and obesity in French children: a case-control, multicentre study. **Br J Dermatol** 2014 Oct 31.

A. Taïeb, F. Boralevi, J. Seneschal, S. Merhand, V. Georgescu, C. Taieb, K. Ezzedine. Atopic Dermatitis Burden Scale for Adults: Development and Validation of a New Assessment Tool. **Acta Derm Venereol** 2014 Aug 14.

M..Rouzaud, M. Sevrain, A.P.Villani, T. Barnetche, C. Paul, M.A. Richard, D. Jullien, L. Misery, M. Le Maître, S. Aractingi, F. Aubin, P. Joly, A. Cantagrel, J.P. Ortonne , M. Beylot-Barry. Is there a psoriasis skin phenotype associated with psoriatic arthritis? Systematic literature review. **J Eur Acad Dermatol Venereol**. 2014 Aug;28 Suppl 5:17-26

M. Sevrain, A.P.Villani, M. Rouzaud, T. Barnetche, C. Paul, M.A. Richard, M. Beylot-Barry, D. Jullien, S. Aractingi, F.Aubin, P. Joly, M. Le Maitre, A. Cantagrel, J.P. Ortonne , L.Misery. Treatment (biotherapy excluded) of psoriatic arthritis: an appraisal of methodological quality of international guidelines. **J Eur Acad Dermatol Venereol**. 2014 Aug;28 Suppl 5:33-9

M. Sevrain, M.A. Richard, T. Barnetche, M. Rouzaud, A.P. Villani , C.Paul, M. Beylot-Barry, D. Jullien, S. Aractingi, F. Aubin, P. Joly, M. Le Maitre, A. Cantagrel, J.P. Ortonne, L. Misery. Treatment for palmoplantar pustular psoriasis: systematic literature review, evidence-based recommendations and expert opinion.**J Eur Acad Dermatol Venereol**. 2014 Aug;28 Suppl 5:13-6.

M. Viguier, C. Livideanu, M. Beylot-Barry, M.A. Richard, C. Paul, H. Bachelez, F. Aubin; Groupe de Recherche sur le Psoriasis.

Observational case series on a group of psoriasis patients who failed to respond to any TNF blockers. **J Dermatolog Treat.** 2014 Feb;25(1):75-7.

N.Colliou, D.Picard, F.Caillot, S.Calbo, S.Le Corre,A.lim, B.Lemercier, B.LeMauff, M.Maho-Vaillant, S.Jacquot, C.Bedane, P.Bernard, F.Caux, C.Prost, E.Delaporte, M.S.Doutre, B.Dreno, N.Franck, S.Ingen-Housz-Oro, O.Chosidow, C.Pauwels, C.Picard,JC Roujeau, M.Sigal, E.Tancrede-Bohin,, I.Templier, R.Eming,M.Hertl, M.D'Incan, P.Joly, P.Musette Long-term remissions of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response **Sci Transl Med** 2013; March 6;5(175):175ra30

J.Seneschal, B.Milpied, A.Taieb. Cutaneous drug eruptions associated with the use of biologies and cutaneous drug eruptions mimicking specific skin disease. **Chem Immunol Allergy**. 2012; 97:203-16

M. Viguier, F.Aubin, E. Delaporte, C. Pagès, C. Paul, M. Beylot-Barry, C. Goujon, M. Rybojad, H. Bachelez; Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie. Efficacy and safety of tumor necrosis factor inhibitors in acute generalized pustular psoriasis **Arch Dermatol**. 2012 Dec;148(12):1423-5.

A. Maza, M.A. Richard, F. Aubin, J.P. Ortonne, S. Prey, H. Bachelez, M. Beylot-Barry, C. Bulai-Livideanu, M. Lahfa, J. Nougué, X. Mengual, M. Le Moigne, V. Lauwers-Cances, C. Paul. Significant delay in the introduction of systemic treatment of moderate to severe psoriasis: a prospective multicentre observational study in outpatients from hospital dermatology departments in France. **Br J Dermatol.** 2012 Sep;167(3):643-8.

M. Viguier, C. Pagès, F. Aubin, E. Delaporte, V. Descamps, C. Lok, M. Beylot-Barry, J. Seneschal, L. Dubertret, J.J. Morand, B. Dréno, H. Bachelez; Groupe Français de Recherche sur le Psoriasis. Efficacy and safety of biologics in erythrodermic psoriasis: a multicentre, retrospective study. **Br J Dermatol**. 2012 Aug;167(2):417-23.

S.leger, D.Picard, S.Ingen-Housz-Oro, JP Arnault, F.Aubin, F.Carsuzaa, G.Chaumentin, J.Chevran-Breton, O.Chosidow, B.Crickx, M.D'Incan, M.Dandurand, S.Debarbieux, E.Delaporte, O.Dereure, M.S. Doutre, G.Guillet, D.Jullien, I.Kupfer,J.P.Lacour, F.Leonard, C.Lok, L.Machet, L.Martin, C.Paul, JM Pignon,C.Robert, L.Thomas,P.J.Weiller, V.Ferranti, D.Gilbert, P.Courville, E.Houivet, J.Benichou,P.Joly Prognostic factors of paraneoplastic pemphigus **Arch Dermatol** 2012; 148:1165-72

D.Laharie, J.Seneschal, T.Shaeverbeke, M.S.Doutre, M.Longy-Boursier, J.L.Pellegrin, E.Chabrun, S.Villars, F.Zerbib, V.de Lédinghen. Assessment of liver fibrosis with transient elastography and FibroTest patients treated with methotrexate for chronic inflammatory disases: A case-control study. **J Hepatol**. 2010. 1035-40

Y. Jin, S.A. Birlea, P.R. Fain, K. Gowan, S.L.Riccardi, P.J. Holland, C.M. Mailloux, A.J.D. Sufit, S.M. Hutton, A. Amadi-Myers, D.C. Bennett, M.R. Wallace, W.T. McCormack, E.H. Kemp, D.J. Gawkrodger, A.P. Weetman, M. Picardo, G. Leone, A. Taïeb , T. Jouary, K. Ezzedine, N. Geel, J. Lambert, A. Overbeck, R.A. Spritz. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo**. N Engl J Med** 2010; 362: 1686-97.

J.Seneschal, B.Milpied, B.Vergier, S.Lepreux, T.Schaeverbeke, A.Taieb. Cytokine imbalance with increased production of IFN alpha in psoriasiform eruptions occurring under anti-TNF treatments**. Br J Dermatol**: 2009; 161: 1081-8

A.Taieb, M. Picardo: Clinical practice. Vitiligo. **N Engl J Med** 2009: 360: 160-9

P.Joly, JC Roujeau,J.Benichou,M.D'Incan, E.Delaporte, B.Dreno, C.Bedane, A.Sparsa, I.Gorin, E.Tancrede-Bohin, B.Sassolas, C.Lok, JC Guillaume, M.S.Doutre, MA Richard, F.Caux, C.Prost, P.Plantin, O.Chosidow C.Pauwells,P.Saiag, V.Descamps, J. Chevrant-Breton, O.Dereure, MF Hellot, E.Esteve, P.Bernard A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid **J Invest Dermatol** 2009;129:1681-7

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Partner : Diabetology Channel	
Localization Haut-Lévêque	**Institution : CHU Bordeaux**

Head : Vincent Rigalleau
Key personnal : Laurence Blanco, Marie Hugo, Henri Gin

Field of expertise:

The Diabetology channel is a part of the Endocrinology-Nutrition Department of the CHU of Bordeaux. The clinical ward includes 30 beds, and two ambulatory care networks (diabetic pregnancy and diabetic foot).

Previous contributions :

1- Nutritional an Metabolic follow-up of Rheumatoid Arthritis (RA)

This is a collaborative study between our Unit and the Dept of Rheumatology (T Schaeverbeke). Like other inflammatory diseases, RA has nutritional complications: Rheumatoid Cachexia and the Metabolic Syndrom. Using indirect calorimetry and long term actimetry, we are studying how Resting and Physical Activity-Related energy expenditure are altered by the disease and its nutritional complications, and the impact of glucocorticoids and biotherapies on these complications. A special interest is focused on the mood and cognitive impacts in collaboration with the NutriNeuro team (L Capuron). Presently (May 2015), 57 patients have been included in the cross sectional study, and 20 have had a second evaluation three months later, one article is submitted and another is in preparation. Studying the nutritional outcome of other inflammatory diseases (Intestinal, or others) is an important perspective.

2-Immunotherapy of Type 1 Diabetes (T1D): Participation to the multicentric DIAB-IL2 trial

DIAB-IL2 is a multicentric international randomized controlled trial of Interleukin 2 in recent onset T1D, the principal investigator is D Klatzmann (Paris), Bordeaux is one of the four first french centers registered to participate (with Paris, Lyon and Lille). Our unit, the pediatric endocrinology unit (Pr Barat), and the Immunology Dept (Pr Blanco) are involved in the project. The first inclusions in Bordeaux are expected for summer 2015.

Expected contribution to the AIR DHU

1-A Randomized controlled trial on GlucoCorticoid induced diabetes

The frequency of admissions for glucose control and education for GC-induced diabetes is growing. The underlying disease are multiple (Inflammatory diseases, GVH…). Three years ago, a simplified strategy based on the use of intermediar lenght of action insulin (Isophane insulin) has been shown as effective for the treatment of New Onset Diabetes After Transplantation, which shares some characteristics with GC induced diabetes: the patients who were precocely treated with morning Isophane insulin to prevent the rise of evening plasma glucose had 73% less NODAT during the follow-up, and all were insulin-independent one year after (Hecking M, J Am Soc Nephrol 2012). The elegant trial that established this strategy included only 50 patients, we therefore suggest that a similar trial can be performed in Bordeaux monocenter, which can help to structure the BIRD. The especial link between our unit and the Endocrinology Dept (Pr Tabarin) will be a winning card for this project.

2-Type 2 Diabetes and Obesity as Inflammatory Diseases

The information on the potential importance of chronic low-grade inflammation, and gut microbiote alterations, on the deleterious consequences of Obesity and T2D is growing, however its relevance for the clinician is not clear. Among the patients hospitalized for T2D in our ward, with no overt infections, 50% have usCRP>5 mg/L, preliminary work from our team suggests that their metabolic fonction may differ, with low respiratory quotients that predispose to weight loss. Why some patients, not others, do develop inflammation, and whether this may influence their prognosis (nutritional status and diabetic vascular complications) is unknown.

As a member of the DHU ARGID, our team will have the opportunity to develop a two-step strategy to describe the clinical meaning of low-grade inflammation in T2D, and Obesity, in collaboration with the Obesity Channel of our Dept (Pr Gatta-Cherifi):

1st, cross sectional: Are T2D and obese patients with LG- inflammation different?

Beside nutritional investigations (body composition analysis, energy expenditure), the study of the fonction of their inflammasome (Dr Faustin) is an especially interesting perspective, as some clinical observations (Dr Kaminski, Pr Neau) suggest that widely used antidiabetic drugs as DPP4-inhibitors may alter this function.

2nd, longitudinal: Are vascular complications more agressive in T2D patients with low-grade inflammation? Our special link with the LEHA team (Lifelong Exposure, Health and Aging, C Delcourt, C Féart, C Helmer, MN Delyfer) of the ISPED will help establish a cohort of long standing T2D, extending our collaboration with other Diabetes-specialized team of the new Region (Pr S Hadjadj, Poitiers), with the

team of MC Durrieu and Marc Plawinski (Institute of Chemistry & Biology of Membranes & Nanoobjects, IECB) for the analysis of microparticles, and with the Nuclear Medicine team (JB Corcuff, J Brossaud) for the detection of Advanced Glycation Endproducts in biological fluids. The participation of Dr K Mohammedi (Paris), who will join our team on November 2016 after his post-doc fellowship in Sidney, on the analysis the peripheral arterial disease in the ADVANCE trial, will be a critical advantage to establish this cohort.

Main grants since 2009
Grant ALFEDIAM 2009 (APDT2 project, C Fagour, Collaboration Fort de France – Bordeaux)

Relevant publications and patents in the field since 2001:

1-V. Rigalleau, C. Binnert, K. Minehira, N. Stefanoni, P. Schneiter, E. Henchoz, O. Matzinger, C. Cayeux, E. Jéquier, L. Tappy.

In normal men, free fatty acids reduce peripheral, but not splanchnic glucose uptake. Diabetes 2001,50 : 727-32.
2-L Baillet, Rigalleau V, Aparicio M, Barthe N, Gin H. Energy expenditure following oral glucose load in ten uremic patients before and after three months on a ketoacid-supplemented very-low protein diet. Metabolism 2001, 50 : 335-41.
3-V Rigalleau, C Rabemanantsoa, H Gin. A 3-day insulin-induced normoglycemia improves carbohydrate oxidation in type 2 diabetic patients. Metabolism 2002, 51 :1484-8.
4-V. Rigalleau, C. Lasseur, S. Pécheur, P. Chauveau, C. Combe, C. Perlemoine, L. Baillet, H. Gin . Resting energy expenditure in uremic, diabetic, and uremic diabetic subjects. J Diabetes Complications 2004 ;18 :237-41.

5-Hadjadj S, Pean F, Gallois Y, Passa P, Aubert R, Weekers L, Rigalleau V, Bauduceau B, Bekherraz A, Roussel R, Dussol B, Rodier M, Marechaud R, Lefebvre PJ, Marre M. Different patterns of insulin resistance in relatives of type 1 diabetic patients with retinopathy or nephropathy: the genesis france-belgium study. Diabetes Care. 2004;27:2661-8.
6-V. Rigalleau, L. Baillet-Blanco, C. Perlemoine, L.R. Salmi, H. Gin .Normal plasma triglycerides are associated with increased risk of insulin requirement in poorly controlled type 2 diabetic patients. Diabetic Medicine 2005,22 :877-81.

7- Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Liu C, Chauveau P, Baillet-Blanco L, Beauvieux MC, Combe C, Gin H. Estimation of glomerular filtration rate in diabetic subjects: Cockcroft or MDRD formula ? Diabetes Care 2005, 28 :838-43.
8-Perlemoine C, Macia F, Tison F, Coman I, Guehl D, Burbaud P, Cuny E, Baillet L, Gin H, Rigalleau V. Effects of subthalamic nucleus deep brain stimulation and levodopa on energy production rate and substrate oxidation in Parkinson's disease.Br J Nutr. 2005; 93:191-8.
9-Rigalleau V, Beauvieux M, Gallis J, Gin H, Schneiter P, Tappy L. Effects of hyperglycemia on glucose metabolism before and after oral glucose ingestion in normal men. Am J Physiol Endocrinol Metab. 2006, 290:E1198-204.
10-Rigalleau V, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P , Combe C, Gin H.Glucose control influences Glomerular Filtration Rate and its prediction in diabetic subjects. Diabetes Care 2006;29:1491-5.

11-A Secchiutti, C Fagour, C Perlemoine, H Gin, J Durrieu, V Rigalleau. Air displacement plethysmography can detect moderate changes in body composition. European Journal of Clinical Nutrition 2007; 61 : 25-9.
12-M. Le Carvennec, C. Fagour, E. Adenis-Lamarre, C. Perlemoine, H. Gin, V. Rigalleau . Body composition of obese subjects by air Displacement Plethysmography : the influence of hydration. Obesity 2007; 15 : 78-84.

13-Rigalleau V, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P , Aparicio M, Combe C, Gin H.
Bone loss in diabetic patients with chronic kidney disease. Diabetic Medicine 2007; 24:91-93.

14-Raffaitin C, Lasseur C, Chauveau P, Barthe N, Gin H, Combe C, Rigalleau V. Nutritional status in patients with diabetes and chronic kidney disease : a prospective study. Am J Clin Nutr 2007, 85 : 96-101.

15-Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N, Chauveau P, Combe C, Gin H. Normoalbuminuric renal insufficient diabetic patients: A lower risk group Diabetes Care 2007, 30 : 2034-9.

16-Beauvieux MC, Le Moigne F, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P, Combe C, Gin H, Rigalleau V.New Predictive Equations Improve Monitoring of Kidney Function in Patients with Diabetes. Diabetes Care 2007, 30: 1979-87.
17-Fagour C, Gonzalez C, Suberville C, Higueret P, Rabemanantsoa C, Beauvieux MC, Gin H, Rigalleau V. Early decrease in resting energy expenditure with bed-time insulin therapy. Diabetes & Metabolism, Diabetes Metab. 2009; 35:332-5

18-Pezzino S, Florenty , Fagour C, Gin H, Rigalleau V. Remedial actions for the physical inactivity of hospitalized patients with type 2 diabetes. Diabetes Care 2010 ;33 :1960-1

19-Rubin S, Le Piffer AL, Rougier MB, Delyfer MN, Korobelnik JF, Redonnet Vernhet I, Marchal C, Goizet C, Mesli S, Gonzalez C, Gin H, Rigalleau V. Sight threatning phenylketonuric encephalopathy in a young adult, reversed by diet. JIMD Reports 2013; 10:83-5

20-Geneviève M, Vivot A, Gonzalez C, Raffaitin C, Barberger-Gateau P, Gin H, Rigalleau V. Skin autofluorescence is associated with past glycemic control and complications in type 1 diabetes mellitus. Diabetes Metab. 2013;39: 349-54

21-Gonzalez C, De ledinghen V, Vergniol J, Foucher J, Le Bail B, Carlier S, Maury E, Gin H, Rigalleau V. Hepatic steatosis, carbohydrate intake, and food quotient in patients with NAFLD. Int J Endocrinol 2013; 428542

22-Saulnier PJ, Gand E, Ragot S, Ducrocq G, Halimi JM, Hulin-Delmotte C, Llaty P, Montaigne D, Rigalleau V, Roussel R, Velho G, Sosner P, Zaoui P, Hadjadj S, for the SURDIAGEN Study group. Association of serum concentration of TNFR1 with all-cause mortality in patients with type 2 Diabetes and Chronic Kidney Disease: Follow-up of the SURDIAGENE cohort. DiabetesCare 2014; 37: 1425-31

23-Gonzalez C, Fagour C, Maury E, Cherifi B, Salandini S, Pierreisnard A, Masquefa-Giraud P, Gin H, Rigalleau V. Early modifications in respiratory quotient and energy expenditure predict later weight in patients treated for uncontrolled Type 2 Diabetes Diabetes Metab., 2014 (44):299-304

24-Rajaobelina K, Cougnard-Gregoire A, Delcourt C, Gin H, Barberger-Gateau P, Rigalleau V. Autofluorescence of skin advanced glycation end products: marker of metabolic memory in the elderly. J Gerontol A Biol Sci Med Sci Accepté 11/2014

25- Maury E , Savel J , Grouthier V , Rajaobelina K, Corvo L, Lorrain S , Gonzalez C, Gin H, Barberger-Gateau P , Rigalleau V. Is skin autofluorescence a marker of metabolic memory in pregnant women with diabetes? Diabetic Medicine, accepté le 25/03/2015

Partner : Service de Médecine Interne et Maladies Infectieuses	
Localization : Hôpital Saint-André, Bordeaux	**Institution : CHU de Bordeaux**

Head : Fabrice Bonnet (PU-PH)
Key personnal : Philippe Morlat (PU-PH), Marie-Anne Vandenhende (PH)

Field of expertise:
A research clinic department involved in the management of chronic inflammatory diseases, and complications of long-term immunosuppression in the field of HIV infection and use of immunosuppressive drugs.

Previous contributions :
F Bonnet is the principal Investigator (PI) of the **Aquitaine Cohort** (Grant from the French National Agency against HIV), a large cohort of HIV-infected patients (3875 patients in active follow-up in 2013). One of the main objectives of the cohort is to describe the incident morbidity in people with immunosuppression.
F Bonnet is the PI of the **INFIM Cohort** (Grant from PHRC 2013), a cohort of patients with inflammatory diseases treated with immunosuppressive/biological agent. The objective of this cohort is to describe the long-term morbidity of these patients.
P Morlat and F Bonnet are PI or coinvestigators of many observational and phase IIIstudies in the field of HIV infection and inflammatory diseases

Expected contribution to the AIR DHU
Description of the incident morbidity of people treated for inflammatory disease. Identification of risk factors for severe morbid events occurring during the course of inflammatory diseases, prevention and management.

Main grants since 2009
Mortalité 2010 (ANRS 2010) : A national study about the causes of death in people livinh with HIV in 2010.
INFIM Cohort (PHRC 2013)
Aquitaine Cohort (ANRS 2015)
The SAGA Study : (PHRC 2014) : Mortality and economic impact of stopping statins in people aged of 75 and over: a pragmatic clinical trial
A national case-control study about the risk of lung cancer in people treated with ritonavir (ANRS 2011)

Relevant publications and patents in the field since 2001:

1 M Bruyand, R Thiébaut, G Chêne, S Lawson-Ayayi, P Joly, JL Pellegrin, M Decoin, A Sasco, D Neau, P Morlat, F Bonnet. Role of Uncontrolled HIV RNA Level and Immunodeficiency in the Occurrence of Malignancy in HIV-Infected Patients during the Combination Antiretroviral Therapy Era: Agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort. *Clin Inf Di* 2009 ; 49 : 1109-16.
2 M Bruyand, F Dabis, MA Vandenhende, E Lazaro, D Neau, O Leuleux, S Geffard, P Morlat, G Chêne, F Bonnet. **A higher risk of hepatocarcinoma is associated with HIV-induced immune deficiency, ANRS CO3 Aquitaine Cohort, 1998-2008.** *J Hepatol* 2011 ; 55 : 1058-62.

3 B Terrier, E Krastinova, I Marie, D Launay, A Lacraz, P Belenotti, I de Saint-Martin, T Quemeneur, A Huart, F Bonnet, G Le Guenno, JE Kahn, O Hinschberger, P Rullier, E Diot, E Lazaro, F Bridoux, T Zénone, F Carrat, O Hermine, JM Léger, X Mariette, P Senet, E Plaisier, P Cacoub. Management of non-infectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey. *Blood* 2012 ; 119 : 5996-6004.

4 F Bonnet, H Amieva, F Marquant, M Bruyand, FA Dauchy, P Mercié, C Greib, L Richert, D Neau, P Dehail, F Dabis, P Morlat, JF Dartigues, G Chêne. Cognitive disorders in HIV-infected patients: are they HIV-related? ANRS CO3 Aquitaine Cohort, Bordeaux, France, 2007-2009. *AIDS* 2013 ; 27 : 391-400.
5 P Morlat, A Vivot, MA Vandenhende, FA Dauchy, J Asselineau, E Déti, Y Gérard, E Lazaro, P Dufau, D Neau, F Bonnet, G Chêne **Role of traditional risk factors and antiretroviral drugs in the incidence of chronic kidney disease, ANRS CO3 Aquitaine Cohort,**

France, 2004-2008. *Plos One* 2013 ; 8 : 66223**.**

6 B Terrier, I Marie, D Launay, A Lacraz, P Belenotti, L de Saint-Martin, T Quemeneur, A Huart, F Bonnet, G Le Guenno, JE Kahn, O Hinschberger, P Rullier, E Diot, E Lazaro, F Bridoux, T Zenone, F Carrat, O Hermine, JM Léger, X Mariette, P Senet, E Plaisier, P Cacoub. **Predictors of early relapse in patients with non-infectious mixed cryoglobulinemia vasculitis: results from the French nationwide CryoVas survey.** Autoimmun Rev 2014 ; 10 Jan (Epub ahead of print)

7 M Vandenhende, C Roussillon, S Henard, D Salmon, P Cacoub, A Georget, A Aouba, E Rosenthal, T May, D Costagliola, G Chene, P Morlat, F Bonnet for the ANRS EN20 Mortalité 2010 study group*. **Cancers are still the leading cause of death in HIV-infected people: Results of the ANRS EN20 Mortality 2010 study group.** Plos One (in press)

Partner : **Hospital unit: Department of Pediatrics**	
Localization : Children's Hospital, Bordeaux	**Institution : University Hospital of Bordeaux**

Head : Thierry LAMIREAU, Pascal PILLET, Jérôme HARAMBAT

Key personnal : Christine Leauté-Labreze (PH), Olivier Richer (PH), Laurent Rebouissoux (PH), Haude Clouzeau (PH), Brigitte Llanas (PH), Nathalie Aladjidi (PH)

Field of expertise:

- A clinical unit devoted to management and follow-up of children with auto-immune or inflammatory diseases: juvenile idiopathic arthritis, hereditary recurrent fevers, systemic lupus erythematosus, childhood ANCA- associated vasculitis, inflammatory bowel diseases, cystic fibrosis, nonalcoholic steatohepatitis, psoriasis, vitiligo...

Previous contributions :

- Clinical trials on anti-TNFα in pediatric inflammatory bowel disease
- Clinical trials on interleukin-1 receptor antagonist in juvenile idiopathic arthritis
- Pharmacokinetic study MMF in children with systemic lupus erythematosus

Expected contribution to the AIR DHU

- access to human materials from different chronic inflammatory diseases in children
- access to pediatric clinical research networks in the field of inflammatory diseases (SOFREMIP, PRINTO, PHARMA-CHILD, GETAID pédiatrique, European Cystic Fibrosis Network, French vasculitis study group)

Main grants since 2009

Relevant publications and patents in the field since 2001:

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Score SIGAPS (période2012-2015) : 2888

Nombre de publications de rang A et B (période 2012-2015): rang A : 68, rang B : 75

Label CIC : CIC plurithématique, axe pédiatrique

Résultats aux appels à projets nationaux ou européens : PHRC Primavera

Actions d'éducation thérapeutique : Insuffisance Rénale Chronique, greffe rénale, Maladies Inflammatoires Chroniques de l'Intestin

Centres de Références Maladies Rares : maladies rénales rares **(**SORARE), Syndrome d'Evans et cytopénie auto-immune (CEREVANCE), Mucoviscidose (CRCM)

Centres de Compétences Maladies Rares : atrésie des voies biliaires (AVB), maladies digestives rares (MARDI), maladie de Wilson, arthrite juvénile idiopathique, maladies auto-inflammatoires,

Démarche d'enseignement intégré au profit des étudiants en médecine et en sciences : enseignement intégré de pédiatrie au étudiants DFASM

Demandes d'inter-CHU : en moyenne 1 par an

Nombre de doctorants et de post-doctorants des 4 dernières années : 2

Nombre d'étudiants en master 2 des 4 dernières années : 3

Séminaires et formations spécifiques dans le domaine de la recherche : réunion annuelle du CEntre De Recherche de l'hôpital des Enfants (CEDRE), organisation de séminaires d'hépatologie pour la Société Européenne de Gastroentérologie Pédiatrique (ESPGHAN)

Partner : **Hospital unit: Departments of Gynecology Obstetrics/Genetic/Pediatric/Nephrology**	
Localization : CHU Bordeaux, Pellegin, centre Aliénor d'Aquitaine	**Institution : CHU Bordeaux**
Head : Pierre Chabanier **Key personnal** : **Stéphanie Brun (CCA), Dominique Carles (PH), Caroline Rooryck-Thambo (PH), Eric Dumas de la Roque (PH), Yahsou Delmas-Garcia (PH), Jean-Benoit Thambo (PU-PH), Hélène Gomer (PH), Dominique Dallay (PU-PH), Jean-Luc Brun (PU-PH), Robert Saura (PU-PH), Frédérique Coatleven (PH), Marie Anne Coustel (PH)**	
Field of expertise: We have a national and international long term reputation in chorionic villus sampling, Bordeaux has the biggest series in France far ahead of other centres. So we highlighted some early placental lesions in the case of inflammatory diseases thanks to our collaboration with the foeto-pathology department which has more than fifteen years of experience in this placental vascular pathology. **Previous contributions :** - pathological and normal pregnancy research unit in Paris INSERM UMR-S 1139 and with Professor Alain Brisson's research unit UMR-CBMN CNRS in Bordeaux to study placental expression of genes of interest and maternal serum markers in pathological pregnancies : vascular intrauterine growth restriction and preeclampsia. - Bordeaux hospital is Competence Center for Thrombotic Microangiopathies (Dr Yahsou Delmas-Garcia) and developed strong network with clinicians (ICU, internal medicine, hematologists, nephrologists, obstetricians, pediatricians…) and biologists of the university hospital and of South-West of France (Aquitaine). The hemostasis laboratory (Dr Ryman) has developed ADAMTS-13 assay with very sensitive full length technique and the assay is available routinely from 2007. - We are developing at present our collaboration with INSERM U-1045 concerning the research on human being fœtal tissue with Dr Eric Dumas de la Roque. - we have the expertise in fœtal echocardiography in case of positive SSA antibody with Professor Jean-Benoit Thambo's department.	
Expected contribution to the AIR DHU	
Main grants since 2009 **PRBB study** (Pré-éclampsie Retard de croissance Brun Bardy): **placental growth factor in maternal blood and dysgravidie, Bordeaux current study** **PHRC PERASTUN** (Prévention de la pré-éclampsie et du retard de croissance intra-utérin par l'aspirine à faible dose chez les primipares ayant des notch utérins bilatéraux au premier trimestre, étude randomisée pragmatique)**, (developer : CHU Tours)**	

Partner : Diabetology Channel	
Localization Haut-Lévêque	**Institution : CHU Bordeaux**

Head : Vincent Rigalleau
Key personnal : Laurence Blanco, Marie Hugo, Henri Gin

Field of expertise:

The Diabetology channel is a part of the Endocrinology-Nutrition Department of the CHU of Bordeaux. The clinical ward includes 30 beds, and two ambulatory care networks (diabetic pregnancy and diabetic foot).

Previous contributions :

1- Nutritional an Metabolic follow-up of Rheumatoid Arthritis (RA)

This is a collaborative study between our Unit and the Dept of Rheumatology (T Schaeverbeke). Like other inflammatory diseases, RA has nutritional complications: Rheumatoid Cachexia and the Metabolic Syndrom. Using indirect calorimetry and long term actimetry, we are studying how Resting and Physical Activity-Related energy expenditure are altered by the disease and its nutritional complications, and the impact of glucocorticoids and biotherapies on these complications. A special interest is focused on the mood and cognitive impacts in collaboration with the NutriNeuro team (L Capuron). Presently (May 2015), 57 patients have been included in the cross sectional study, and 20 have had a second evaluation three months later, one article is submitted and another is in preparation. Studying the nutritional outcome of other inflammatory diseases (Intestinal, or others) is an important perspective.

2-Immunotherapy of Type 1 Diabetes (T1D): Participation to the multicentric DIAB-IL2 trial

DIAB-IL2 is a multicentric international randomized controlled trial of Interleukin 2 in recent onset T1D, the principal investigator is D Klatzmann (Paris), Bordeaux is one of the four first french centers registered to participate (with Paris, Lyon and Lille). Our unit, the pediatric endocrinology unit (Pr Barat), and the Immunology Dept (Pr Blanco) are involved in the project. The first inclusions in Bordeaux are expected for summer 2015.

Expected contribution to the AIR DHU

1-A Randomized controlled trial on GlucoCorticoid induced diabetes

The frequency of admissions for glucose control and education for GC-induced diabetes is growing. The underlying disease are multiple (Inflammatory diseases, GVH…). Three years ago, a simplified strategy based on the use of intermediar lenght of action insulin (Isophane insulin) has been shown as effective for the treatment of New Onset Diabetes After Transplantation, which shares some characteristics with GC induced diabetes: the patients who were precocely treated with morning Isophane insulin to prevent the rise of evening plasma glucose had 73% less NODAT during the follow-up, and all were insulin-independent one year after (Hecking M, J Am Soc Nephrol 2012). The elegant trial that established this strategy included only 50 patients, we therefore suggest that a similar trial can be performed in Bordeaux monocenter, which can help to structure the BIRD. The especial link between our unit and the Endocrinology Dept (Pr Tabarin) will be a winning card for this project.

2-Type 2 Diabetes and Obesity as Inflammatory Diseases

The information on the potential importance of chronic low-grade inflammation, and gut microbiote alterations, on the deleterious consequences of Obesity and T2D is growing, however its relevance for the clinician is not clear. Among the patients hospitalized for T2D in our ward, with no overt infections, 50% have usCRP>5 mg/L, preliminary work from our team suggests that their metabolic fonction may differ, with low respiratory quotients that predispose to weight loss. Why some patients, not others, do develop inflammation, and whether this may influence their prognosis (nutritional status and diabetic vascular complications) is unknown.

As a member of the DHU ARGID, our team will have the opportunity to develop a two-step strategy to describe the clinical meaning of low-grade inflammation in T2D, and Obesity, in collaboration with the Obesity Channel of our Dept (Pr Gatta-Cherifi):

1st, cross sectional: Are T2D and obese patients with LG- inflammation different?

Beside nutritional investigations (body composition analysis, energy expenditure), the study of the fonction of their inflammasome (Dr Faustin) is an especially interesting perspective, as some clinical observations (Dr Kaminski, Pr Neau) suggest that widely used antidiabetic drugs as DPP4-inhibitors may alter this function.

2nd, longitudinal: Are vascular complications more agressive in T2D patients with low-grade inflammation? Our special link with the LEHA team (Lifelong Exposure, Health and Aging, C Delcourt, C Féart, C Helmer, MN Delyfer) of the ISPED will help establish a cohort of long standing T2D, extending our collaboration with other Diabetes-specialized team of the new Region (Pr S Hadjadj, Poitiers), with the

team of MC Durrieu and Marc Plawinski (Institute of Chemistry & Biology of Membranes & Nanoobjects, IECB) for the analysis of microparticles, and with the Nuclear Medicine team (JB Corcuff, J Brossaud) for the detection of Advanced Glycation Endproducts in biological fluids. The participation of Dr K Mohammedi (Paris), who will join our team on November 2016 after his post-doc fellowship in Sidney, on the analysis the peripheral arterial disease in the ADVANCE trial, will be a critical advantage to establish this cohort.

Main grants since 2009
Grant ALFEDIAM 2009 (APDT2 project, C Fagour, Collaboration Fort de France – Bordeaux)

Relevant publications and patents in the field since 2001:

1-V. Rigalleau, C. Binnert, K. Minehira, N. Stefanoni, P. Schneiter, E. Henchoz, O. Matzinger, C. Cayeux, E. Jéquier, L. Tappy.

In normal men, free fatty acids reduce peripheral, but not splanchnic glucose uptake. Diabetes 2001,50 : 727-32.

2-L Baillet, Rigalleau V, Aparicio M, Barthe N, Gin H. Energy expenditure following oral glucose load in ten uremic patients before and after three months on a ketoacid-supplemented very-low protein diet. Metabolism 2001, 50 : 335-41.

3-V Rigalleau, C Rabemanantsoa, H Gin. A 3-day insulin-induced normoglycemia improves carbohydrate oxidation in type 2 diabetic patients. Metabolism 2002, 51 :1484-8.

4-V. Rigalleau, C. Lasseur, S. Pécheur, P. Chauveau, C. Combe, C. Perlemoine, L. Baillet, H. Gin . Resting energy expenditure in uremic, diabetic, and uremic diabetic subjects. J Diabetes Complications 2004 ;18 :237-41.

5-Hadjadj S, Pean F, Gallois Y, Passa P, Aubert R, Weekers L, Rigalleau V, Bauduceau B, Bekherraz A, Roussel R, Dussol B, Rodier M, Marechaud R, Lefebvre PJ, Marre M. Different patterns of insulin resistance in relatives of type 1 diabetic patients with retinopathy or nephropathy: the genesis france-belgium study. Diabetes Care. 2004;27:2661-8.

6-V. Rigalleau, L. Baillet-Blanco, C. Perlemoine, L.R. Salmi, H. Gin .Normal plasma triglycerides are associated with increased risk of insulin requirement in poorly controlled type 2 diabetic patients. Diabetic Medicine 2005,22 :877-81.

7- Rigalleau V, Lasseur C, Perlemoine C, Barthe N, Raffaitin C, Liu C, Chauveau P, Baillet-Blanco L, Beauvieux MC, Combe C, Gin H. Estimation of glomerular filtration rate in diabetic subjects: Cockcroft or MDRD formula ? Diabetes Care 2005, 28 :838-43.

8-Perlemoine C, Macia F, Tison F, Coman I, Guehl D, Burbaud P, Cuny E, Baillet L, Gin H, Rigalleau V. Effects of subthalamic nucleus deep brain stimulation and levodopa on energy production rate and substrate oxidation in Parkinson's disease.Br J Nutr. 2005; 93:191-8.

9-Rigalleau V, Beauvieux M, Gallis J, Gin H, Schneiter P, Tappy L. Effects of hyperglycemia on glucose metabolism before and after oral glucose ingestion in normal men. Am J Physiol Endocrinol Metab. 2006, 290:E1198-204.

10-Rigalleau V, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P , Combe C, Gin H.Glucose control influences Glomerular Filtration Rate and its prediction in diabetic subjects. Diabetes Care 2006;29:1491-5.

11-A Secchiutti, C Fagour, C Perlemoine, H Gin, J Durrieu, V Rigalleau. Air displacement plethysmography can detect moderate changes in body composition. European Journal of Clinical Nutrition 2007; 61 : 25-9.

12-M. Le Carvennec, C. Fagour, E. Adenis-Lamarre, C. Perlemoine, H. Gin, V. Rigalleau . Body composition of obese subjects by air Displacement Plethysmography : the influence of hydration. Obesity 2007; 15 : 78-84.

13-Rigalleau V, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P , Aparicio M, Combe C, Gin H.
Bone loss in diabetic patients with chronic kidney disease. Diabetic Medicine 2007; 24:91-93.

14-Raffaitin C, Lasseur C, Chauveau P, Barthe N, Gin H, Combe C, Rigalleau V. Nutritional status in patients with diabetes and chronic kidney disease : a prospective study. Am J Clin Nutr 2007, 85 : 96-101.

15-Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N, Chauveau P, Combe C, Gin H. Normoalbuminuric renal insufficient diabetic patients: A lower risk group Diabetes Care 2007, 30 : 2034-9.

16-Beauvieux MC, Le Moigne F, Lasseur C, Raffaitin C, Perlemoine C, Barthe N, Chauveau P, Combe C, Gin H, Rigalleau V.New Predictive Equations Improve Monitoring of Kidney Function in Patients with Diabetes. Diabetes Care 2007, 30: 1979-87.

17-Fagour C, Gonzalez C, Suberville C, Higueret P, Rabemanantsoa C, Beauvieux MC, Gin H, Rigalleau V. Early decrease in resting energy expenditure with bed-time insulin therapy. Diabetes & Metabolism, Diabetes Metab. 2009; 35:332-5

18-Pezzino S, Florenty , Fagour C, Gin H, Rigalleau V. Remedial actions for the physical inactivity of hospitalized patients with type 2 diabetes. Diabetes Care 2010 ;33 :1960-1

19-Rubin S, Le Piffer AL, Rougier MB, Delyfer MN, Korobelnik JF, Redonnet Vernhet I, Marchal C, Goizet C, Mesli S, Gonzalez C, Gin H, Rigalleau V. Sight threatning phenylketonuric encephalopathy in a young adult, reversed by diet. JIMD Reports 2013; 10:83-5

20-Geneviève M, Vivot A, Gonzalez C, Raffaitin C, Barberger-Gateau P, Gin H, Rigalleau V. Skin autofluorescence is associated with past glycemic control and complications in type 1 diabetes mellitus. Diabetes Metab. 2013;39: 349-54

21-Gonzalez C, De ledinghen V, Vergniol J, Foucher J, Le Bail B, Carlier S, Maury E, Gin H, Rigalleau V. Hepatic steatosis, carbohydrate intake, and food quotient in patients with NAFLD. Int J Endocrinol 2013; 428542

22-Saulnier PJ, Gand E, Ragot S, Ducrocq G, Halimi JM, Hulin-Delmotte C, Llaty P, Montaigne D, Rigalleau V, Roussel R, Velho G, Sosner P, Zaoui P, Hadjadj S, for the SURDIAGEN Study group. Association of serum concentration of TNFR1 with all-cause mortality in patients with type 2 Diabetes and Chronic Kidney Disease: Follow-up of the SURDIAGENE cohort. DiabetesCare 2014; 37: 1425-31

23-Gonzalez C, Fagour C, Maury E, Cherifi B, Salandini S, Pierreisnard A, Masquefa-Giraud P, Gin H, Rigalleau V. Early modifications in respiratory quotient and energy expenditure predict later weight in patients treated for uncontrolled Type 2 Diabetes Diabetes Metab., 2014 (44):299-304

24-Rajaobelina K, Cougnard-Gregoire A, Delcourt C, Gin H, Barberger-Gateau P, Rigalleau V. Autofluorescence of skin advanced glycation end products: marker of metabolic memory in the elderly. J Gerontol A Biol Sci Med Sci Accepté 11/2014

25- Maury E , Savel J , Grouthier V , Rajaobelina K, Corvo L, Lorrain S , Gonzalez C, Gin H, Barberger-Gateau P , Rigalleau V. Is skin autofluorescence a marker of metabolic memory in pregnant women with diabetes? Diabetic Medicine, accepté le 25/03/2015

Partner : department of nephrology, transplantation and dialysis	
Localization : Pellegrin Hospital	**Institution : Bordeaux University Hospital**

Head : P. Merville

Key personnal : L. Couzi, T. Bachelet, K. Moreau, H. Kaminski

Field of expertise:

- **Renal transplantation**
- **CMV infection**
- **Lupus nephritis**
- **Sensitized patient**

Expected contribution to the AIR DHU

- **access to clinical database of more than 2000 kidney graft recipients or patients with chronic renal failure on waiting list and serum samples**
- **access to renal biopsies of kidney grafts**
- **access to clinical and hisotological data of a cohort of lupus nephritis**
- **expertise on therapeutic education of kidney transplant recipients**

Main grants since 2009

- Etude investigateur (Laboratoire Novartis, promotion CHU de Bordeaux) pour l'étude EVERCMV, 2013 ; Essai clinique de phase IV ouvert multicentrique randomisé prospectif comparant chez les patients transplantés rénaux séropositifs pour le cytomégalovirus, l'incidence de l'infection à cytomégalovirus entre deux stratégies immunosuppressives : Everolimus (Certican®) - doses réduites de cyclosporine A (Neoral®) versus acide mycophénolique (Myfortic®) - doses standard de cyclosporine (Neoral®)
- Participation to national PHRC in transplantation : Tumorapa 1 et N (Lyon), Taxi (Lille), Epigren and Ephegren, Orphavic (Limoges), Vitale, Treve, Tribute (APHP), Rituxerah (Tours), Pirat (St Etienne).
- Participation to phase II, III and IV international clinical trials in kidney trasplantation (25 since 2001)

Relevant publications and patents in the field since 2001:

Cytomégalovirus infection in transplant recipients resolves when circulating gamma delta T lymphocytes expand, suggesting a protective antiviral role. Lafarge X, Merville P, Cazin MC, Bergé F, Potaux L, Moreau JF, Déchanet-Merville J.
J. Infect. Dis. 2001 ; 1 ; 184 (5) : 533-41.

Induction versus noninduction in renal transplant recipients with tacrolimus-based immunosuppression.
Mourad G, Garrigue V, Squifflet JP, Besse T, Berthoux F, Alamartine E, Durand D, Rostaing L, Lang P, Baron C, Glotz D, Antoine C, Vialtel P, Romanet T, Lebranchu Y, Al Najjar A, Hiesse C, Potaux L, Merville P, Touraine JL, Lefrancois N, Kessler M, Renoult E, Pouteil-Noble C, Cahen R, Legendre C, Bedrossian J, Le Pogamp P, Rivalan J, Olmer M, Purgus R, Mignon F, Viron B, Charpentier B.
Transplantation. 2001; 27;72(6):1050-5

Functional quantification of cyclosporine A and FK506 in human whole blood by flow cytometry using the green fluorescent protein as an interleukin-2 reporter gene. Taupin JL, Merville P, McBride T, Potaux L, Moreau JF.
J. Immunol. Methods 2001; 1; 256 (1-2): 77-87.

Potential role of soluble CD40 in the humoral immune response impairment in uraemic patients. Contin C, Pitard V, Delmas Y, Pelletier N, Defrance T, Moreau JF, Merville P, Déchanet-Merville J.
Immunology 2003 ; 110 (1) : 131-40.

A three-arm study comparing immediate tacrolimus therapy with antithymocyte globulin induction therapy followed by tacrolimus or cyclosporine A in adult renal transplant recipients.
Charpentier B, Rostaing L, Berthoux F, Lang P, Civati G, Touraine JL, Squifflet JP, Vialtel P, Abramowicz D, Mourad G, Wolf P, Cassuto E, Moulin B, Rifle G, Pruna A, Merville P, Mignon F, Legendre C, Le Pogamp P, Lebranchu Y, Toupance O, Hurault De Ligny B, Touchard G, Olmer M, Purgus R, Pouteil-Noble C, Glotz D, Bourbigot B, Leski M, Wauters JP, Kessler M.
Transplantation. 2003; 27;75(6):844-51.

Lower incidence of chronic allograft nephropathy at 1 year post-transplantation in patients treated with mycophenolate mofetil. Merville P, Bergé F, Deminière C, Morel D, Chong G, Durand D, Rostaing L, Mourad G, Potaux L.
Am. J. Transplant. 2004; 4(11) :1769-75.

Immune dysfunction of uremic patients: potential role for the soluble form of CD40. Contin C, Couzi L, Moreau JF, Déchanet-Merville J, Merville P.
Nephrologie 2004; 25 (4):119-126.

Coordinated expression of Ig-like inhibitory MHC class I receptors and acquisition of cytotoxic function in human CD8+ T cells. Anfossi N, Doisne JM, Peyrat MA, Ugolini S, Bonnaud O, Bossy D, Pitard V, Merville P, Moreau JF, Delfraissy JF, Déchanet-Merville J, Bonneville M, Vivier E.
J. Immunol. 2004; 15; 173 (12):7223-9.

Shared reactivity of Vd2neg T cells against CMV-infected cells and tumor intestinal eptithelial cells. Halary F, Pitard V, Dlubek D, Krzysiek R, de la Salle H, Merville P, Dromer C, Emilie D, Moreau JF, Dechanet-Merville J.
J. Exp. Med 2005; 16; 201 (10): 1567-78.

Activation of mesangial cells by platelets in systemic lupus erythematosus via a CD154-dependent induction of CD40. Delmas Y, Viallard JF, Solanilla A, Villeneuve J, Pasquet JM, Belloc F, Dubus P, Déchanet-Merville J, Merville P, Blanco P, Pellegrin JL, Nurden AT, Combe C, Ripoche J.
Kidney Int. 2005; 68(5): 2068-2078.

Variability of of UL18, UL40, UL111a and US3 immunomodulatory genes among human cytomegalovirus clinical isolates from renal transplant recipients.
Garrigue I, Corte MF, Magnin N, Couzi L, Capdepont S, Rio C, Merville P, Dechanet-Merville J, Fleury H, Lafon ME.
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Partner : Neuroimaging department	
Localization : Hopital Pellegrin	**Institution : CHU de Bordeaux**

Head : Pr Vincent Dousset (PU-PH)

Key personnal : 1 PHU (Thomas Tourdias), 5 PH (Sandrine Molinier, Elise de Roquefeuil, Xavier Barreau, Jerôme Berge, Patrice Ménégon), 2 clinical research assistant (Iris Lemoine, Julie Blanchard).

Field of expertise: The neuroimaging department of Bordeaux University hospital is in charge of all the imaging exams for the exploration of head, neck and spinal cord. The department has also developed strong expertise in neuroimaging research and is currently hosting 10 academic research projects and 12 research projects in collaboration with the industry. Some of our group (Pr Vincent Dousset, Dr Thomas Tourdias) are also permanent member of the team of Stéphane Oliet ("Glia-neuron interactions", Neurocentre Magendie, INSERM U862) and have made significant contribution in developing and validating imaging biomarkers reflecting specific components of neurological disorders. Such development and validation are translational, from animals (for direct imaging-to-histology correlates), to clinical applications for patients. The group has a particular focus on understanding the pathophysiology of multiple sclerosis (MS) especially by using non invasive imaging tools that can be developed and validated in the animal model and then transferred to patients with MS.

Previous contributions : Among others, Dousset *et al.* established in the past that a dedicated magnetic resonance parameter called magnetization transfer ratio (MTR) was a robust and reproducible metric to objectively quantify brain destruction *in vivo* (Radiology 1992, more than 550 citations). This metric is now very popular to quantify brain alteration induced by MS and we are still demonstrating the strength of MTR in particular clinical situations (Tourdias et al. Stroke 2007).
Intra-venous injection of contrast agent is frequently used in neuroimaging and we have also significantly contributed to the first demonstration that a new class of contrast agent called USPIO (for ultra-small iron oxide nanoparticles) can specifically reflect macrophage infiltration in the brain during neuro-inflammation (Dousset et al. MRM 199, 167 citations). We have conducted the first European multicenter clinical trial (Tourdias et al. Radiology 2012) demonstrating the impact of USPIO to non-invasively monitor the inflammatory component of MS.

Expected contribution to the AIR DHU: The neuroimaging department will be involved in cerebral imaging of the inflammatory disorders of the central nervous system such as MS, but also in evaluating by imaging the cerebral consequences of systemic inflammatory disorders and the cerebral toxicity of their treatments. The neuroimaging department will also contribute to the understanding of the molecular, cellular and tissular determinants of MS with the other members of the team of Stéphane Oliet (Neurocentre Magendie, INSERM U862).

Main grants since 2009

-Vincent Dousset is the director of the labEx TRAIL: 9 M€
-Vincent Dousset is the Node Coordinator of France Life Imaging (FLI): 3.7 M€
-Vincent Dousset is the co-diecteor of the imaging section of a national cohort on MS patients (OFSEP: Observatoire Français de la Slcérose en Plaques) Cohorts ANR tender of the "Investments for the Future" program: 10 M€
-Vincent Dousset is the PI of the inter-regional PHRC "BBS": 200 K€
-Thomas Tourdias is the PI of the projects "MEMO-MS" funded by the labEx BRAIN: 120 K€
-Thomas Tourdias is co-PI of the project "HL-DTI" funded by IdEx: 145 K€
-Thomas Tourdias is responsible of the cellular and small animal section of the project "IBIO-NI" funded by the labEx TRAIL: 250 K€ + recent consolidation of 60 K€.

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31. Dousset V, Doche B, Petry KG, Brochet B, Delalande C, Caille JM. **"Correlation between clinical status and macrophage activity imaging in the central nervous system of rats".** Acad Radiol. 2002 May;9 Suppl 1:S156-9. *Impact factor 1.30*

32. Filippi M, Dousset V, McFarland HF, Miller DH, Grossman RI. **"Role of magnetic resonance imaging in the diagnosis and monitoring of multiple sclerosis: consensus report of the White Matter Study Group".** J Magn Reson Imaging. 2002 May;15(5):499-504. Review. *Impact factor 2.75 –Rank C*

33. Ingle GT, Stevenson VL, Miller DH, Leary SM, Rovaris M, Barkhof F, Brochet B, Dousset V, Filippi M, Montalban X, Kalkers NF, Polman CH, Rovira A, Thompson AJ. **"Two-year follow-up study of primary and transitional progressive multiple sclerosis".** Mult Scler. 2002 Apr;8(2):108-14. . *Impact factor 4.86*

Partner : Service de médecine vasculaire	
Localization Hôpital St André, 1 rue Jean Burguet, 33075 Bordeaux	**Institution :** CHU Bordeaux

Head : professeur Joël Constans
Key personnal : docteur Carine Boulon, docteur Sophie Skopinski

Field of expertise:
Vascular medicine in all its fields (arterial, venous, microcirculatory and lymphatic diseases)
In particular microcirculation and systemic sclerosis (SSc)

Previous contributions :
Pr Constans PI of PHRC "ERAMS" published in 2007 (arterial stiffness in systemic sclerosis), PI of the project "SCLEROCAP" supported by french vascular medicine and microcirculation societies currently ongoing,
Dr Boulon PI of PHRC about the development of a clinical score for diagnosis of critical ischaemia.
Participation to multicenter trials DUO (digit ulcers in SSc), ITINERAIR Sclerodermie (PAH in SSc), FASCINATE (tocilizumab in SSc)
Dr Boulon: coordination of therapeutic Education Program in systemic sclerosis patients approved in 2015 by the Agence Régionale de Santé

Contributions in teaching vascular inflammatory diseases:

***Teaching in Bordeaux university*:** vascular acrosyndromes (5th Year medical students), seminar on microcirculation (vascular medicine specialty students),

Writing chapters of teaching books:
prognosis of systemic sclerosis (J. Constans) and full skin capillaroscopy (C. Boulon), in **capillaroscopy atlas** (Collège des Enseignants de Médecine Vasculaire), 2013 (J. Constans and C. Boulon members of redaction committee); systemic sclerosis (J. Constans), aortitis (C. Boulon) in **textbook of vascular medicine** (coordination J. Constans), 2012; systemic sclerosis (J. Constans), Horton's disease (S. Skopinski), C. Boulon et J. Constans members of redaction committee, **pocket book of vascular medicine** (Collège des Enseignants de Médecine Vasculaire, yearly editions); systemic sclerosis (Plan national de diagnostic et de soins) : treatment of Raynaud's phenomenon chapter (J. Constans); systemic sclerosis textbook : Raynaud's phenomenon chapter (J. Constans)

Expected contribution to the AIR DHU
Expertise of vascular explorations for other components of DHU
Active file> 100 patients with SSc
Ongoing "SCLEROCAP" project about capillarocopy and digit pressures for prognosis of SSc
Close relations with the Association of sclerodermic patients in France

Main grants since 2009
PI Dr Boulon: PHRC starting in 2015 about a clinical score for critical ischaemia ("PREDICMI")

Relevant publications and patents in the field since 2001:

1: van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, SchuerweghAJ, Marijt EW, Vonk MC, Schattenberg AV, Matucci-Cerinic M, Voskuyl AE, van de Loosdrecht AA, Daikeler T, Kötter I, Schmalzing M, Martin T, Lioure B, Weiner SM, Kreuter A, Deligny C, Durand JM, Emery P, Machold KP, Sarrot-Reynauld F, Warnatz K, Adoue DF, **Constans J**, Tony HP, Del Papa N, Fassas A, Himsel A, Launay D, LoMonaco A, Philippe P, Quéré I, Rich É, Westhovens R, Griffiths B, Saccardi R,

vanden Hoogen FH, Fibbe WE, Socié G, Gratwohl A, Tyndall A; EBMT/EULAR Scleroderma Study Group. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA. 2014 Jun 25;311(24):2490-8.

2: Guillevin L, Hunsche E, Denton CP, Krieg T, Schwierin B, Rosenberg D, Matucci-Cerinic M; DUO Registry Group. Functional impairment of systemic scleroderma patients with digital ulcerations: results from the DUO Registry. Clin Exp Rheumatol. 2013 Mar-Apr;31(2 Suppl 76):71-80.

3: Denton CP, Krieg T, Guillevin L, Schwierin B, Rosenberg D, Silkey M, Zultak M, Matucci-Cerinic M; DUO Registry investigators. Demographic, clinical and antibody characteristics of patients with digital ulcers in systemic sclerosis: data from the DUO Registry. Ann Rheum Dis. 2012 May;71(5):718-21.

4: Solanilla A, Villeneuve J, Auguste P, Hugues M, Alioum A, Lepreux S, Ducroix JP, Duhaut P, Conri C, Viallard JF, Nurden AT**, Constans J**, Ripoche J. The transport of high amounts of vascular endothelial growth factor by blood platelets underlines their potential contribution in systemic sclerosis angiogenesis. Rheumatology (Oxford). 2009 Sep;48(9):1036-44

5: Tiev KP, Diot E, Clerson P, Dupuis-Siméon F, Hachulla E, Hatron PY, **Constans J**, Cirstéa D, Farge-Bancel D, Carpentier PH. Clinical features of scleroderma patients with or without prior or current ischemic digital ulcers: post-hoc analysis of a nationwide multicenter cohort (ItinérAIR-Sclérodermie). J Rheumatol. 2009 Jul;36(7):1470-6.

6: Hachulla E, de Groote P, Gressin V, Sibilia J, Diot E, Carpentier P, Mouthon L, Hatron PY, Jego P, Allanore Y, Tiev KP, Agard C, Cosnes A, Cirstea D, **Constans J**, Farge D, Viallard JF, Harle JR, Patat F, Imbert B, Kahan A, Cabane J, Clerson P, Guillevin L, Humbert M; Itinér AIR-Sclérodermie Study Group. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum. 2009 Jun;60(6):1831-9.

7: Hachulla E, Carpentier P, Gressin V, Diot E, Allanore Y, Sibilia J, Launay D, Mouthon L, Jego P, Cabane J, de Groote P, Chabrol A, Lazareth I, Guillevin L, Clerson P, Humbert M; ItinérAIR-Sclérodermie Study Investigators. Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study. Rheumatology (Oxford). 2009 Mar;48(3):304-8.

8: Bérezné A, Ranque B, Valeyre D, Brauner M, Allanore Y, Launay D, Le Guern V, Kahn JE, Couderc LJ, **Constans J**, Cohen P, Mahr A, Pagnoux C, Hachulla E, Kahan A, Cabane J, Guillevin L, Mouthon L. Therapeutic strategy combining intravenous cyclophosphamide followed by oral azathioprine to treat worsening interstitial lung disease associated with systemic sclerosis: a retrospective multicenteropen-label study. J Rheumatol. 2008 Jun;35(6):1064-72.

9: **Constans J**, Germain C, Gosse P, Taillard J, Tiev K, Delevaux I, Mouthon L, Schmidt C,

Granel F, Soria P, Lifermann F, Etienne G, Bonnet F, Zoulim K, Farge-Bancel D, Marie I, Allanore Y, Cabane J, Amonchot A, Macquin-Mavier I, Saves M, Zannad F, Conri C; ERAMS investigators. Arterial stiffness predicts severe progression in systemic sclerosis: the ERAMS study. J Hypertens. 2007 Sep;25(9):1900-6.

10: Taïeb A, **Constans J**, Mahon FX. [A new therapeutic avenue for severe systemic sclerosis: imatinib mesylate]. Rev Med Interne. 2008 Mar;29(3):173-5.

11: Chamaillard M, Heliot-Hosten I, **Constans J**, Taïeb A. Bosentan as a rescue therapy in scleroderma refractory digital ulcers. Arch Dermatol. 2007 Jan;143(1):125-6.

12: Marjanovic Z, Gerber I, Toledano C, Hen-Solal J, Damade R, de Saint-Cyr I, Sarrot-Reynauld F, Ilié D, Daneshpouy M, Mounier N, Ruivard M, Tyndall C, Vidal E, Quere I, Durand JM, **Constans J**, Farge D. [Therapeutic intensification and autologous stem cell transplantation in autoimmune diseases]. Presse Med. 2005 Feb 26;34(4):311-8.

13: Blann AD, **Constans J**, Carpentier P, Renard M, Satger B, Guérin V, Boisseau MR, Neau-Cransac N, Conri C. Soluble P selectin in systemic sclerosis: relationship with von Willebrand factor, autoantibodies and diffuse or localised/limited disease. Thromb Res. 2003 Feb 15;109(4):203-6.

14: **Constans J**, Skopinski S, Barcat D, Conri C. [Cardiovascular involvement in systemic sclerosis]. Ann Med Interne (Paris). 2002 Jun;153(4):242-9.

15: Gosse P, Taillard J, **Constans J**; ERAMS Study Investigators. Evolution of ambulatory measurement of blood pressure and parameters of arterial stiffness over a 1-year period in patients with systemic sclerosis: ERAMS study. J Hum Hypertens. 2002 Sep;16(9):627-30.

16: **Constans J**, Gosse P, Conri C, Clémenty J. [Measurement of arterial distensibility by the QKd method a new vascular marker]. Rev Med Interne. 2002 Mar;23(3):308-11.

Hépato-gastroentérologie

Sur le plan de la recherche fondamentale :

- Classement des UMR identifiées à la FHU :
- indicateurs bibliométriques des EPST /HCERES (5 dernières années)
- Liste des publications des 5 dernières années à fort impact :

- Varon C, Mocan I, Mihi B, Péré-Védrenne C, Aboubacar A, Moraté C, Oleastro M, Doignon F, Laharie D, Mégraud F, Ménard A. Helicobacter pullorum cytolethal distending toxin targets vinculin and cortactin and triggers formation of lamellipodia in intestinal epithelial cells. J Infect Dis. 2014;209:588-99 (IF : 6,0).
- Varon C, Duriez A, Lehours P, Ménard A, Layé S, Zerbib F, Mégraud F, Laharie D. Study of Helicobacter pullorum proinflammatory properties on human epithelial cells in vitro. Gut 2009; 58: 629-35 (IF : 14,7).
- Laharie D, Asencio C, Asselineau J, Bulois P, Bourreille A, Moreau J, Bonjean P, Lamarque D, Pariente A, Soulé JC, Charachon A, Coffin B, Perez P, Mégraud F, Zerbib F. Association between entero-hepatic Helicobacter species and Crohn's disease: a prospective cross-sectional study. Aliment Pharm Ther 2009; 30: 283-93 (IF : 5,7).

- Nombre de titulaires d'une HDR en 2015 :

3 (David Laharie, Victor de Lédinghen, Frank Zerbib)

- Nombre de chercheurs statutaires

Aucun.

- Nombre et qualité des plateformes et des animaleries, Niveau de contribution au bon fonctionnement des plates- formes mutualisées.

Aucune.

Sur le plan de la recherche de transfert : non concerné

- Résultats aux appels d'offres DGOS/INSERM sur la recherche de transfert (4 dernières années),
- Nombre de cohortes et de biocollections en 2015,
- Structuration d'une démarche de transfert vers la clinique,
- Nombre et qualité des structures associées (FCS, CTRS, RTRS).

<u>Sur le plan de la recherche clinique :</u>

- Nombre d'essais cliniques de phase précoce (I et II) des 4 dernières années :

  Environ 1 essai de phase II par an depuis 10 ans dans le domaine des Maladies Inflammatoires Chroniques de l'Intestin (MICI)
- Nombre de protocoles promus et nombre en tant qu'associé (académiques et industriels, en tant que coordonnateur ou investigateur) des 4 dernières années :

  215 protocoles de recherche clinique en hépato-gastroentérologie au Groupe Hospitalier Sud depuis 2011
- Score SIGREC (le plus récent) :

  Nombre d'études : 21 (DL) + 51 (VDL) + 31 (FZ) = 103
- Score SIGAPS (période 2012-2015) :

  D. Laharie : 342

  V. de Lédinghen : 836

  F. Zerbib : 436
- Nombre de publications de rang A et B (période 2012-2015) :

  D. Laharie : 23

  V. de Lédinghen : 42

  F. Zerbib : 19

- Label CIC
- Résultats aux appels à projets nationaux ou européens (PHRC, STIC, INCA, ANR...) des 4 dernières années,

  Aucune demande.
- Nombre de protocoles multicentriques académiques promus des 4 dernières années :

  6
- Participation aux grands réseaux internationaux de recherche, sociétés savantes :

  Centre investigateur du Groupe d'Etude sur les Affections Inflammatoires Digestives (GETAID) depuis 2001, dont le secrétaire élu depuis 2013 est D. Laharie

  Participation active au travaux et recommandation de l'European Crohn's Colitis Organisation (ECCO)

  Centre investigateur du Club Français de Motricité Digestive

  Centre investigateur de l'Association Française d'Etude du Foie (AFEF) dont le secrétaire depuis 2014 est V. de Lédinghen
- Nombre d'inclusions en 2014 (tous protocoles confondus hors RNI) :

  Entre 80 et 100 sur le service d'hépato-gastroentérologie du Groupe Hospitalier Sud.

<u>Sur le plan des soins :</u>

- Liste des innovations diagnostiques et thérapeutiques des 4 dernières années :

  Développement de l'intérêt du FibroScan dans les maladies chroniques du foie
- Implication dans la démarche de certification de la has (pep, epp, rmm, rcp...),
- Actions d'éducation thérapeutique,

Mise en place d'une structure d'éducation thérapeutique dans le domaine des hépatites virales et des maladies inflammatoires chroniques de l'intestin

- Participation aux réseaux de santé :

  Centre d'expertise régionale dans le domaine des hépatites virales, des maladies inflammatoires chroniques de l'intestin et des troubles de la motricité intestinale

  Coordination et animation de réunion de concertation pluri-disciplinaire dans chacun de ces domaines.
- Démarche de santé publique, d'évaluation et de shs,
- Programmes de prévention, de dépistage et d'éducation pour la santé,
- Centres de référence et de compétences sur les maladies rares et autres.

<u>Sur le plan de l'enseignement :</u>

- Démarche d'enseignement intégré au profit des étudiants en médecine et en sciences

  Participation à l'enseignement intégré (théorique et pratique) des étudiants de DCEM 1 et de DCEM2
- Notoriété des services dans la formation des internes (cf : demandes d'inter-chu, échanges à l'échelle de l'inter-région ouest...),

  Deuxième rang national de choix pour la spécialité à l'ECN (rang du dernier choix pour la spécialité lors de l'ECN 2014 : 600e)

  Accueil d'un interne DES en inter-CHU / an
- Nombre de doctorants et de post-doctorants des 4 dernières années

  Aucun
- Nombre d'étudiants en master 2 des 4 dernières années,

  2

- Partenariats d'échanges internationaux,
- Séminaires et formations spécifiques dans le domaine de la recherche.

Sur le plan de la valorisation :

- Nombre de brevets licenciésdes4dernièresannées,
- Nombre de start up incubées,
- Contrats conclus avec le secteur privé des 4 dernières années,
- Existence ou non d'une fondation.

  Non.

Partner : Hospital Unit: Department of rheumatology	
Localization: Hôpital Pellegrin, Bordeaux	**Institution: University Hospital of Bordeaux**

Head: Thierry Schaeverbeke

Key personnal: Bernard Bannwarth (PU-PH), Thomas Barnetche (Bio-expert), Nadia Mehsen (PH), Nicolas Poursac (PH), Christophe Richez (PU-PH), Marie-Elise Truchetet (CCA)

Field of expertise:

A research clinic department devoted:

- To early diagnosis of inflammatory diseases, including rheumatoid arthritis, spondyloarthritis, systemic sclerosis, systemic lupus erythematosus and autoinflammatory diseases, in close collaboration with rheumatologists from the Aquitaine area;
- To management and standardized follow-up of patients suffering of the same chronic inflammatory diseases;
- To screening for co-morbidities from the same population;
- To treatment for co-morbidities, especially osteoporosis, of patients from our department and other departments in charge of chronic inflammatory diseases.

Previous contributions:

Industrial research

French coordinating investigator center for Phase III clinical trials :

- ***TORPEDO*****:** Comparative double blind placebo controlled clinical study on tocilizumab rapid efficacy on patients relief in rheumatoid arthritis with an inadequate response to DMARDs or anti TNF
- ***IM133-066:*** A Phase IIb, Randomized, Multi-Center, Double-Blind, Dose-Ranging Study to Evaluate the Efficacy and Safety of Clazakizumab in Subjects with Moderate to Severe Active Rheumatoid Arthritis who have Experienced an Inadequate Response to TNF inhibitors

- Investigation center for Phase Ib, II, III and IV clinical trials in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus, systemic sclerosis, hand osteoarthritis and osteoporosis : 60 to 70 per year.

Academic research

Coordinating center in national clinical studies :

- ***STOP:*** Interest of continuous non-steroidal anti-Inflammatory drug treatment in Ankylosing Spondylitis patients treated by anti-TNF therapy in the prevention of radiographic outcomes (French national PHRC)
- **VISS:** Vasculopathy and inflammation in systemic sclerosis

Investigation center in French national PHRCs:

- ***ROC*****:** Therapeutic strategy in patients with rheumatoid arthritis and insufficient response to a first Anti-TNF
- ***VACIMRA*****:** VACcination In Méthotrexate treated Rheumatoid Arthritis patients
- ***STRASS*****:** Impact of Progressive spacing of TNF-blocker injections in rheumatoid arthritis patients in DAS28 remission
- ***SPACING*****:** Effect of spacing of Anti-TNF drugs in Ankylosing Spondylitis with low disease activity
- ***TOLEDO*****:** TOward the Lowest Effective DOse of Abatacept or Tocilizumab
- ***COMEDRA*****:** Impact of a nurse led-program on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis

Investigation center in 2 multicenter observational cohorts following patients with rheumatoid arthritis (***ESPOIR cohort***, member of the scientific committee) and with ankylosing spondylitis spondylitis (***DESIR cohort***, member of the executive committee)

Investigation center in national registries or clinical studies:

- ***AIR (Auto-Immunité Rituximab) -PR***: Follow-up of rituximab-treated RA patients (also PI for ancillary studies)
- ***AIR***: Follow-up of rituximab-treated auto-immune disease patients

- ***ORA***: Follow-up of abatacept-treated RA patients
- ***REGATE***: Follow-up of tocilizumab-treated RA patients
- ***RECOVER*** : Efficacy and safety of Rituximab in systemic sclerosis patients
- ***ECHO-LUPUS***: Dopper Ultrasonography for the evaluation of articular lesions in systemic lupus erythematosus

Investigation center in international cohorts:
- ***RABIODAM***: Prospective Validation of Soluble Biomarkers as Predictors of Structural Damage in Rheumatoid Arthritis
- ***ABI-RA-P01***: Anti-Biopharmaceutical Immunization: Prediction and analysis of clinical relevance to minimize the risk of immunization in Rheumatoid arthritis patients
- ***SCaR***: Systemic sclerosis clinical repository
- ***LUTS***: low urinary tracts in scleroderma

Participation to the scientific committee of the FAI²R (Rare autoimmune and autoinflammatory diseases network)

Expected contribution to the AIR DHU

Development and setting of tools to facilitate collaborations within the DHU, and for both clinical and translational research:

- Interaction with general practitioner/rheumatologist from private practice/rheumatologist from public hospitals of Aquitaine, for the early management of inflammatory diseases.
- Implementation of electronic CRF already developed, dedicated to each inflammatory diseases and used in the whole university hospital of Bordeaux

For clinical practice:

- Screening and management of early stages of inflammatory rheumatic diseases
- Screening and management of co-morbidities in inflammatory rheumatic diseases

For clinical research:

- Conception and setting of clinical trials in early stages of inflammatory rheumatic diseases
- Investigation for environmental factors in inflammatory rheumatic diseases

For translational research:

- Access to human materials from different chronic inflammatory diseases
- Statistical analysis of combined clinical (ECRF) and biological data

Main grants since 2009

- French national clinical program 2014 (PHRC): Interest of continuous non-steroidal anti-Inflammatory drug treatment in Ankylosing Spondylitis patients treated by anti-TNF therapy in the prevention of radiographic outcomes: the STOP study (509 533€)
- Roche laboratory supported clinical study 2014: Characterization of the effect of tocilizumab in vivo and in vitro on T follicular helper cells in rheumatoid arthritis patients and secondly on B cells maturation: the TociHelper study – ML29237 (126 000€)
- Société Française de Rhumatologie 2013: Identification, quantification, characterization et target of extra-cellular mitochondrial DNA in rheumatoid arthritis (10000€)
- SFR transbiomed 2013: Identification, quantification, characterization et target of extra-cellular mitochondrial DNA in rheumatoid arthritis (16000€)
- SIRIUS grant from UCB Pharma 2012: Effect of IgE on plasmacytoid dendritic cells in systemic lupus erythematosus pathogenesis through interferon-alpha downregulation (20000€)
- PASSERELLE grant from Pfizer 2010: Effect of anticitrullinated protein IgE in rheumatoid arthritis pathogenesis: Impact on tumor necrosis factor alpha secretion (55000€)
- Société Française de Rhumatologie 2009: Interaction between myeloid dendritic cells and T lymphocytes in lupus pathogenesis: role of OX40-OX40L couple (16000€)
- Groupe Français de Recherche sur la Sclérodermie 2010: Functional characteristics of T cells in SSc individuals and impact of in vivo Iloprost (20000€)

- Société Française de Rhumatologie 2011: Rôle de l'activation endothéliale et du couple OX40/OX40L sur la modulation de la réponse lymphocytaire T chez les patients sclérodermiques (20000€)

- Groupe Français de Recherche sur la Sclérodermie 2014: Contribution of endothelial cells in the Thymic Stromal Lymphopoietin (TSLP) production and pro-fibrotic cytokine secretion by T cells in human SSc pathophysiology (15000€)

Relevant publications and patents in the field since 2001:

Seror R, Le Gall-David S, Bonnaure-Mallet M, Schaeverbeke T, Cantagrel A, Minet J, Gottenberg JE, Chanson P, Ravaud P, Mariette X. Anti-Porphyromonas gingivalis antibodies titres are associated with non-smoking status in early rheumatoid arthritis: Results from the ESPOIR cohort. **Arthritis Rheumatol**. 2015 Mar.

Richez C, Yasuda K, Bonegio RG, Watkins AA, Aprahamian T, Busto P, Richards RJ, Liu CL, Cheung R, Utz PJ, Marshak-Rothstein A, Rifkin IR. IFN regulatory factor 5 is required for disease development in the FcgammaRIIB-/-Yaa and FcgammaRIIB-/- mouse models of systemic lupus erythematosus. **J Immunol**. 2010 Jan 15;184(2):796-806.

Richez C, Schaeverbeke T, Dumoulin C, Dehais J, Moreau JF, Blanco P. Myeloid dendritic cells correlate with clinical response whereas plasmacytoid dendritic cells impact autoantibody development in rheumatoid arthritis patients treated with infliximab. **Arthritis Res Ther**. 2009 Jun 29;11(3):R100.

Richez C, Yasuda K, Watkins AA, Akira S, Lafyatis R, van Seventer JM, Rifkin IR. TLR4 ligands induce IFN-alpha production by mouse conventional dendritic cells and human monocytes after IFN-beta priming. **J Immunol**. 2009 Jan 15;182(2):820-8.

Truchetet ME, Brembilla NC, Montanari E, Lonati P, Raschi E, Zeni S, Fontao L, Meroni PL, Chizzolini C. Interleukin-17A+ cell counts are increased in systemic sclerosis skin and their number is inversely correlated with the extent of skin involvement. **Arthritis Rheum**. 2013 May;65(5):1347-56. doi: 10.1002/art.37860.

Truchetet ME, Allanore Y, Montanari E, Chizzolini C, Brembilla NC. Prostaglandin I(2) analogues enhance already exuberant Th17 cell responses in systemic sclerosis. **Ann Rheum Dis**. 2012 Dec;71(12):2044-50.

Truchetet ME, Beven L, Renaudin H, Douchet I, Férandon C, Charron A, Blanco P, Schaeverbeke T, Contin-Bordes C, Bébéar C. Potential role of Mycoplasma hominis in interleukin (IL)-17-producing CD4+ T-cell generation via induction of IL-23 secretion by human dendritic cells. **J Infect Dis**. 2011 Dec 1;204(11):1796-805.

Dougados M, Wood E, Combe B, Schaeverbeke T, Miceli-Richard C, Berenbaum F, Koppiker N, Dubanchet A, Logeart I. Evaluation of the nonsteroidal anti-inflammatory drug-sparing effect of etanercept in axial spondyloarthritis: results of the multicenter, randomized, double-blind, placebo-controlled SPARSE study. **Arthritis Res Ther**. 2014 Nov 27;16(6):481

Dougados M, Soubrier M, Perrodeau E, Gossec L, Fayet F, Gilson M, Cerato MH, Pouplin S, Flipo RM, Chabrefy L, Mouterde G, Euller-Ziegler L, Schaeverbeke T, Fautrel B, Saraux A, Chary-Valckenaere I, Chales G, Dernis E, Richette P, Mariette X, Berenbaum F, Sibilia J, Ravaud P. Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: results of a prospective, multicentre, randomised, controlled trial (COMEDRA). **Ann Rheum Dis**. 2014 May

SIGAPS score of Rheumatology department: 2012
H-index: Thierry Schaeverbeke 33; Christophe Richez 16; Bernard Bannwarth 30

Partner : Internal Medecine.	
Localization : Haut-Lévêque Hospital	**Institution : CHU Bordeaux**

Head : Pr Jean-Luc Pellegrin (PU-PH)
Key personal : Pr Jean-François VIALLARD (PU-PH), Pr Estibaliz LAZARO (PU-PH), Dr Carine GREIB (PH), Dr Isabelle RAYMOND (PH)

Field of expertise:
A research clinic unit devoted to diagnosis, management and treatment of:
1/ autoimmune diseases, especially focused on autoimmune cytopenia (immune thrombocytopenia, autoimmune hemolytic anemia), primary vasculitis and systemic lupus erythematosus.
2/ Primary immunodeficiencies in adults
In the context of rare diseases plan of the french ministry of Health, our department of Internal Medicine is labeled as competence center in autoimmune diseases and primary adult immunodeficiencies in Aquitaine.

Previous contributions : We have conducted in our Department several clinical trials over the last 5 years:
- PI for Phase III clinical trials : GSK (Trial BREVAS in ANCA-associated Vascultis)
- Investigator for Phase III clinical trials : NEOVACS (Trial IFN-K-001 in Lupus), GSK (Trial JAK115919 and BLISS LN in Lupus; Trials in immune thrombocytopenia), BIOGEN (Trail ATLAS in Lupus), ASTRA-ZENECA (Trial MEDI 545 in Lupus), UCB (Trial EMBODY SL009 and EMBODY SL012 in Lupus), AMGEN (Trials in immune thrombocytopenia)

We have also participated in several institutional trials conducted by teams from different French Hospital: Trial ADHRENCE SLE (APHP, Lupus), trial WIN LUPUS (CHU Marseille, Lupus), trials MAINRITSAN 2 and STATVAS (APHP, Vasculitis), trial LUPSENIC (CHU Nantes, Lupus), DEFI (APHP, Primary adult immunodeficiencies).
We have also conducted an interregional PHRC (Trial ALTADIH) in adults with common variable immunodeficiency and a trial in immune thrombocytopenia (CHU Bordeaux, Trial IMMUNOTI). Our team also leads 3 ongoing trials funded by the interregional PHRC:
1/ Trial CLOPUS in Lupus
2/ Trial IL-2 in autoimmune hemolytic anemia
3/ Trial INFIM in Lupus
Our team also contributes to several immunology laboratory's studies on providing blood samples.

Expected contribution to the AIR DHU
Access to human materials from different autoimmune diseases with a high quality of phenotyping (see "recognized resources").
- implementation of our expertise on therapeutic education in other departments of the DHU

Main grants since 2009
Interregional PHRC and internal grants from the Bordeaux University Hospital

Relevant publications and patents in the field since 2001:
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Rivière E, **Viallard JF**, Guy A, Kilani B, Vieira-Dias J, Pons AC, Couffinhal T, Pellegrin JL, James C. Intrinsically impaired platelet production in some patients with persistent or chronic immune thrombocytopenia. Br J Haematol. 2015 (In press).

Number of HDR: 3

Phase 1 and 2 clinical trial: 2

Academic protocol: 42

Protocols from industry: 41

National implication (cohort, society….): French society of internal medicine, French group for vasculitis, Center of reference for autoimmune cytopenia, CEREDIH, Cohort FAIR2R, Fondation arthritis, CRI-IMIDIATE

Education: certificate for education in HIV, Autoimmune diseases and Gaucher disease.

Annex 4: Description of the research structure associated with the FHU

Research Partner : ATIP-AVENIR (Julien Seneschal)	
Localization : **Bâtiment TP Zone Sud, 4ème étage** **143, rue Léo Saignat** **33076. Bordeaux Cedex**	**Institution :** **INSERM 1035**

Head : Pr Taieb Alain (PU-PH)

Key personnal : Julien Seneschal (Professor HDR), Katia Boniface (Assistant Professor), Jérôme Rambert (Engineer), Fabienne Lucchese (Assistant), Denis Thiolat (Technician), 1 post-doc, 1 PhD student, 1 master research student.

Field of expertise: Immune mechanisms of skin disorders: Vitiligo, Atopic dermatitis, psoriasis and pathogenesis of cutaneous skin adverse events under targeted therapies indicated for inflammatory skin disorders.

Previous contributions: The ATIP-AVENIR team has been created in 2014; the main projects are related to 1/characterization of the phenotype and function of immune cells infiltrating the skin in vitiligo and subsequent identification of potential targets important for future development of targeted therapies in the disease. 2/ Contribution of oxidative stress and energetic metabolism in skin depigmentation mediated by immune system. 3/ Analysis of the role of basophils in the development of atopic dermatitis (ANR TSLP Network: Principal Investigator Mei Li, IGBMC, Strasbourg) 4/ Analysis of the immunological mechanisms implied in the development of skin adverse reactions under targeted therapies used in inflammatory skin disorders.

Recognized Resources: Keratinocytes and melanocytes primary cultures, 3D reconstructed pigmented epidermis, Extraction of skin immune cells from human samples, Flow Cytometry, cell sorting, Molecular Biology, Lentiviral Plateform.

Expected contribution to the FHU

Experimental models of skin inflammation, Analysis of the phenotype and function of skin immune cells involved at early stage or during progression of inflammatory and auto-immune diseases

Analysis of the immune mechanisms involved in skin adverse events induced by targeted therapies indicated for auto-immune and inflammatory skin diseases. This team has already good connections with several clinical and research partners, as Julien Seneschal did his PhD program under the supervision of Patrick Blanco

Main grants since 2009 (relevant to the project)

- ANR:1
-French society of Dermatology
-ATIP/AVENIR
-French Society for reaserach in Dermatology

Relevant publications and patents in the field since 2010:

R.Y. Wagner, F. Luciani, M. Cario-André, A. Rubod, V. Petit, L. Benzekri, K. Ezzedine, S. Lepreux, E. Steingrimsson, A. Taieb, Y. Gauthier, L. Larue, V. Delmas. Altered E-Cadherin Levels and Distribution in Melanocytes Precede Clinical Manifestations of vitiligo. **J Invest Dermatol** 2015 Jan 29

A. Bertolotti, K. Boniface, B. Vergier, D. Mossalayi, A. Taieb, K. Ezzedine, J Seneschal. Type I Interferon signature in the initiation of the immune response in vitiligo. **Pigment Cell Melanoma Res**. 2014 May : 398-407

J. Seneschal, X. Jiang, T.S. Kupper : Langerin+ Dermal DC, but not Langerhans cells, are required for effective CD8 mediated immune responses after skin scarification with Vaccinia Virus (VACV). **J Invest Dermatol**. 2014 : 686-94

J.Seneschal, R.A.Clark, A. Gehad, Clare M. Baecher-Allan, T.S. Kupper. Human Epidermal Langerhans Cells Maintain Immune Homeostasis in Skin by Activating Skin Resident Regulatory T Cells. **Immunity**. 2012: 873-84

K. Boniface, W.M. Blumenschei, K. Brovont-Porth, M.J. McGeachy, B. Basham , B. Desai, R. Pierce, T.K. McClanahan, S. Sadekova, R. de Waal Malefyt. Human Th17 cells comprise heterogeneous subsets including IFNγ-producing cells with distinct properties from the Th1 lineage.**J. Immunol., 2010**; 185(1):679-687.

K. Boniface, K.S. Bak-Jensen, Y. Li, W.M. Blumenschein, M.J. McGeachy, T.K. McClanahan, B.S. McKenzie, R.A. Kastelein, D.J. Cua, R. de Waal Malefyt. Prostaglandin E2 regulates Th17 cell differentiation and function through cyclic-AMP and EP2/EP4 receptor signaling **J. Exp. Med**. 2009; 206(3):535-548.

J.Seneschal, B.Milpied, B.Vergier, S.Lepreux, T.Schaeverbeke, A.Taieb. Cytokine imbalance with increased production of IFN alpha in psoriasiform eruptions occurring under anti-TNF treatments. **Br J Dermatol**: 2009; 161: 1081-8

R.C. Axtell, B.A. de Jong, K. Boniface, L.F. van der Voort, R. Bhat, P. De Sarno, R.cNaves, M. Han, F. Zhong, J.G. Castellanos, R. Mair, T. Christakos, I. Kolkowitz, L. Katz, J. Killestein, C.H. Polman, R. de Waal Malefyt, L. Steinman, C. Raman. T helper type 1 and 17 cells determine efficacy of interferon-beta in multiple sclerosis and experimental encephalomyelitis. **Nature Medicine, 2010**; 16(4):406-412.

Patent

Methods of treating autoimmune diseases in a subject and in vitro diagnostic assays. Patent Application n°10/042, 644.

Use of allogeneic cell lines to load antigen-presenting cells to elicit or eliminate immune responses. Patent application n°10/110, 553.

Methods and pharmaceutical composition for neutralising the cytotoxic activity of extracellular histone proteins. Patent number: 14 306 445.9.

Antagonistic anti-ox40l antibody to block inflammatory effector t cells. In Process

Number of people involved in the project: 7

Number of "HDR": 2

Academic Multicentric Trials: 2

Teaching: Master in microbiology and Immunology

International Exchange: 1/year.

Start-up: Establishment of the industry transfer unit AQUIDERM 2014 (Grant from Aquitaine Region)

ANR: 1

Collaborative networks: a)LITEC: Laboratoire, Inflammation, Tissus, Epithéliaux, et Cytokines, Poitiers, France: Jean-Claude Lecron, b) BioAlternatives, Gençay, France: François X. Bernard c)HSDRC: Harvard Skin Disease Research Center, Boston, USA: Thomas S. Kupper, d)Merck/Schering Plough Biopharma, Palo Alto, USA: R. de Waal Malefyt, e)University of Massachussets Medical School, Department of Dermatology, Worcester, USA: John Harris, f) Development Genetics of Melanocytes, Orsay, France: L. Larue.

Patent: "Combination Therapy for Treatment of Immune Disorders". Patent application file (Schering-Plough Biopharma). International publication number **WO 2008/106131**. Inventeurs: Bowman EP, Cua DJ, Kastelein RA, Miller KL, Kleinschek MA, Bak-Jensen KS, Boniface K, McKenzie BS, De Waal Malefyt R.

"Compositions for Enhancing Keratinocyte Migration and Epidermal Repair via a Receptor Containing OSMRb as a Subunit, and Applications Thereof". International publication number **WO 2006/063865**. Inventeurs: Lecron JC, Gascan H, Morel F, Chevalier S, Bernard FX, Boniface K, Diveu C. (KB)

Localization : Université de Bordeaux Bât TP - Zone sud - 3ème étage 146, rue Léo-Saignat 33076 Bordeaux cedex	**Institution :** **INSERM U1045**

Head : Pr Marthan Roger (PU-PH)

Key personnal : Patrick BERGER, PU-PH ; Marie-Luce CHOUKROUN, MCU-PH ;Gaël DOURNES, CCA ; Isabelle DUPIN, MCF ; Michaël FAYON, PU-PH ; Pierre-Olivier GIRODET, MCU-PH ; Gilles HILBERT, PU-PH; François LAURENT, PU-PH ; Julie MACEY, PH; Roger MARTHAN, PU-PH; Michel MONTAUDON, PU-PH; Matthieu THUMEREL, PH; Thomas TRIAN, MCF; Frédéric VARGAS, PU-PH

Asthma and chronic obstructive pulmonary disease (COPD) are very frequent airway diseases (i.e., 5 and 4 million patients in France, respectively). Whereas asthma mortality has dramatically decreased within the last 20 years, uncontrolled asthma still has major consequences on morbidity, quality of life, and economic burden. Severe asthmatics represent 5 to 10% of all asthmatics and generate a large proportion of resource expenditure. By contrast, the mortality of COPD continues to increase. It is now the 4th cause of death worldwide and projections predict that COPD will reach the 3rd cause of death in 2030. Various phenotypes have been described in both diseases. For instance, frequent exacerbations can predominate in a subgroup of severe asthmatic patients with fixed airflow obstruction but also in COPD patients. Moreover, these patients present a higher rate of lung function decline over time.

Both asthma and COPD are inflammatory diseases, which are characterized by different patterns of bronchial remodelling. In asthma in particular, there is an increased mass of the bronchial smooth muscle (BSM) within the entire bronchial tree, which is related to a decrease in lung function. For instance, during the previous contract, we demonstrated the key role of mitochondrial biogenesis in the BSM remodelling of severe asthmatics. In COPD, the increased mass of BSM appears less important as compared to the peribronchial fibrosis, both of which being limited to the distal airways. Bronchial remodelling was initially thought to be the consequence of an incomplete repair process following inflammation. However, the early onset of this process, suggests that remodelling and particularly BSM remodelling in asthma may be the cause and not the consequence of chronic inflammation. Nevertheless, the pathophysiology of bronchial remodelling of both asthma and COPD remains largely unknown. In addition, the consequences of exacerbations in both diseases on the bronchial remodelling have to be described and understood. The main cause of these exacerbations is viral infection of the bronchial epithelial layer. Indeed, viruses are found in approximately 80% of wheezing episodes in school-aged children and in 50 to 75% in adults. Human rhinovirus is the most common virus found during an exacerbation. However, there are only symptomatic drugs available today for the treatment of both diseases and their exacerbations. Therefore, new treatments able to modify the natural history of these diseases are urgently needed. Our hypothesis is that bronchial remodelling should be a primary target of these innovative treatments.

To date, bronchial remodelling can only be assessed using bronchial biopsies or surgical specimens. Non-invasive tools are thus necessary to assess this remodelling in vivo. Multi-detector resolution computed tomography (CT) was limited to the measurement of bronchial thickness in vivo. For instance, during the previous contract, we developed a new tool of bronchial imaging using CT and 3D reconstruction software, which allows toassess bronchial dimensions of bronchi up to the 10th generation.

Thus, the scientific scope of bronchial remodelling Team is focused on these remodelling, in terms of pathophysiology to understand the mechanisms and identify new therapeutic targets, but also in terms of imaging to assess bronchial remodelling noninvasively. For this purpose, we developed translational approaches using a strong collaboration with the Clinical Investigation Centre (CIC) of Bordeaux.

Scientific policy

Our goals are (i) to improve the comprehension of the mechanisms involved in bronchial remodelling of both asthma and COPD, in order to identify new therapeutic targets, test the efficacy of innovative treatments on these targets in clinical trials; and (ii) to develop new imaging tools to assess bronchial remodelling noninvasively.

We are one of the few laboratories in Europe only focused on bronchial remodelling in obstructive airway diseases. Moreover, we are able to address various scopes from the pathophysiology to both imaging and proof of concept clinical trials, which strengthen our national and international positions.

Expected contribution to the FHU

This team is an important constituent of the DHU since it is the only team working on lung inflammation. This team expects to develop new collaborations within the FHU particularly in the microbiota program in the context of autoimmunity (rheumatoid arthritis as an example). Moreover this team is already working in close connection with different clinical and research partners of the FHU.

Main grants since 2009 (relevant to the project)

- The team leader (P Berger) and one member of the team (F Laurent) belong to the steering committee of the LabEx TRAIL.
- One member of the team (R Marthan) is the director of the Doctoral school "Life and Health Sciences" (ED SVS 154).
- A member of the team (PO Girodet) is the acting head of the respiratory axis of the clinical research center CIC-P of Bordeaux (CHU de Bordeaux).
- The team has obtained 1 171 k€ of research contracts from mainly ANR and PHRC

(1) Bronchial remodelling in asthma (763 k€)

- AirDustMito /ANR: 250 k€. PI: P Berger. Effects of chronic exposure of Airways to house Dust mite on bronchial asthmatic smooth muscle Mitochondria.
- Remodel'asthme / PHRC + Recherche Clinique translationnelle Inserm/DHOS: 190 k€. PI: P Berger. Effects of gallopamil on bronchial smooth muscle remodelling in severe asthma: a double blind study.
- Asthmatreat /ANR 148 k€. PI: R Marthan (partner in a multicenter contract coordinated by Nicolas Glaichenhaus). Asthma and beta2 adrenergic receptor.
- Ptit'asthme / PHRC 175 k€. PI: M Fayon. Risk factors for early remodelling in severe asthma in children.

(2) Bronchial remodelling in COPD (185 k€)

- Firebrob / fondation du souffle 20 k€. PI: P Berger. "Rôle des fibrocytes dans les exacerbations de la broncho-pneumopathie chronique obstructive (BPCO)".
- Fibrochir / AOI 12 k€. PI: M Thumerel. Role of FIBROcytes in the bronchial remodelling of chronic obstructive pulmonary disease.
- SENA / AOI 25 k€. PI: F Vargas. Etude randomisée, contrôlée évaluant l'assistance ventilatoire asservie à l'activité électromyographique (NAVA) comparée à l'aide inspiratoire chez les patients en sevrage difficile de la ventilation mécanique
- VNI-HD / PHRC 128 k€. PI: G Hilbert. Essai Clinique randomisé de l'oxygène haut débit (OPTIFLOW) compare à l'oxygène standard en ventilation non invasive séquentielle.

(3) Imaging of bronchial remodelling in asthma and COPD (223 k€)

- COBRA Scan / LabEx TRAIL 134 k€. PI: F Laurent. Quantitative computed tomography for phenotyping COPD within COBRA cohort.
- EMPHYREM / AOI 24 k€. PI: G Dournes. Assessement of emphysema in COPD patients using 1.5T MR imaging with ultrashort echo time (UTE) pulse sequences (EMPHYREM study)
- MucoIRM / AOI 30 k€. PI: J Macey. Assessment of lung involvement in cystic fibrosis patients using 1.5T MR imaging with ultrashort echo time (UTE) pulse sequences
- NEKOMRI / LabEx TRAIL 35 k€. PI: F Baldacci & F Laurent. MRI sequence for bronchial wall segmentation and analysis.

Industrial partnerships

- The team director actively contributes to several international boards of drugs companies (Glaxo-Smith Kline, Boehringer-Ingelheim, Novartis, and Takeda).
- The team has obtained 267 k€ of research contracts from industries
- Pierre Fabre 59 k€. PI: P Berger. Title confidential.
- GlaxoSmithKline 135 k€. PI: P Berger. Title confidential.
- Astra-Zeneca 30 k€. PI: M Fayon. Title confidential.
- Firebrob / Takeda 43 k€. PI: P Berger. Role of FIbrocytes in the BRonchial REmodeling of Chronic OBstructive pulmonary disease

Patents

1. Berger P, Trian T, Rossignol R, Marthan R, Tunon de Lara JM, Girodet PO.
Bronchial smooth muscle remodeling involves calcium-dependent enhanced mitochondrial biogenesis in asthma. US national patent submitted 18 Jun 2009 (N°12/487,273).
2. Berger P, Dupin I, Girodet PO.

New compositions and methods of treating and/or preventing Chronic Obstructive Pulmonary Disease. European patent submitted 28 Jan 2015 (EP N°15152886.6).

Relevant publications and patents in the field since 2001:

Trian T, Moir LM, Ge Q, Burgess JK, Kuo C, King NJ, Reddel HK, Black JL, Oliver BG, McParland BE. Rhinovirus-induced exacerbations of asthma: How is the {beta}2-adrenoceptor implicated**? Am J Respir Cell Mol Biol.** 2010 ; 43(2) : 227-33.

Bara I, Ozier A, Girodet PO, Carvalho G, Cattiaux J, Begueret H, Thumerel M, Ousova O, Kolbeck R, Coyle AJ, Woods J, Tunon de Lara JM, Marthan R, Berger P.
Role of YKL-40 in bronchial smooth muscle remodeling in asthma.
Am J Respir Crit Care Med 2012 ; 185(7) : 715-722.

Girodet PO, Ozier A, Carvalho G, Ilina O, Ousova O, Gadeau AP, Begueret H, Wulff H, Marthan R, Bradding P, Berger P.The KCa3.1 blocker TRAM-34 attenuates airway remodeling and eosinophilia in a mouse asthma model. **Am J Respir Cell Mol Biol** 2013, 48(2) : 212-219. Recommandé par la "Faculty of 1000".

Dournes G, Laurent F, Coste F, Dromer C, Blanchard E, Picard F, Baldacci F, Montaudon M, Girodet PO, Marthan R, Berger P. CT measurement of airway remodeling and emphysema in advanced COPD: correlation with pulmonary hypertension.
Am J Respir crit Care Med 2015, 191 (1) : 63-70.

Trian T, Allard B, Dupin I, Carvalho G, Ousova O, Maurat E, Bataille J, Thumerel M, Begueret H, Girodet PO, Marthan R, Berger P. House dust mites induce proliferation of severe asthmatic smooth muscle cells via an epithelium-dependent pathway.
Am J Respir crit Care Med 2015, 2015, 191 (5) : 538-546. Recommandé par la "Faculty of 1000".

Girodet PO, Dournes G, Thumerel M, Begueret H, Dos Santos P, Ozier A, Dupin I, Trian T, Montaudon M, Laurent F, Marthan R, Berger P. A Double-Blind, Placebo-Controlled Trial of Gallopamil for Severe Asthma. **Am J Respir crit Care Med** 2015, 191 (8): 876-883.

Dournes G, Grodzki D, Macey J, Berger P, Girodet PO, Chateil JF, Fayon M, Montaudon M, Laurent F.Quiet sub-millimetric MRI of the lung is feasible using PETRA sequence at 1.5 T: a technical note. **Radiology** 2015, March in press.

Number of people involved in the project: 8

Number of "HDR": 9

Academic Multicentric Trials: 3

International Exchange: 2/year.

ANR: 3

Number of patent licensed (4 last years): 0

Research Partner : CIRID	
Localization : **Bâtiment 1B Zone Nord, 1er étage** **143, rue Léo Saignat** **33076. Bordeaux Cedex**	**Institution :** **UMR/CNRS5164**

Head : Pr Moreau Jean-François

Key personnal : Julie Merville (DR), Myriam Capone (CR), Dorothé Duluc (MCF), Nicolas Larmonier (PU), Estibaliz Lazaro (MCU-PH), Christophe Richez (PU-PH), Marie-Elise Truchetet (CCA), Pierre Duffau (MCU-PH), Cécile Bordes (MCU-PH), Isabelle Douchet (AI-CNRS), Benjamin Faustin (Postdoc), Thomas Pradeu (CR), Jonathan Visentin (AHU), Maria Matsuda-Mamani (MCF), Pierre Merville (PU-PH), Lionel Couzi (PU-PH).

The global aim of the team since several years is to understand the **cellular and molecular mechanisms of human T lymphocyte activation in normal or pathological conditions**. A special focus is made on gd T lymphocytes and on autoimmune diseases, two topics on which our members have developed an expertise, important tools and national and international collaborations since many years. Modulation of T cell activation is a general concern in the prevention or cure of various diseases including cancer, infections and autoimmune disorders. The delineation of the mechanisms leading to this activation is a prerequisite towards this goal. In this context, understanding the way of activation, regulation or action of T lymphocytes represent the main scientific objective of our research team with specific regards to:

i) the **human** gd **T lymphocytes** which play an important role in immunity to neoplasia and pathogen infections by sensing and reacting to cellular stress. As the basic understanding of how gd T cells are specifically stimulated is still elusive, we analyze the molecular mechanisms underlying gd T cell activation and the functional consequences of this in different models: cytomegalovirus (CMV) infection, malaria and tumor surveillance

ii) human T cells represent important effectors in the context of **systemic autoimmune disorders**. Our aim is to understand the underpinnings of the chronic imbalance between effector (CD8 and follicular helper T cells) and regulatory T cells in autoimmune disorders. To this end, we pay special attention to the role of innate and environmental cells such as dendritic cells (DC), platelets and endothelial cells on autoimmune T cell activation.

The specific feature of the team is to **combine basic research** addressing mechanistic issues about T cell activation and interactions with target or partner cells, and **clinical research** to translate our results into therapeutic trials or patient monitoring. All our projects are developed in close interaction with Bordeaux University Hospital and the blood bank (EFS Aquitaine Limousin) that are instrumental for optimal development of our studies. The fact that several researchers and physicians share their time between our unit and the University Hospital (in departments of Immunology, Transplantation, Internal Medicine and Rheumatology) facilitates the bench to bedside translation of our results and the interface to discuss clinical issues feeding our research. As an illustration of this translational activity, results from our research led to the development of three PHRC and the participation to one phase IV clinical trial during the current period.

Expected contribution to the FHU

This team is an important constituent of the DHU since it is the only team working on fundamental immunology. Therefore its contribution appears obvious.

Main grants since 2009 (relevant to the project)

- ANR
-French society of Rheumatology
-Arthritis foundation
-FRM team 2013
- French society of Internal medecine
-PHRC regional: 2

Relevant publications and patents in the field since 2010:

Tauzin S, Chaigne-Delalande B, Selva E, Khadra N, Daburon S, Contin-Bordes C, Blanco P, Le Seyec J, Ducret T, Counillon L, Moreau JF, Hofman P, Vacher P, Legembre P. The naturally processed

CD95L elicits a c-yes/calcium/PI3K-driven cell migration pathway. PLoS Biol. 2011 Jun;9(6):e1001090

Contin-Bordes C, Lazaro E, Richez C, Jacquemin C, Caubet O, Douchet I, Viallard JF, Moreau JF, Pellegrin JL, Blanco P. Expansion of myelin autoreactive CD8+ T lymphocytes in patients with neuropsychiatric systemic lupus erythematosus. Ann Rheum Dis. 2011;70:868-71.

Duffau P, Seneschal J, Nicco C, Richez C, Lazaro E, Douchet I, Bordes C, Viallard JF, Goulvestre C, Pellegrin JL, Weil B, Moreau JF, Batteux F**, Blanco P**. Platelet CD154 Potentiates Interferon-{alpha} Secretion by Plasmacytoid Dendritic Cells in Systemic Lupus Erythematosus**. Sci Transl Med**. 2010 Sep 1;2(47):47ra63.

Pradeu T, Cooper EL. The danger theory: 20 years later. **Front Immunol.** 2012 Sep 17;3:287.

Willcox CR, Pitard V, Netzer S, Couzi L, Salim M, Silberzahn T, Moreau JF, Hayday AC, Willcox BE, Déchanet-Merville J. Cytomegalovirus and tumor stress surveillance by binding of a human γδ T cell antigen receptor to endothelial protein C receptor. **Nat Immunol**. 2012 Sep;13(9):872-9.

Eric Boilard, **Patrick Blanco** and Peter A. Nigrovic. Platelets: Active players in the pathogenesis of arthritis and systemic lupus erythematosus. **Nat Rev Rhumatol**. 2012 Sep;8(9):534-42.

Pradeu T, Jaeger S, Vivier E. The speed of change: towards a discontinuity theory of immunity? **Nat Rev Immunol.** 2013 Oct;13(10):764-9.

Clément Jacquemin, Nathalie Schmitt, Cécile Contin-Bordes, Yang Liu, Priya Narayanan, Julien Seneschal, Typhanie Maurouard, David Dougall, Emily Spence Davizon, Hélène Dumortier, Isabelle Douchet, Loïc Raffray, Christophe Richez, Estibaliz Lazaro, Pierre Duffau, Marie-Elise Truchetet, Liliane Khoryati, Patrick Mercié, Lionel Couzi, Pierre Merville, Thierry Schaeverbeke, Jean-François Viallard, Jean-Luc Pellegrin, Jean-François Moreau, Sylviane Muller, Sandy Zurawski, Robert L. Coffman, Virginia Pascual, Hideki Ueno and **Patrick Blanco**. OX40 Ligand contributes to the pathogenesis of autoimmunity by promoting T follicular helper response. **Immunity.** 2015 Jun 16;42(6):1159-70.

Kaminski H, Garrigue I, Couzi L, Taton B, Bachelet T, Moreau JF, Déchanet-Merville J, Thiébaut R, Merville P. Surveillance of γδ T Cells Predicts Cytomegalovirus Infection Resolution in Kidney Transplants. **J Am Soc Nephrol.** 2015 Jun 8

Patents

Methods of treating autoimmune diseases in a subject and in vitro diagnostic assays. Patent Application n°10/042, 644.

Use of allogeneic cell lines to load antigen-presenting cells to elicit or eliminate immune responses. Patent application n°10/110, 553.

«METHODS AND PHARMACEUTICAL COMPOSITION FOR NEUTRALISING THE CYTOTOXIC ACTIVITY OF EXTRACELLULAR HISTONE PROTEINS». Patent number: 14 306 445.9.

ANTAGONISTIC ANTI-OX40L ANTIBODY TO BLOCK INFLAMMATORY EFFECTOR T CELLS. In Process

Number of people involved in the project: 15

Number of "HDR": 11

Academic Multicentric Trials: 6

Teaching: Master in microbiology and Immunology

International Exchange: 2/year.

Start-up: CEllomet (benjamin Faustin)

ERC grant: 1

ANR: 3

Number of patent licensed (4 last years): 1

Research Partner : ARNA	
Localization : **Université de Bordeaux** **146 rue Léo Saignat** **BATIMENT 3A** **33076 Bordeaux cedex**	**Institution :** **INSERM U869**

Head : Dr Jean Louis Mergny (DR / INSERM).

Key personal : Jean-Jacques Toulmé (DRCEE/INSERM), Laurent Azéma (MCU)

Summary of the research

The activity of the team is dedicated to the design and the use of synthetic oligonucleotides. Our research is focused on the identification, characterization and use of aptamers. Aptamers are single chain oligonucleotides, identified through a combinatorial process of in vitro directed evolution, for their ability to bind a pre-determined target. High affinity binders displaying a high specificity are generally obtained making aptamers a validated alternative to antibodies. Their synthesis, chemical modification, handling, storage is easier than that of proteins. They can be engineered into biotechnological tools (probes, sensors).

We raised aptamers against a wide variety of targets ranging from small bioorganic molecules to peptides, synthetic polymers, nucleic acids, proteins. In particular we characterized aptamers to a human matrix metalloprotease (MMP9). An anti-MMP aptamer was secondarily converted into a probe for imaging sections of human tumors by scintigraphy. A optical fluorescence probe derived from this aptamer allowed the detection of A350 melanoma xenografts in a mouse model (unpublished). A combination of two different anti-MMP9 aptamers targeting two different regions of this metalloprotease was used in a sandwich type assay for its quantitation in serum (unpublished).

Taking advantage of loop-loop interactions, RNA hairpin aptamers were engineered for the specific detection of a small ligand through a mechanism resting on ligand-induced conformation change of the aptamer. Such a biosensor can be included in a multiplex device allowing the simultaneous quantitative detection of several molecules either on a biochip or in solution.

The team has strong interactions with Novaptech, a business unit created by J.-J. Toulmé in 2008, that offers services to both industry and academic laboratories for the design of aptamer-derived tools.

Expected contribution to the FHU

We can raise aptamers against any target of interest for inflammation. This could be a biomarker for diagnostics or a protein/enzyme for target validation. We have the requested expertise in molecular biology, in biophysical measurements and in nucleic acid chemistry for the development of oligonucleotide aptamers.

Main grants since 2009 (relevant to the project)

ANR 2010-2014: Rational design of a sensitive and enantiospecific electrocatalytically-amplified aptasensor for amphetamine- derivatives drugs.

ANR 2011-2015 : Video Imaging of biological and bioinspired nanosystems.

LabEx TRAIL 2013-2016 : Imaging melanomas with aptamers.

Maturation Aquitaine Science Transfert 2014-2015 : Selection of kissing aptamers.

UE – ITN 2015-2018 : RNA-based technologies for single-cell metabolite analysis.

INCa 2015-2016: Discoidin domain receptors (DDR) involvement in melanoma progression and invasion.

Relevant publications and patents in the field since 2001:

1. Dausse, E., Taouji, S., Evadé, L., Di Primo, C., Chevet, E. and Toulmé, J.J. (2011) HAPIscreen, a method for high-throughput aptamer identification. ***J Nanobiotechnology***, **9**, 25.
2. Di Primo, C., Dausse, E. and Toulmé, J.J. (2011) Surface plasmon resonance investigation of RNA aptamer-RNA ligand interactions. ***Methods Mol Biol***, **764**, 279-300.
3. Renaud de la Faverie, A., Hamon, F., Di Primo, C., Largy, E., Dausse, E., Delaurière, L., Landras-Guetta, C., Toulmé, J.J., Teulade-Fichou, M.P. and Mergny, J.L. (2011) Nucleic acids targeted to drugs: SELEX against a quadruplex ligand. ***Biochimie***, **93**, 1357-1367.
4. Shukla, G.C., Haque, F., Tor, Y., Wilhelmsson, L.M., Toulmé, J.J., Isambert, H., Guo, P., Rossi, J.J., Tenenbaum, S.A. and Shapiro, B.A. (2011) A boost for the emerging field of RNA nanotechnology. ***ACS Nano***, **5**, 3405-3418.
5. Taouji, S., Dausse, E., Evade, L., Di Primo, C., Toulmé, J.J. and Chevet, E. (2011) Advances in binder

identification and characterisation: the case of oligonucleotide aptamers. ***N Biotechnol***, **29**, 550-554.
6. Bui, L., Abbou, S., Ibarboure, E., Guidolin, N., Staedel, C., Toulmé, J.J., Lecommandoux, S. and Schatz, C. (2012) Encapsidation of RNA-polyelectrolyte complexes with amphiphilic block copolymers: toward a new self-assembly route. ***J Am Chem Soc***, **134**, 20189-20196.
7. Da Rocha Gomes, S., Miguel, J., Azéma, L., Eimer, S., Ries, C., Dausse, E., Loiseau, H., Allard, M. and Toulmé, J.J. (2012) (99m)Tc-MAG3-aptamer for imaging human tumors associated with high level of matrix metalloprotease-9. ***Bioconjug Chem***, **23**, 2192-2200.
8. Delauriere, L., Dong, Z., Laxmi-Reddy, K., Godde, F., Toulmé, J.J. and Huc, I. (2012) Deciphering aromatic oligoamide foldamer-DNA interactions. ***Angew Chem Int Ed Engl***, **51**, 473-477.
9. Loscher, M., Schosserer, M., Dausse, E., Lee, K., Ajuh, P., Grillari-Voglauer, R., Lamond, A.I., Toulmé, J.J. and Grillari, J. (2012) Inhibition of pre-mRNA splicing by a synthetic Blom7alpha-interacting small RNA. ***PLoS One***, **7**, e47497.
10. Durand, G., Lisi, S., Ravelet, C., Dausse, E., Peyrin, E. and Toulmé, J.J. (2014) Riboswitches based on kissing complexes for the detection of small ligands. *Angew Chem Int Ed Engl*, **53**, 6942-6945.
11. Evade, L., Dausse, E., Taouji, S., Daguerre, E., Chevet, E. and Toulmé, J.J. (2015) Aptamer-mediated nanoparticle interactions: from oligonucleotide-protein complexes to SELEX screens. ***Methods Mol Biol*, 1297**, 153-167.
12. Goux, E., Lisi, S., Ravelet, C., Durand, G., Fiore, E., Dausse, E., Toulmé, J.J. and Peyrin, E. (2015) An improved design of the kissing complex-based aptasensor for the detection of adenosine. ***Anal Bioanal Chem*.** (ahead of print)

Patent: 4

Number of patent licensed (4 last years): 0

Start-up: 1

Number of researchers involved in the project: 2

Number of "HDR": 2

Research Partner : LaBRI - "Image and Sound" and "MABioVis" teams	
Localization : **LaBRI, bât A30, Université de Bordeaux** **351, crs de la Libération** **33405 Talence cedex**	**Institution :** **Laboratoire Bordelais de Recherche en Informatique** **UMR 5800 CNRS / UB / INP Bordeaux**

Head : P. Weil (DR, CNRS) - Head of LaBRI.

Key personnal : Pascal DESBARATS (PR, UB) - head of "Image and Sound" team, Jean-Philippe DOMENGER (PR, UB), Fabien BALDACCI (MCF, UB), Anne VIALARD (MCF, UB), Pierrick COUPÉ (CR, CNRS), Macha NIKOLSKI (DR, CNRS)- Head of CBiB, Guillaume BLIN (PR, UB) - head of "MABioVis" team, Raluca Uricaru (MdC, UB)

Advances in "-omics", imaging, and other advanced biomedical technologies in recent years have resulted in the exponential growth of biomedical data, and have started the era of "Big Data" in health and biomedicine. The general goal of our research team is to develop methods to improve the acquisition, analysis, modeling, synthesis, and interaction with these data. The data manipulated by the team represent a wide spectrum from genetic data to 2D or 3D images and video.

From genetics to pathway analysis. Genomic studies of human disease and drug response aim to find one or a few culprit variants among millions of possible suspects. We focus on the development of methods to quickly and reliably shortlist such variants, and the genes and pathways in which they may cluster. In particular, Next Generation Sequencing (NGS) analysis is one of the main topics of our team. For example, we develop methods for the identification of driver mutations in cancer. Moreover, NGS-based metagenomic studies are more and more employed to identify the genetic determinants of microbiota-responsive traits (ex. response to treatment). In particular, our team is involved in the development of methods for taxonomic assignment (Alonso, 2014; Soueidan, 2014) and we have recently applied these methods to the case of rheumatoid arthritis. The strength of our team to gather expertise on both theoretical algorithmic aspects as well as on applied aspects of data interpretation and analysis.

From image reconstruction to image analysis. Our researches focus on the control of the complete image processing chain: from image acquisition to high level analysis. We develop new methods for image reconstruction, filtering, segmentation and analysis. The richness of our inter-disciplinary collaborations has allowed us to investigate several modalities: « natural images » (photography and video), biological and medical imaging (CT and micro-CT, MRI, ultrasound, confocal and multi-photon microscopy ...) and Non-Destructive Control techniques (such as Terahertz imaging). The strength of our team is its ability to develop methods and algorithms for each link of these processing chains while maintaining consistency for a given acquisition technique. For instance, 3D segmentation is performed on medical images using patch-based methods (for anatomical brain structure segmentation), snakes (for cardiac segmentation) or tubular structure identification (for bronchi or vessels segmentation). Recently, near real time patch-based method has been developed in our team for anatomical structures segmentation. This last advanced approach is currently integrated in a web-based service for remote online processing of MRI (http://volbrain.upv.es). This service is the result of a long-term collaboration with the Polytechnic University of Valencia.

Expected contribution to the FHU

Linking genetics and images. Imaging genetics and epigenetics is a novel research direction that seeks to understand the association of image-based phenotypes with genetic variations and environmental influence. Our team is well positioned to undertake the linking signatures at the genetic scale to parameters of image-based models, that currently remains an open challenge.

Main grants since 2009 (relevant to the project)

- Projet Broncho4D, LabEx Trail (F. Baldacci)
- Projet « Genotype to Phenotype », UB (M. Nikolski)
- Projet Elixir-Excelerate, EU (M. Nikolski)

Relevant publications and patents in the field since 2001:

D. Alonso-Alemany, A. Barre, S. Beretta, P. Bonizzoni, M. Nikolski, G. Valiente, Further Steps in TANGO: Improved Taxonomic Assignment in Metagenomics, Bioinformatics (2013), doi: 10.1093/bioinformatics/btt256

P. Coupé, J. V. Manjon, M. Chamberland, M. Descoteaux, B. Hiba. Collaborative patch-based super-resolution for diffusion-weighted images. NeuroImage, 83:245-261, 2013

P. Coupé, S. F. Eskildsen, J. V. Manjon, V. Fonov, D. L. Collins and ADNI. Simultaneous Segmentation and Grading of Anatomical Structures for Patient's Classification: Application to Alzheimer's Disease. NeuroImage, 59(4):3736–3747, 2012.

P. Coupé, J. V Manjon, V. Fonov, J. Pruessner, M. Robles, D. L. Collins. Patch-based Segmentation using Expert Priors: Application to Hippocampus and Ventricle Segmentation. NeuroImage, 54(2): 940–954, 2011.

P. Berger, V. Perot, P. Desbarats, J.M. Tunon-de-Lara, R. Marthan, F. Laurent. Airway Wall Thickness in Cigarette Smokers: Quantitative Thin-Section CT Assessment. Radiology 235 (3), 1055-1064

N. Grenier, I. Mendichovszky, B. Denis De Senneville, S. Roujol, P. Desbarats, M. Pedersen, K. Wells, J. Frokiaer, I. Gordon. Measurement of glomerular filtration rate with magnetic resonance imaging: principles, limitations, and expectations. Seminars in nuclear medicine 38 (1), 47-55

M. Montaudon, P. Desbarats, P. Berger, G. De Dietrich, R. Marthan, F. Laurent. Assessment of bronchial wall thickness and lumen diameter in human adults using multi-detector computed tomography: comparison with theoretical models. Journal of anatomy 211 (5), 579-588

P. Morel, X. Wu, G. Blin, S. Vialette, R. Flynn, et al.. Spot Weight Adaptation for Moving Target in Spot Scanning Proton Therapy. Frontiers in Oncology, Frontiers, 2015, 15 pp.

H. Soueidan, L. Schmitt, T. Candresse and M. Nikolski Finding and identifying the viral needle in the metagenomic haystack: Trends and Challenges, Frontiers in Microbiology 2014, 5, 739

H. Soueidan, F. Maurier, A. Groppi, P. Sirand-Pugnet, F. Tardy, C. Citti, V. Dupuy and M. Nikolski, Finishing bacterial genome assemblies with Mix, BMC Bioinformatics 2013, 14(Suppl 15):S16

R. Uricaru, G. Rizk, V. Lacroix, E. Quillery, O. Plantard, et al.. Reference-free detection of isolated SNPs. Nucleic Acids Research, Oxford University Press (OUP): Policy C - Option B, 2014, pp.1 - 12

Patent

Procédé de modélisation d'une pièce formée de tissus osseux. Coqueugniot H., Desbarats P., Dutailly B., Dutour O. Université de Bordeaux, Université Aix-Marseille.

BR39066/EP/vh (France).

Number of people involved in the project: 8 (full-time position)

Number of "HDR": 4

Academic Multicentric Trials: 7

Teaching: Master in Bioinformatics and informatics (specialty ISV) + International master BioImagery (16PhD + 2 PostDoc).

International Exchange: 3-6/year.

Number of patent licensed (4 last years): 4

Research Partner : ATIP AVENIR Nathalie Schmitt	
Localization : **bât 1B, Zone Nord** **143, rue Léo Saignat** **33076. Bordeaux Cedex**	**Institution :** **Institution :** **UMR/CNRS 5164**
Head : Pr Moreau Jean-François (PU-PH). **Key personnal:** Nathalie Schmitt. Other persons to be recruited include a technician, a post doc, and a PhD student.	

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease, which results from the autoimmune destruction of myelin and associated collateral tissues within the central nervous system (CNS)1. While several treatment options are currently available, no treatment completely stops the disease progression. Furthermore, the response to treatments is largely different among patients, and no patient stratification strategy is currently available for treatment options. Therefore, deeper understanding of the pathogenesis is necessary to develop more efficient treatment strategies. Our long-term goal is to develop a novel therapeutic approach for MS, which aims at inhibiting the generation and/or the functions of pathogenic CD4 T cells. Undoubtedly, mouse studies using the experimental autoimmune encephalitis (EAE) model have contributed substantially to the understanding of MS pathogenesis. However, human immune system is not identical with mouse immune system2, and the findings in EAE models do not always apply to human MS3. Therefore, to determine the nature of pathogenic CD4 T cells in MS, it is essential to analyze samples obtained from patients.

MS includes several clinically distinct subtypes, including relapsing-remitting form (RRMS), secondary progressive form (SPMS), and primary progressive form (PPMS). While MS has been classically regarded as a white matter disease, the intense involvement of the grey matter in the MS pathogenesis has become evident during the past decade4. Indeed, grey matter alterations appear to correlate more strongly with physical and cognitive disability than white matter alterations5. Interestingly, cortical grey matter demyelination was found to be more prominent in the progressive forms (SPMS and PPMS)6. However, how and whether the type of pathogenic CD4 T cells involved in the alterations of grey matter and white matter in MS are different remains largely unknown.

While previous studies on mouse EAE models7 and samples from MS patients8 have demonstrated the pathogenic roles of Th1 and Th17 cells, recent evidence also suggests the involvement of T follicular helper (Tfh) cells in MS pathogenesis. Tfh cells represent a CD4 T cell subset specialized for the provision of help to B cells, and play an essential role for the formation of germinal centers (GC) in secondary lymphoid organs9. Ectopic GCs are found in the brain lesions of more than 40% of the secondary progressive MS patients10. Notably, the formation of ectopic GCs in progressive MS patients is largely limited to inflamed meninges and associated to large cortical lesions. The development of meningeal GCs was found to positively correlate with the disease severity10. These observations suggest the involvement of Tfh cells in MS pathogenesis, particularly in progressive forms that affect cortical grey matter. We surmise that differences in the clinical course and disease severity among MS patients might be associated with the differences in dominant type of pathogenic CD4 T cells. In this line, distinct T cell subsets might contribute to different aspects of CNS inflammation.

In our preliminary study, we aimed to determine how the phenotype and the cytokine expression profiles of memory CD4 T cells in blood are different between RRMS patients and age-matched controls. We found that memory CD4 T cells expressing the integrin β7 in RRMS patients display multiple distinct features from those in control subjects. Furthermore, we found both blood β7+ Tfh and β7+ non-Tfh cell (including Th1 and Th17 cells) displayed altered phenotype and functions in MS patients. Collectively, **we hypothesize that both β7+ Tfh and β7+ non-Tfh cells play pathogenic roles in MS, yet contribute to distinct aspects**. We surmise that β7+ non-Tfh cells might play major inflammatory roles in white matter, and cause neuronal damage via inflammatory cytokines and cytotoxic molecules. In contrast, β7+ Tfh cells might promote the formation of ectopic GCs in meninges and induce damage of cortical grey matter through the generation of myelin-specific autoantibodies. Accordingly, the dominant type of altered CD4 T cell subsets might be different among clinically distinct subtypes.

To examine whether the alteration of specific CD4 T cell subset is associated with specific types of CNS lesions in MS patients, we established a collaboration with Dr. Thomas Tourdias (Neurocentre Magendie, Bordeaux University), who has extensive expertise in MRI in MS patients11,12. MS activity can be assessed non-invasively with advanced MRI that is able to provide a much more detailed phenotype as

compared to the three-class clinical phenotype (RRMS, SPMS and PPMS)13,14, and sensitively quantifies the alteration of the blood brain barrier that is associated with the inflammatory component of the disease11,12. Furthermore, Dr, Tourdias is currently validating more advanced MRI method named diffusion tensor imaging (DTI) which can provide indirect quantitative data reflecting tissue organization and microstructure such as ectopic GC formation. By applying these most advanced MRI technologies in the neuroscience field, we expect to assess the CNS lesions of MS patients in unprecedented detail and determine the correlation

Expected contribution to the FHU: Nathalie will join the UMR/CNRS 5164 in January 2016. She is currently working at the Baylor Institute for Immunology Research and has interacted over the past with Patrick Blanco. Her project is based on a collaboration with the labex Brain, and Trail. The neuroradiology department who is within the FHU is associated to this project. In addition Nathalie has a solid expertise on effector T cell phenotyping and will be of significant help in many.

Main grants since 2009 (relevant to the project)
- ATIP/AVENIR 2015
- IDEX Bordeaux (Junior Chair): 2015

Relevant publications and patents in the field since 2010:

Schmitt N, Liu Y, Bentebibel S E, Munagala I, Bourdery L, Venuprasad K, Banchereau J, Ueno H. The cytokine TGF-β co-opts signaling via STAT3-STAT4 to promote the differentiation of human TFH cells. **Nature immunology**. 2014; 15: 856-865.

Schmitt N, Bentebibel SE, Ueno H. Phenotype and functions of memory Tfh cells in human blood. **Trends Immunol**. 2014 Sep;35(9):436-442.

Schmitt N, Ueno H. Blood tfh cells come with colors. **Immunity**. 2013;39:629-30.

Schmitt N, Bustamante J, Bourdery L, Bentebibel SE, Boisson-Dupuis S, Hamlin F, Tran MV, Blankenship D, Pascual V, Savino DA, Banchereau J, Casanova JL, Ueno H. IL-12 receptor beta1 deficiency alters in vivo T follicular helper cell response in humans. **Blood**. 2013;121:3375-85.

Bentebibel SE*, Lopez S*, Obermoser G*, Schmitt N*, Mueller C, Harrod C, Flano E, Mejias A, Albrecht RA, Blankenship D, Xu H, Pascual V, Banchereau J, Garcia-Sastre A, Palucka AK, Ramilo O, Ueno H. Induction of ICOS+CXCR3+CXCR5+ TH cells correlates with antibody responses to influenza vaccination. **Sci Transl Med**. 2013;5:176ra32. **Equal contributor*

Bentebibel SE, Schmitt N, Banchereau J, Ueno H. Human tonsil B-cell lymphoma 6 (BCL6)-expressing $CD4^+$ T-cell subset specialized for B-cell help outside germinal centers. **Proc Natl Acad Sci U S A.** 2011;108:E488-97.

Ueno H, Klechevsky E, Schmitt N, Ni L, Flamar AL, Zurawski S, Zurawski G, Palucka K, Banchereau J, Oh S. Targeting human dendritic cell subsets for improved vaccines. **Semin Immunol.** 2011;23:21-7.

Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, Zurawski G, Foucat E, Dullaers M, Oh S, Sabzghabaei N, Lavecchio EM, Punaro M, Pascual V, Banchereau J, Ueno H. Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. **Immunity**. 2011;34:108-21

Ueno H, Schmitt N, Klechevsky E, Pedroza-Gonzalez A, Matsui T, Zurawski G, Oh S, Fay J, Pascual V, Banchereau J, Palucka K. Harnessing human dendritic cell subsets for medicine. **Immunol Rev**. 2010;234:199-212.

Ueno H, Schmitt N, Palucka AK, Banchereau J. Dendritic cells and humoral immunity in humans. **Immunol Cell Biol.** 2010;88:376-80.

Banchereau J, Klechevsky E, Schmitt N, Morita R, Palucka K, Ueno H. Harnessing human dendritic cell subsets to design novel vaccines. **Ann N Y Acad Sci.** 2009;1174:24-32.

Schmitt N, Morita R, Bourdery L, Bentebibel SE, Zurawski SM, Banchereau J, Ueno H. Human dendritic cells induce the differentiation of IL-21-producing T follicular helper-like cells through IL-12. **Immunity**. 2009;31:158-69.

Research Partner : CBMN	
Localization : **Institut Européen de Chimie & Biologie (IECB)** **2 rue Escarpit** **33607 Pessac**	**Institution :** **UMR/CNRS 5248** Institute of Chemistry & Biology of Membranes & Nanoobjects (UMR5248 CBMN) CNRS - Universite Bordeaux - Bordeaux INP Allée. Geoffroy Saint-Hilaire 33600 Pessac

Head : Dr Erick Dufourc (DR CNRS)

Key personnal : Laurent Plawinski (IR-CNRS), Christel Chanseau (AI-EN), Sylvain Nlate (MCU), Marie-Christine Durrieu (DR INSERM)

The aim of our group is the synthesis of controlled surfaces to favour membrane adhesion (cells, microvesicles, …) for biological engineering (tissue engineering, clinical treatment, diagnosis, …). A special focus is made on vascular and bone tissue engineering, regeneration and repair. This will lead our group to imagine original approaches of surface treatment of the materials to promote adhesion, cellular communication, and regeneration of vascular or osseous tissues. We have developed expertises in organic chemistry (Dr S. Nlate), surface functionalization (C. Chanseau & Dr MC Durrieu) and cell biology (Dr L. Plawinski & Dr MC Durrieu) and national and international collaborations since many years (Waterloo (Canada), Laval (Quebec), Louvain-la-Neuve (Belgium), Liege (Belgium), Lisbon (Portugal), Toronto (Canada), Luxemburg, Tohoku (Japan) Universities).

We focus on 4 axes:

1) <u>Functional nanostructured materials for Mesenchymal Stem Cells stemness or differentiation</u>

Three strategies will be used to study *in vitro* the preservation of the human Mesenchymatic Stem Cells (hMSC) stemness and the production of mature osteoblastic cells (OB). A fine understanding of conditions required to promote specific differentiation towards OB's, or the preservation of MSC's stemness, is still lacking. We are working on the impact of bioactive nanomorphologies of titanium on stem cell fate, the influence of bioactive nanohelical shape on stem cell fate and the synthesis of multifunctionalized and microstructured materials for bone tissue engineering.

2) **<u>Engineered bioactive micro-, nano-structured materials for vascularization</u>**

Angiogenesis, the formation of new blood vessels by a process of sprouting from pre-existing ones, is also a critical challenge for the establishment and maintenance of large engineered tissues. Here, an important target is to develop innovative model systems allowing to simulate the formation of blood vessels in a reconstructing bone, starting from colonization by endothelial cells forming first a closed-up channel, followed by vessel stabilization by pericytes or smooth muscle cells.

3) **<u>Bioactive nanostructured materials to fight bone infection</u>**

Prosthesis-related infection is described as a devastating failure scenario of an orthopaedic implant and is difficult to treat. Standard antibiotic protocols that are effective against other infections, generally fail to achieve cure in this case. The project proposed here consists in the controlled release (optimal rate and at correct time) of gentamicin grafted onto nanoparticles, at the site of implantation. These nanoparticles will be designed in order to respond to changes in environmental pH. A cleavage reaction of the active particle molecule bond, activated by a modification of the pH, which occurs under pathological conditions, induces a controlled release of gentamicin.

4) **<u>Cell microvesicles for a diagnosis kit or for tissue engineering</u>**

Our project focuses on the improving of the material functionalization process to capture microvesicles and on the validation of this novel procedure in a diabetic test applicable to blood, urine and tears. The expected product is a kit assay which allows capture of microvesicles from biological fluids, and their identification with provided reagents. This will be the first test assay available for routine clinical practice. Moreover, the use of microvesicles will be tested in tissue engineering to favour vascularization or osteogenesis, with 2 PhDs starting in 2015.

The specific feature of our group is to design bioactive, bioinspired materials and to measure the impact of thèse smart materials *in vitro* and *in vivo*.

Dr. Durrieu's many contracts include 15 industrial contracts (11 as coordinator): HEXABIO (2004-2007),

SPINE NEXT (2004-2005), ETECT (2003), SANORTHO (2003-2004), TEKNIMED (2005-2006), RESCOLL (2010-2013 as cotutelle PhD), PHYSIOL (Belgium) (2011-2014 as cotutelle PhD), FLUOFARMA (2012-2015 as cotutelle PhD), AQUITAINE SCIENCE TRANSFERT (2014-2015). MC Durrieu is involved within a "Fonds Unique Interministériel" (FUI) contract with RESCOLL, CONFARMA, VOXCAN, AQUITAINE SCIENCE TRANSFERT (2014-2017), an Innovative Training Networks (ITN)/ Call H2020-MSCA-ITN 2014 in which she coordinates one axis entitled "bone tissue engineering" in collaboration with 3 compagnies (SCREVO (Netherlands), IT4IP (Belgium), NOVADIP (Belgium) and also 54 public contracts of which 24 have been coordinated by her. Since 4 years, her group obtained 22 contracts (5013 k€) with 9 with industry (4153 k€).

Within the framework of this FHU, we will focus on the axis entitled « cell microvesicles for a diagnosis kit ». Three parts are proposed. Dr Nlate (MCU) has in charge the Part 1 « synthesis and characterization of original polynuclear complexes », Mrs Chanseau & Dr Durrieu focus on the Part 2 « Functionalization of the surface of materials with these complexes » and Drs Plawinski, Durrieu & Rigalleau have in charge the Part 3 « isolation and identification of the microvesicles captured onto the surface of materials ».

Expected contribution to the FHU

This team is an important constituent of the DHU since it is the only team working on the synthesis of a well-characterized kit for diagnosis applicable to different pathologies. Therefore its contribution appears obvious.

Main grants since 2009 (relevant to the project)

- ANR Blanc "PicoBio" (Partner: MC Durrieu)
- GIS Advanced Materials in Aquitaine (MC Durrieu)
- Accord FRSQ-INSERM (MC Durrieu)
- Région Aquitaine (3 projects) (MC Durrieu)
- ANR Emergence-Tec « Bioimplant » (MC Durrieu)
- Actions intégrées Luso-Française (MC Durrieu)
- Région Wallone (Partner : MC Durrieu)
- GMN NSERC Create Program (Partner : MC Durrieu)
- Program FCT (Fundação para a Ciência e a Tecnologia) (Partner : MC Durrieu)
- ANR Blanc « PicoBond » (Partner : MC Durrieu)
- PEPS CNRS (Partner : MC Durrieu)
- Program Samuel de Champlain (MC Durrieu)
- Aquitaine Science Transfert Maturation Project (MC Durrieu)
- Fonds Unique Interministériel (FUI) program (Partner : MC Durrieu)
- IDEX program (MC Durrieu)
- Call H2020-MSCA-ITN-2014 (Partner : MC Durrieu, L Plawinski)
- Aquitaine Science Transfert Maturation Project (MC Durrieu , L Plawinski, S. Nlate)
- China Scolarship Council (MC Durrieu, S Nlate, L Plawinski)
- Erasmus Mundus (MC Durrieu)
- projet Université Bordeaux – Dpt Sciences & Technologies (S. Nlate)

Relevant publications and patents in the field since 2010:

A. Cheng, O.F. Zouani. K.Glinel, A. Jonas, **MC Durrieu**, Bioactive chemical nanopatterns impact human mesenchymal stem cell fate, Nanoletters, 2013, 13, 3923

R.K. Das, O.F. Zouani, C.Labrugère, R.Oda, **M.C. Durrieu**. 2013. Influence of Nanohelical Periodicity on Stem Cell Differentiation, ACS Nano, 2013, 7(4) ; 3351.

O.F.Zouani, Y.Lei, **M.C.Durrieu.**Micropatterning Reveals that Pericytes, Stem Cell-Like Cells, but not Mesenchymal Stem Cells are Recruited to Support Vasculogenic Tube

Stabilization. 2013, Small, 9(18), 3070

Y.Lei, OF. Zouani, M. Rémy, L. Rami, **MC Durrieu**, 2013, Modulation of Lumen Formation by Microgeometrical Bioactive Cues and Migration Mode of Actin Machinery, Small, 2013 9(7):1086-95

O.F. Zouani, J. Kalisky, E. Ibarboure, **M.C. Durrieu**, 2013, Effect of BMP-2 from Matrices of Different Stiffnesses for the Modulation of Stem Cell Fate, 2013. Biomaterials. 34(9), 2157–2166

Lacroix, R; **Plawinski, L;** Robert S; Doeuvre L; Sabatier F; de Lizarrondo SM; Mezzapesa A; Anfosso F; Leroyer, Aurelie S.; Poullin P; Jourde N; Njock MS; Boulanger CM.; Angles-Cano E; Dignat-George, F; Leukocyte- and endothelial-derived microparticles: a circulating source for fibrinolysis. Haematologica-the Hematology Journal, 2012, 97, 1864-1872

Dejouvencel T; Doeuvre L; Lacroix R; **Plawinski, L**; Dignat-George F; Lijnen, HR; Angles-Cano E; Fibrinolytic cross-talk: a new mechanism for plasmin formation. Blood, 2010, 115, 2048-2056

Braeckmans K; Buyens K; Bouquet W; Vervaet C; Joye P; De Vos F; **Plawinski, L;** Doeuvre L; Angles-Cano E; Sanders NN.; Demeester J; De Smedt SC.; Sizing Nanomatter in Biological Fluids by Fluorescence Single Particle Tracking. Nano Letters, 2010, 10, 4435-4442

Patents

Durrieu M.C., Quemener D., Baquey Ch., Sabaut-Heroguez V., Biomatériaux bioactifs pour le relargage contrôlé de principes actifs, WO2006008386**,** FR2871701

Sabaut-Heroguez V., Quemener D**., Durrieu M.C**., Particules polymères stimulables présentant des fonctions réactives, leur procéd d'obtention, et leurs utilisations, WO2006008387, FR2871803

Durrieu MC., Zouani OF., Substituts osseux greffés par des peptides mimétiques de la protéine humaine BMP-2, PCT/FR2014/050601, 2013

Durrieu MC, Héroguez V, Pichavant L, Carrié H, EP14307083.7 : Polymers particules and biomaterials comprising the same

Durrieu MC, Héroguez V, Pichavant L, Carrié H, EP15305857.3: Polymers particules and biomaterials comprising the same

Belle C; Gellon G; **Plawinski L**; Doeuvre L; Angles Cano E; Complexes métalliques dinucléaires greffés, et leur utilisation en tant que capteurs de microparticules cellulaires.PCT/FR2012/050610

Number of people involved in the project: 4 & 3 engineers (CDD, Aquitaine Science Transfert program) & 3 PhDs

Number of "HDR": 2 (MC Durrieu & Sylvain Nlate) + 1 ADT (L Plawinski)

Academic Multicentric Trials: 0

Teaching:

L1 : Organic Chemistry (Dr S. Nlate)
L2 : Organic Chemistry (Dr S. Nlate)
L3 : Organometallic Chemistry and Catalysis (Dr S. Nlate)
Master 2 : Catalysis for sustainable chemistry (Dr S. Nlate)

Master Biomatériaux et Dispositifs Médicaux (BIDIM) (Dr MC Durrieu)

International Exchange:
Since 2000, Dr. Durrieu's teaching involvement has had her supervise 17 PhDs (9 cotutelle (with Canada, Portugal, Belgium, Luxemburg), 7 PhDs in progress), 15 post-doctorates (2 in progress)

Dr Durrieu is member of the governing board of the International Doctoral School in Functional Materials (www.idsfunmat.u-bordeaux1.fr) (PhD carried out in co-supervision between universities from two # countries in collaboration with an industry partner). There are 76 students from 31 nationalities. Dr Durrieu is the head of IDS-FunMat promotions 2012-2013 and 2013-2014.

MC Durrieu has successfully applied for "follow-up funding" via a Marie-Curie ITN project 'EJD-FunMat' (3.8 M€). She coordinates one axis entitled "bone tissue engineering" in collaboration with 3 compagnies (SCREVO (Netherlands), IT4IP (Belgium), NOVADIP (Belgium)).

Start-up: 0

ERC grant: 0

ANR: 3

Number of patent licensed (4 last years):
1 operating licence patent should be signed soon with Teknimed company (Toulouse, France) and another one is under discussion with Rescoll Company (Pessac, France).

Research Partner : CRCTB	
Localization : **IECB** **2 rue Robert Esarpit** **33 600 Pessac**	**Institution :** **INSERM1045**

Head : Pr Roger Marthan
Key personnal : Elisabeth Génot (DR), IJsbrand Kramer (PU), Isabelle Fremaux (AI-INSERM).

Endothelial cells contribute to the pathophysiology of most diseases. We are studying how environmental cues impact on these cells and translate into alterations of their functions, focusing on changes in extracellular matrix composition/rigidity and cytokine contexts. Our studies aim at a better understanding the cellular and molecular processes affecting endothelial cell behavior in human diseases such as pathological vessel remodeling, with the long term goal to identify molecular targets for therapeutic intervention.
A special focus is made on Transforming growth factor-β, a multifunctional cytokine which plays an important role in the development and maintenance of homeostasis of the vascular systems by regulating functions of endothelial cells and smooth muscle cells. Analysing the effects of TGFβ on cytoskeleton organisation led us to discover actin-rich structures named podosomes in aortic endothelial cells and more recently, on in microvascular cells. Because podosomes are found in cells travelling across tissues, i.e., invasive cells, our research aims at characterising endothelial podosomes, elucidate the molecular mechanisms involved in their assembly and disassembly, explore the signals leading to their formation and establish the consequences of their induction.
We have studied the role of podosomes in vascular genetic disorders involving hyperactivation of TGFß signaling pathways such as Marfan syndrome or those involving defective TGFß signaling such as Hereditary Hemorrhagic Teleangiectasia (HHT). Rare diseases are good models for common diseases with similar manifestations and our research has brought significant advances in understanding of the deleterious consequences of TGFß homeostasis.
We have developed an expertise, important tools and national and an international network (invadosome consortium) over the last decade. TGFß **is a pleiotropic cytokine and alteration of its homeostasis during inflammatory responses and in autoimmune diseases is associated with tissue damage through either proteolytic or fibrotic actions.** Located at the interface between blood and tissues, endothelial cells receive multiple signals from both sides and react to stressors by modulating their cellular functions. As a consequence, endothelial dysfunction (defined by the loss or impairment of function or the acquisition of new functions) is an early step in most vascular diseases. TGFß occupies a center stage in various diseases including cancer, infections and autoimmune disorders. The delineation of the mechanisms by which it leads to endothelial cell dysfunction is a prerequisite to better control the early stages of these diseases. In this context, understanding the effects of TGFß on endothelial cells and the impact of the microenvironment represents the main objective of our research

The specific feature of the team is to work at the interface of **basic research and physiopathology**

Expected contribution to the FHU
This team is an important constituent of the DHU since it is the only team working on fundamental endothelial cell biology.

Main grants since 2009 (relevant to the project)
- ANR
- ITN, FP7
- Fondation de France
- Ligue contre le Cancer

Relevant publications and patents in the field since 2010:

- Veillat V, Spuul P, Daubon T, Egaña I, Kramer I, Génot E.Podosomes: Multipurpose organelles? Int **J Biochem Cell Biol.** 2015; 65:52-60.

- Spuul P. Chi PY, Billottet C, Chou CF, Genot E. Microfluidic devices for the study of actin cytoskeleton in constricted environments: Evidence for podosome formation in endothelial cells exposed to a confined environment. **Methods**, in press 2015

- Curado F, Egana I, Spuul P, Daubon T, Veillat V, Leclercq A, Duhamel, P. Gontier E, Génot E. ALK1 and ALK5 play antagonistic roles in podosome formation. **Mol. Cell. Biol.,** 34(24):4389-403.

- Klingberg F, Chow ML, Koehler A, Boo, S, Buscemi L, Thomas M. Quinn TM, Alman B, Génot E, Hinz B. Pre-stress in the extracellular matrix sensitizes latent TGF-β1 for activation. **J. Cell Biol**., 2014,207(2):283-97.

- Génot E and Gligorijevic B. Invadosomes Invadosomes in their natural habitat**. Eur J Cell Biol.,** 2014, 93(10-12):367-79.

- Seano, G., Daubon T., Primo L, Génot E. Podosomes as novel players in endothelial biology. **Eur J Cell Biol.**, 2014, 93(10-12):405-12.

- Rehm K, Panzer L, van Vliet V, Génot E, Linder S. Drebrin preserves endothelial integrity by stabilizing nectin at adherens junctions. **J Cell Sci.,** 2013 Aug 15;126(Pt 16):3756-69.

- Génot E, Sorrentino V, Daubon T, Buccione R. FGD1 as a central regulator of extracellular matrix remodelling-lessons from faciogenital dysplasia. **J cell Sci.,** 2012;125(Pt 14):3265-70.

- Juin A, Planus E, Guillemot F, Horakova P, Albiges-Rizo C, Génot E, Moreau V, Saltel F. Extracellular matrix rigidity controls podosome induction in microvascular endothelial cells. **Biol Cell.,** 2013 Jan;105(1):46-57.

- Juin A, Billottet C, Moreau V, Destaing O, Albiges-Rizo C, Rosenbaum J, Saltel F*, Génot E*. Physiological type I collagen organization induces the formation of a novel class of linear invadosomes. **Mol. Biol. Cell.,** 2012 Jan;23(2):297-309.

- Daubon T, Buccione R. Génot E. The Aarskog-Scott syndrome protein Fgd1 regulates podosome formation and extracellular matrix remodeling in TGFb-stimulated aortic endothelial cells**. Mol. Cell. Biol.** 2011(22):4430-4441.

- Kremerskothen J, Stölting M, Wiesner C, Korb-Pap A, van Vliet V, Linder S, Huber TB, Rottiers P, Reuzeau E, Génot E, Pavenstädt H. Zona occludens proteins modulate podosome formation and function. **FASEB J.** 2011 Feb;25(2):505-14.

- Quideau S, Douat-Casassus C, Delannoy López DM, Di Primo C, Chassaing S, Jacquet R, Saltel F, Génot E. Binding of filamentous actin and winding into fibrillar aggregates by the polyphenolic C-glucosidic ellagitannin vescalagin. **Angew Chem Int Ed Engl.** 2011 May 23;50(22):5099-104.

Patent

- Quideau, S.; Génot, E.; Saltel, F.; Douat-Casassus, C.; Delannoy Lopez M. D. C-Glucosidic Ellagitannin Compounds for Use for Altering the Supramolecular Arrangement of Actin. European Patent N° EP11305186.

Number of people involved in the project: 3

Number of "HDR": 2

Teaching: International Master "Molecular Biology and Biomedicine", University of the Basque Country (Bilbao, Spain)
Cell biology introductory course (1st year), life sciences students
Cell biology introductory course (1st year), biological-engineering students
Signal transduction in development (3rd year), health science students

ANR: 1

Number of patent licensed (4 last years): 1

Partner : USC EA 3671 IHMC	
Localization University of Bordeaux	**Institution : INRA- University of Bordeaux**

Head : Cécile Bébéar

Key personnal : Thierry Schaeverbeke (PU-PH), Sabine Pereyre (MCU-PH), Bertille de Barbeyrac (MCU-PH), Olivia Peuchant (MCU-PH), Charles Cazanave (MCU-PH), Julien Goret (AHU)

Field of expertise:

The USC EA 3671 is resolutely committed in translational research in infectiology, especially, in respiratory and urogenital tract infections due to human mycoplasmas and chlamydiae. Our laboratory is internationally renowned for its expertise in the field of mycoplasmal infections for more than 25 years. Moreover, it has been nominated by the Ministry of Health and the 'Institut de Veille Sanitaire' (InVS) as the French National Reference Centre (CNR) for chlamydial infections since 1999 (http://www.cnrchlamydiae.u-bordeaux2.fr).

Our unit is a laboratory dedicated to the study of mycoplasmal and chlamydial infections in humans. These bacteria have a number of features in common. They are responsible for genital infections and respiratory infections where inflammation play a role and may be involved in chronic diseases such as asthma. They are difficult to culture and are susceptible to the same families of antibiotics. Our objective has been to gain a better understanding of the pathogenic role of these bacteria, to increase our knowledge of their epidemiology and to improve methods of detection and treatment of the infections they cause.

Three main domains of research have been delineated:

- Comparative genomics of human mycoplasmas
- Interaction of mycoplasmas with their host
- Epidemiology and diagnosis of mycoplasmal and chlamydial infections. This domain includes the research activities of the CNR for chlamydiae infections.

Previous contributions :

During the last 5 years, the unit has accumulated a number of excellent results, some of which attract special attention:

1) Comparison of *Mycoplasma pneumoniae* infections in asthmatic children versus asthmatic adults.

M. pneumoniae has been implicated in asthma exacerbations and chronic asthma. A 2-year longitudinal study has been conducted to investigate the role of *M. pneumoniae* infections in 168 and 20 hospitalized children and adults, respectively, with asthma exacerbation compared with outpatients (88 children and 48 adults) with chronic asthma (without an exacerbation). The prevalence of *Chlamydia pneumoniae* and respiratory viruses was also assessed in these 2 populations. *M. pneumoniae* infection was more prevalent in children with chronic asthma compared with children with exacerbation, while the reverse was true in adults. Children seen for chronic asthma were significantly more likely to be infected with *C. pneumoniae* than children hospitalized for an asthma exacerbation. In contrast with some other data, the present study suggests that these two microorganisms do not play a direct role in the pathogenicity of acute or chronic asthma in most children.

2) Potential role of *Mycoplasma hominis* in interleukin (IL)–17–producing CD41 T-Cell generation via induction of IL-23 secretion by human dendritic cells.

M. hominis, a human urogenital pathogen, is involved in genital and extragenital infections and arthritis, particularly in immunocompromised patients. The interleukin (IL) 23/T helper (Th) 17 axis is associated with inflammatory and autoimmune diseases. The aim of this study was to assess the IL-23 response to *M. hominis* in human dendritic cells (hDCs) and the CD4+ T-cell differentiation in response to *M. hominis*–infected hDCs. *M. hominis* induced the maturation of hDCs with predominant IL-23 secretion in a Toll-like receptor 2–dependent manner. The in vitro immunomodulatory capacity of *M. hominis* was contained in a lipoprotein-enriched fraction. *M. hominis*–activated DCs induced IL-17–producing CD4+ T cells. Our findings demonstrate a major role for the IL-23/Th17 axis in the defense against *M. hominis* and indicate a potential role for these bacteria in inflammatory and autoimmune diseases.

3) Development of Multiple-Locus VNTR analysis (MLVA) for the molecular typing of human mycoplasmas, *M. pneumoniae*, *M. hominis* and *Mycoplasma genitalium*.

Molecular typing methods more discriminant than those existing are needed to explore human mycoplasmal infections, especially outbreaks due to *M. pneumoniae*. We have developed for human mycoplasmas the

Multiple-Locus Variable-Number Tandem-Repeat analysis (MLVA), a new epidemiological tool based on whole-genome analysis, which is more discriminant than the previous typing methods described, especially for *M. pneumoniae*. It has been used to investigate several *M. pneumoniae* outbreaks in 2010-2012 in France and in Israel by our unit. We also developed it for *M. hominis* (for which it showed *M. hominis* as a heterogeneous species. For *M. genitalium*, the discriminatory power of the developed MLVA was too high to be used in epidemiologic studies of sexual networks.

4) Development of a MLVA typing system for *Chlamydia trachomatis*.
We focused our MLVA scheme on genovar E which predominates in most populations worldwide. This system does not require culture and therefore can be performed directly on DNA extracted from positive clinical specimens. This MLVA, including the study of 5 VNTRs, was applied to a collection of 220 genovar E and 94 non-E genovar *C. trachomatis* isolates and specimens obtained from 251 patients and resulted in 38 MLVA types. All anorectal genovar E isolates from men who have sex with men exhibited the same MLVA type, suggesting clonal spread. In comparison to other genotyping methods, MLVA displayed the highest discriminatory power and does not require a time-consuming sequencing step.

5) Development of real-time PCR molecular tools to detect macrolide resistance directly from specimens positive for *M. pneumoniae* or *M. genitalium*. The resistance of *M. pneumoniae* and *M. genitalium* to macrolides and related antibiotics is mainly linked to point mutations in 23S rRNA. In view of the recent spread of a large number of macrolide-resistant *M. pneumoniae* and *M. genitalium* strains worldwide, we developed a real-time PCR assay, using probe hybridisation and melting curve analysis, to detect 23S rRNA-mutated strains of *M. pneumoniae* or *M. genitalium* directly from specimens. Resistant mutants were found in France at prevalence ranging from 8 to 10% for *M. pneumoniae* between 2005 and 2011 and of 13-14% in *M. genitalium* between 2006 and 2012.

Expected contribution to the AIR DHU

Locally, our unit will be involved in the **IDEX** ('Initiative d'Excellence') project of the new merged University of Bordeaux with our participation to cohort iShare. We will be also part of the **transversal pole on Synthetic Biology** and our research projects are particularly well integrated in the translational and clinical research conducted by the **SFR TransBioMed** (http://www.transbiomed.u-bordeaux2.fr), University of Bordeaux, to which we will belong. Our long-date collaboration with the team Mollicutes (Alain Blanchard) of UMR INRA 1332, BFP constitutes a strength and provides the Bordeaux University a unique mycoplasma pole with recognized expertise in basic and applied researches in human, animal, and plant mycoplasmology. Regionally, we wish to achieve and strengthen collaborations with the team Pathogénèse des infections à mycoplasmes (Christine Citti), of UMR INRA 1225, IHAP, Toulouse, on topics like genetic tools and antibiotic resistance in mycoplasmas, within the context of the "One world, one health" initiative.

On the bases of the present work, the following major projects of the unit will be further developed:

1. Comparative genomics of human mycoplasmas

2. Host-pathogen interaction

We have studied the effects of *M. hominis* on the maturation and activation of hDCs and the CD4+ T cell differentiation in response to *M. hominis*-infected hDCs. Extraction of *M. hominis* membranes with Triton X-114 demonstrated that the lipoprotein-enriched detergent phase can stimulate the pro-inflammatory cytokine production by hDCs. The team will pursue the project by studying **the bioactive fraction of *M. hominis* which activates the hDCs, and the immune response of hDCs to *M. hominis* infection**. First, the *in vitro* surface lipoproteome of *M. hominis* will be characterized and we will determine whether *M. hominis* lipoprotein genes are differentially expressed upon contact with hDCs. Then, a further project will be to identify the lipoproteins involved in the interaction of *M. hominis* with hDCs and try to produce synthetic lipopeptides from the candidate immunomodulatory lipoproteins identified. A last step will be to study the transcriptional response of hDCs after co-incubation with *M. hominis*. This project will be conducted in collaboration with Laure Beven, UMR INRA 1332, and Cécile Bordes, UMR CNRS 5164, University of Bordeaux.

The CNR for chlamydial infections will participate in the study coordinated by Jean-Michel Molina (APHP

Hôpital Saint-Louis) to evaluate a **prophylaxis strategy of *C. trachomatis* infection with oral doxycycline in men who have sex with men**. In collaboration with Roger Legrand (CEA, Fontenay-aux-roses), the goal of the assay will be to develop an experimental model of vaginal and rectal infection of *C. trachomatis* in macaques treated orally by doxycycline versus placebo.

Although major advances have been made in the comprehension of the processes leading to inflammatory arthritides, the cause of these disorders is still unknown. At this time, only few studies have been dedicated to microbiota investigation in human inflammatory arthritides. We plan to describe **oral, respiratory and gut microbiota in rheumatoid arthritis and gut microbiota in spondyloarthritis**, in recent and established forms of the disease, where human mycoplasmas could be involved. We plan to investigate modification of this microbiota under TNF and other cytokines inhibitors. Thierry Schaeverbeke, professor of rheumatology in our unit, will coordinate this project in our unit in collaboration with Christophe Hubert and Macha Nikolski, CGF Bordeaux, CBiB. **Here is a major part that we are planning to extend over the 5 coming years with the recruitment of several people involved in the field of microbiota and in close connection with the immunological team.**

3. Etiology and epidemiology of mycoplasmal and chlamydial infections

The expertise of the unit in the domain of human mollicutes and its designation as the French CNR for chlamydial infections leads us to develop molecular typing techniques and to conduct epidemiological studies of these two genera of bacteria.

The CNR for chlamydial infections will pursuit its prevalence studies of genital infections by *C. trachomatis*. The CNR will keep on monitoring the spread of the LGV proctitis epidemic by typing rectal strains sent by various sentry laboratories and will pursue the **national sentinel network for the monitoring of LGV in France** established in 2010 with clinicians and biologists. The CNR will be also a major partner of the **sexually transmitted infections project of cohort iShare** conducted by Elisabeth Delarocque-Astagneau and Didier Guillemot, INSERM U657, Institut Pasteur/Univ. Versailles-Saint Quentin. This project consists of a French community based trial to evaluate the efficacy of early screening for *C. trachomatis* and treatment in young women for primary prevention of pelvic inflammatory disease (PID). The control group of the randomized trial, following current recommendations, will allow to better document the natural history of *C. trachomatis* infection, in particular the rate of and time to progression to PID. We will apply to the following calls for projects: French national Projet Hospitalier de Recherche Clinique (PHRC) and appel à projets prevention primaire of INCa/IReSP.

Main grants since 2009

- Projet Hospitalier de Recherche Clinique (PHRC), Appel d'offres Interrégional, 2007-2011: *Mycoplasma pneumoniae* et asthma chez l'adulte et l'enfant. Coordinator: Cécile Bébéar.

- **Projet Hospitalier de Recherche Clinique (PHRC), Appel d'offres local**, **Etude MATIST 2011-2012:** Etude de la prevalence et des facteurs de risqué des infections à *Chlamydia trachomatis*, *Neisseria gonorrhoeae* et *Mycoplasma genitalium* chez les femmes enceintes du CHU de Bordeaux. Coordinator: Olivia Peuchant.

Relevant publications and patents in the field since 2009:

1. O. Peuchant, C. Le Roy, C. Desveaux, A. Paris, J. Asselineau, C. Maldonado, G. Chêne, J. Horovitz, D. Dallay, B. de Barbeyrac*, C. Bébéar*, *co-last authors. 2015. Screening for *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium* should it be integrated into routine pregnancy care in French young pregnant women? Diagn. Microbiol. Infect. Dis. Sous presse.
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Number of HDR: 4

Number of regional PHRC: 3

Center of reference: yes (Chlamydiae infection).

Contract with pharma companies: 13

PH D students/ post doc: 4/2

Research Partner : Centre Emile Durkheim (Emmanuel Langlois)	
Localization : **Université de Bordeaux** **Faculté de sociologie** **3 Ter place de la Victoire** **33076 Bordeaux Cedex** **Science Po Bordeaux** **11 Allées Ausonne** **Domaine Universitaire** **33607 PESSAC Cedex**	**Institution :** **CNRS – UMR 5116**
Head : Andy Smith (DR- Fondation Nationale des Sciences Politiques) **Personnal of the unit : 50** **Key personnal (team "sociology of health") :** Thibault BOSSY (Assistant professor), Sébastien GUIGNER (assistant professor), Béatrice JACQUES (Assistant professor), Emmanuel LANGLOIS (Assistant professor), Pascal RAGOUET (professor), Joël ZAFFRAN (professor)	
The Centre Emile Durkheim is a generalist research unit in the area of sociology and political science. The unit conducts research in five areas: 1 / patterns of identification 2 / vulnerability and inequality, 3/organizations 4/ knowledge 5 / international. The unit uses qualitative and quantitative methods and develops comparative Multiscale Approaches. The axis "vulnerabilities" hosts several research on health : - Scientific controversies - The technical innovations in the medical field - Public health policies - Experience of chronic disease: cancer, AIDS, diabetes - The role of the EU in health -New healthcare organizations - Disability - Drug use and medico-social care	
Expected contribution to the FHU This team works on the subjective experience of chronic diseases (Aids, cancer, hepatitis ...) in its differents dimensions. Our methods are based on qualitative surveys of patients and healthcare professionals. We focuse the course of patients in healthcare organizations.	
Main grants since 2009 (relevant to the project) - ANR - Conseil Régional Aquitaine : - INCa - MILDECA - Ministère de la jeunesse - Observatoire Français des drogues et Toxicomanies	
Relevant publications and patents in the field since 2010: Bossy Thibault, Évrard Aurélien, Gourgues Guillaume, Hoeffler Catherine et Ribémont Thomas, *Les politiques publiques*, Malakoff, Éditions Foucher, coll. Trajectoire, 2015. Guigner, Sébastien, « Gouverner par la comparaison : usages et mésusages des comparaisons	

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Patent : 0

Number of people involved in the project: 2

Number of "HDR": 25 in the unit

Academic Multicentric Trials: 0

Teaching: Master Sociétés Pouvoirs et Représentations (UB/Science PO)

International Exchange:

Start-up: 0

ERC grant: 1

ANR: 6

Number of patent licensed (4 last years): 0

Annex 5 : Description of the Bordeaux Biobank

Bordeaux Biothèques Santé CHU de Bordeaux- (BBS)

Presentation

BBS is a biobank storing biological samples for medical or scientific use. The biobank provides a confidential, secure and qualitative short, medium or long-term preservation. These samples are linked to demographic, biologic or clinical data concerning the patient along with data specific to the sample and its traceability.

Types and nature of samples

- Human tissues, fresh, unfrozen conserved for a short time
- Human tissues, biological liquids or their derivatives frozen for long term conservation
- Micro-organisms, bacteria, viruses, fungi…
- Cells, tissues, organs, blood, serum, plasma
- Proteins, DNA, RNA
- Paraffin blocks, anatomocytopathology slides

Themes

- Cancer
- Neuro-Sciences
- Immuno-Infectious, Inflammatory diseases-
- Genetic-rare diseases
- Cardio-thoracic

Flows

In 2014 BBS collected 200 000 biological samples coming from 200 000 patients and distributed 10 000 samples for scientific studies. The capacity is currently of 1.5 million of samples and will be extended to more than 3 millions of samples.

Conservation and storage of samples

The samples are stored at ambient temperature, or at +4 °C, -20°C, - 80°C, -152°C in refrigerators in air conditioned rooms. Rooms and refrigerators are fitted with alarm devices.

Quality control

The controls established by BBS are:

- DNA quality control
- RNA quality control by RIN measurement (Bioanalyser 2100, Agilent)
- Gene expression control by qPCR
- Cell counting and viability controls (Beckman Coulter Z1, Bioanalyzer 2100, Agilent)
- Serum quality control by CD40 ligand evaluation
- Control for endotoxin presence
- Control for mycoplasma presence

Annex 6 : Past-achievements (Key publications)

Hereafter we have selected some of the important works that have been done in the scope of ID over the past 15 years.

Systemic inflammatory disorders

1. **Blanco P**, Palucka AK, Gill M, Pascual V, Banchereau J. Induction of dendritic cell differentiation by IFN-alpha in systemic lupus erythematosus. **Science** 2001;294:1540-3. (IF: 31.4)
2. **Couzi L**, **Merville P**, Deminière C, **Moreau JF**, Combe C, **Pellegrin JL**, **Viallard JF**, **Blanco P**. Predominance of CD8+ T lymphocytes among periglomerular infiltrating cells and link to the prognosis of class III and class IV lupus nephritis. **Arthritis Rheum**. 2007; 56:2362-70. (IF:7.8)
3. **Duffau P**, **Seneschal J**, Nicco C, **Richez C**, **Lazaro E**, Douchet I, **Bordes C**, **Viallard JF**, Goulvestre C, **Pellegrin JL**, Weil B, **Moreau JF**, Batteux F, **Blanco P**. Platelet CD154 Potentiates Interferon-{alpha} Secretion by Plasmacytoid Dendritic Cells in Systemic Lupus Erythematosus. **Sci Transl Med**. 2010 Sep 1;2(47):47ra63. (IF: 14.4).
4. **Contin-Bordes C**, **Lazaro E**, **Richez C**, **Jacquemin C**, Caubet O, Douchet I, **Viallard JF**, **Moreau JF**, **Pellegrin JL**, **Blanco P**. Expansion of myelin autoreactive CD8+ T lymphocytes in patients with neuropsychiatric systemic lupus erythematosus. **Ann Rheum Dis**. 2011;70:868-71. (IF: 10.4).
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Rheumatic inflammatory diseases

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Annex 7 : Support letters from Health Regional Agency and Aquitaine country

Agence Régionale de Santé Aquitaine

Direction générale

Pr Thierry SCHAEVERBEKE
Pr Patrick BLANCO
Pr Jean-Luc PELLEGRIN

Dossier suivi par :Benoit Elleboode
Téléphone : 05 57 01 44 34
Courriel : benoit.elleboode@ars.sante.fr

Bordeaux, le 21 juillet 2015

Messieurs,

Vous m'avez adressé un projet dans le cadre de la labellisation du Département Hospitalo-Universitaire (DHU) « AIR » : Aquitaine Inflammation Research.

Ce projet intègre l'aspect organisationnel des soins au niveau régional, autour du parcours des patients atteints de maladies inflammatoires.

L'organisation que vous proposez rentre totalement dans notre politique de développement des parcours de soins, et s'appuie sur les nouveaux dispositifs de structures d'appui territoriales prévues par la nouvelle loi santé.

Un certain nombre de thématiques de recherche que vous évoquez, notamment celles concernant un meilleur diagnostic et une prise en charge précoce de ces patients, répond également à nos objectifs d'amélioration de la qualité des prises en charges, mais aussi d'efficience du système de santé.

Sur la base de votre projet, l'A.R.S mettra en oeuvre le parcours de soins des patients affectés de maladies inflammatoires en Aquitaine en mobilisant les moyens nécessaires à cette réalisation.

Je soutiens sans réserve votre projet dont je salue la transversalité au regard du nombre de spécialités concernées.

L'objectif de santé publique visé, tant dans la proposition de parcours de soins que dans le projet de recherche et d'enseignement, n'est pas discutable et demeure essentiel au vue des données dont je dispose sur les maladies concernées.

Mes équipes se tiennent à votre disposition quant aux suites à donner à ce projet.

Je vous prie de croire, Messieurs, à l'assurance de ma considération distinguée.

Michel LAFORCADE
Directeur Général

RÉGION AQUITAINE

Direction générale :

Direction générale adjointe : Olivier Degos
Direction Générale Adjointe : Thibaut Richebois

Pôles : Agriculture, Développement Durable, Tourisme et Développement Economique et Emploi

Affaire suivie par : Carole Doucet et Philippe Gaubert

Poste: 05 57 57 82 45
philippe.gaubert@aquitaine.fr
et carole.doucet@aquitaine.fr

Monsieur le Professeur Roger MARTHAN
Président du Comité de la Recherche
Biomédicale et de Santé Publique
12 rue Dubernat

33404 TALENCE

Bordeaux, le 17 juin 2015

Monsieur le Président,

Les nouvelles règles d'accès au financement de la recherche au niveau national s'orientent vers le soutien à des projets de recherche avec un fort potentiel de transfert rapide vers l'industrie ou vers la société.

Dans ce cadre, il est demandé aux chercheurs d'être structurés autour de projets qui les positionnent comme référence internationale dans leur thématique.

Pour répondre à ces attentes, plusieurs équipes du CHU et laboratoires de recherche de l'université de Bordeaux se sont rapprochées autour du Laboratoire d'Immunologie (Professeur Patrick Blanco), du Service de Médecine Interne et maladies infectieuses (Professeur Jean Luc Pellegrin) et du Service de Rhumatologie (Professeur Thierry Schaeverbeke) pour créer un Département Hospitalo-Universitaire (DHU) permettant de dynamiser la recherche et l'innovation autour des Maladies Inflammatoires.

Ces maladies concernent globalement 300 000 personnes en Aquitaine et sont la 3ème cause de mortalité après le cancer et les maladies cardiovasculaires.

La valeur ajoutée de ce DHU est l'étude des formes précoces des maladies inflammatoires, la forte implication du département de médecine générale pour des études environnementales, nutritionnelles ou des travaux spécifiques à cette spécialité, la diversité et la complémentarité des équipes cliniques hospitalières, et les liens entre les équipes du CHU avec les soins primaires au travers de divers outils de télé médecine et d'une plate-forme téléphonique.

Ce projet s'inscrit en cohérence avec les orientations du Conseil Régional en matière de santé, qui a identifié l'importance du lien entre le CHU et les équipes de soins primaires (Maisons de Santé Pluri professionnelles notamment), le développement des nouveaux usages en e santé avec un tissu industriel très dense et l'importance d'inscrire l'action régionale dans l'accompagnement de l'innovation, en lien avec la croissance des maladies chroniques.

.../..

Ce sont par ailleurs des maladies qui touchent souvent des populations en âge de travailler. Agir de manière préventive pour réduire le risque de développement de pathologies plus lourdes est un objectif qui contribuera à la santé des populations et à la compétitivité de la Région.

De ce fait, le Conseil Régional est très attentif à la création de ce DHU autour des maladies inflammatoires qui est dans une logique d'hôpital hors des murs, de développement de la proximité et des soins primaires, de l'innovation, et du renouveau de l'ensemble des besoins de formations médicales dont les para médicales au cœur de ses préoccupations.

Ce DHU est enfin totalement en cohérence avec les orientations régionales en matière de recherche et de transfert de technologie.

Je vous prie d'agréer, Monsieur le Président, l'expression de mes sentiments respectueux.

Le Président

Alain ROUSSET

14 rue François de Sourdis
33077 Bordeaux Cedex

T. 05 57 57 xx xx
F. 05 57 57 xx xx

www.aquitaine.fr

Aquitaine Science Transfert®
Accélérateur des innovations d'avenir

date 22.07.2015
service Transfert de Technologie
dossier suivi par Carlos Larraya
T 33 (0)5 24 72 12 29
c.larraya@ast-innovations.com
objet Positionnement AST
références PJ2014-152

Dear Sir,

As part of our transfer of activities technology, we are in close contact with Marie-Christine Durrieu's team.

We are in the process of founding the study for using the microvesicles (cell membrane fragments from stressed cells or apoptosis which are found in blood, plasma or other body fluids) to develop a highly sensitive kit at a low cost for the early diagnosis. This project will receive a 364.7 K€ financial assistance for maturation.

Indeed the quality of the scientific work and the complementarity of the team urged us to support this innovation.

The opportunities envisaged for the technology are the development of catch kits and analysis used routinely at low cost for early diagnosis.

The workpackages (in collaboration with Prof. V. Rigalleau) essentially comprises five lines of works :

❶ Diagnose type 2 diabetes earlier.
❷ Monitor diabetes control: Detection of microvesicles carrying markers complex AGE / RAGE.
❸ Identify complications: Screening of microvesicles in the peripheral and autonomic neuropathies.
❹ Identify complications: Screening microvesicles during a kidney pain.
❺ Identify complications: Diagnosing diabetic retinopathy.

These studies allow us to establish a proof of concept of the use of the microvesicles to develop a diagnostic kit for diabetes.

In addition, first contacts were established with the BioRad company which is interested in this technology. A confidentiality agreement, already signed, has allowed us to organize a first meeting with representatives of BioRad on 09.04.2015.

Benoît JEAN-JEAN
Directeur Service Transfert

Filière des Maladies Auto-Immunes et Maladies Auto-Inflammatoires Rares

Pr. Eric HACHULLA, Coordonnateur de la Filière
eric.hachulla@chru-lille.fr

Dr. Alexandre BELOT, Co-coordonnateur de la Filière pour la Pédiatrie
alexandre.belot@chu-lyon.fr

Dr. Hélène MAILLARD, chef de projet de la filière
helene.maillard@chru-lille.fr

Centre de Référence de la Sclérodermie Systémique
Pr. Eric HACHULLA
eric.hachulla@chru-lille.fr

Centre de Référence des Maladies Auto-immunes et Maladies Systémiques Rares
Pr. Thierry MARTIN
thierry.martin@chru-strasbourg.fr
Pr. Jean SIBILIA
jean.sibilia@chru-strasbourg.fr

Centre de Référence du Lupus et du SAPL
Pr. Zahir AMOURA
zahir.amoura@psl.aphp.fr

Centre de Référence des Vascularites Nécrosantes et Sclérodermies Systémiques
Pr. Luc MOUTHON
luc.mouthon@cch.aphp.fr

Centre de Référence des Amyloses d'origine inflammatoire et de la Fièvre Méditerranéenne Familiale
Pr. Gilles GRATEAU
gilles.grateau@tnn.aphp.fr

Centre de Référence pour les Maladies Rhumatologiques et Inflammatoires Rares Pédiatriques
Pr. QUARTIER-DIT-MAIRE
pierre.quartier@nck.aphp.fr

Centre de Référence des Maladies Auto-inflammatoires
Pr. Isabelle KONE-PAUT
isabelle.kone-paut@bct.aphp.fr

Secrétaire / Chargée de mission
M^lle^ Charlotte LEJEUNE
☎ 03.20.44.46.97
charlotte.lejeune@chru-lille.fr

Lille July 22, 2015

The French AutoImmune and AutoInflammatory rare Disease Network (FAI²R) is a heath network particularly dedicated :

- to gather all expert centers in rare autoimmune and inflammatory diseases in a single care network;

- to facilitate access to care and early diagnosis ;

- to promote patient education;

- to ensure epidemiological data of rare autoimmune and inflammatory diseases, linked to the National Bank of Rare Diseases (BNDMR) ;

- to promote clinical and translational research actions;

- to pool resources and expertise at a national level to improve access to orphan drugs and encourage RCT.

The project supported by Dr Christophe Richez entitled « Efficacy in prevention of new flare of intravenous methylprednisolone pulses versus oral prednisone" will evaluate a new strategy of prevention of Lupus flare and the effect on IFN signature. This corresponds to an unmet need in Systemic Lupus Erythematosus.

The project is an opportunity for France to participate to this international academic clinical trial.

The FAI2R network fully supports this initiative and will help to achieve the objective of recruitment of the patient in France with the help of the FAI2R's team founded by the Ministry of Health.

Pr Eric HACHULLA — Coordinator

Dr Alexandre BELOT — Co-Coordinator

CPU
Numerical certification
and reliability

université de BORDEAUX

To who it may concern.

Cluster d'Excellence CPU
Initiative d'Excellence

Bordeaux, July 29th, 2015

As Director of the cluster CPU, I would like to express my strongest support to the project of FHU leaded by Patrick Blanco.

The cluster CPU (that is a federative project of the Idex of Bordeaux) is focused on digital sciences (including scientific computing, image and signal processing and data analysis). One of our 4 main priorities is the application of digital technologies to health and biological sciences. Therefore, the project presented by P. Blanco is a wonderful opportunity to strengthen the collaboration between computer science and the medical part of the university.

I am sure that the labelization of P. Blanco's project would give rise to outstanding synergies between our two programs.

With best regards,

Thierry Colin
Director

Adresse postale
IMB
351 cours de la libération
33405 Talence cedex
http://cpu.labex.u-bordeaux.fr/

TRAIL
Translational Research and
Advanced Imaging Laboratory
université de BORDEAUX

SUBJECT : FHU PROJECT

Bordeaux, July the 22nd, 2015

As Director of LabEx TRAIL, I express my strongest support to the FHU project leaded by Patrick Blanco.

The FHU project will reinforce the multidisciplinarity and the translational forces of Bordeaux and, thus, it will help the LabEx TRAIL to achieve research from the most basic to clinical application and cohort imaging.

As neurological inflammation is one of TRAIL main topics, the FHU program will have numerous interactions with TRAIL funded translational research projects and TRAIL community, focusing collaboration on multiple sclerosis and on MRI sequence development, and using the world-class imaging platform.

This collaboration will create a unique environment to increase knowledge about multiple sclerosis activity and it will contribute to the visibility of the Bordeaux research and clinical communities.

Consequently, I fully support the FHU project and the potential of collaboration between our two programs.

Yours Sincerely,

Vincent Dousset

Director of LabEx TRAIL

TRAIL – Cluster of excellence

146 rue Léo Saignat – 33076 Bordeaux Cedex – France
T 33 (0)5 57 57 45 86 – F 33 (0)5 57 57 35 12
trail.labex-univ-bordeaux.fr

Annex 8 : Governance in French.

	Projet de GOUVERNANCE FHU : INSTANCES de PILOTAGE et COMITES Ce projet devra être validé par les instances des différentes Parties

La création du FHU Aquitaine's Care and Research OrganisatioN for inflammatory and Immune Mediated diseases « ACRONIM » résulte d'un accord de partenariat (accord de consortium) entre **Le Centre Hospitalier Universitaire de Bordeaux (CHU), l'Université de Bordeaux (UB), le Centre National de la Recherche Scientifique (CNRS), l'Institut National de la Santé et de la Recherche Médicale (INSERM)** et toute autre partie (discussions en cours pour autres parties)

Ci-après également désignés individuellement « **Partie** » ou collectivement « **Parties »**.

Les entités composant le DHU/FHU, composantes du CHU, de l'UB, du CNRS et de l'INSERM sont dénommées « **»Equipes** »

Article – 1. Objet

Le Partenariat a pour objet de définir les modalités de participation des Parties et des leurs Equipes au projet FHU « ACRONIM »
Le Partenariat fixe notamment les règles relatives à :

- l'organisation de la gouvernance ;
- la sécurisation des données et des échantillons biologiques ;
- la détermination des droits et obligations des Parties sur la base ;
- l'attribution des droits de propriété intellectuelle issus des études entreprises à partir de la base «ACRONIM» et leur exploitation ;
- les règles de financement.

Article - 2. Composition

Article – 2.1. Comité Directeur

Composition (n=32) :

- Le Directeur de chaque Partie, ou son représentant (CHU, université, CNRS, INSERM) (n=4) ; (pour l'université le directeur du collège santé ou le doyen de l'UFR médicale)
- Un représentant de chaque équipe clinique et de recherche (n=25)
- Trois membres invités représentant:
  - L'Agence Régionale de Santé d'Aquitaine
  - Le Conseil régional d'Aquitaine;
  - La Caisse Primaire d'Assurance Maladie.

Un directeur (coordinateur) du FHU est désigné (élu) au sein des représentants des équipes composant le FHU. Le Coordinateur est le Pr. Patrick Blanco pour la période initiale de 4 ans. Il est secondé par deux coordinateurs adjoints : Pr Thierry Schaeverbeke, Pr Jean-Luc Pellegrin, pour la période initiale de 4 ans.

Missions :

- Instruire l'intégration de nouveaux Centres et l'exclusion des Centres participants ;
- Prévoir la répartition budgétaire des financements obtenus ;

- Valider le rapport d'activité annuel ;
- Définir les grandes orientations stratégiques

Réunion : une à deux fois par an.

Au sein du Comité Directeur, les décisions sont prises à la majorité des voix. Les membres invités ne votent pas. En cas d'égalité, la voix du Coordinateur départage les votes. Chaque réunion du Comité Directeur donne lieu à un compte rendu rédigé par le Coordinateur et transmis par mail à l'attention du secrétariat de direction, et du responsable de chaque équipe. Les comptes rendus seront également adressés par mail pour information aux organismes financeurs, au titre de son soutien financier. Ces documents seront archivés au CHU de Bordeaux.

Article – 2.2. Conseil scientifique, Commissions et Comité de pilotage, advisory board

2.2.1 Conseil scientifique

Composition :

- Le Coordinateur ;
- 1 représentant par Equipe (clinique et recherche n=25) composant le FHU : les chefs de service ou leur représentant, le directeur du département de médecine générale ou son représentant, les directeurs d'unités de recherche ou leur représentant
- Membre invité : l'Agence Régionale de Santé d'Aquitaine
- 3 Experts étrangers désignés par le Comité Directeur

Missions :

- Planification des activités du FHU ;
- Veille technologique et scientifique ;
- Animation ;
- Formation ;
- Mise en œuvre de la démarche qualité.
- Evaluer scientifiquement les projets ;
- Evaluer le bilan de l'activité ;
- Déterminer les droits d'accès aux données et/ou identifier les échantillons pertinents dans le cadre d'études menées par les Centres ;
- Déterminer les conditions d'accès et la mise à disposition des données et des échantillons au profit de tiers publics ou privés ;
- Déterminer le contenu des mentions relatives au Partenariat et à la base ACRONIM au sein des publications et communication ;
- Conseiller les Parties en matière d'investissements technologiques et stratégiques ;
- Rédiger un rapport scientifique annuel des projets en cours

Réunion : une fois par an

Au sein du Comité Scientifique, les décisions sont prises à la majorité des voix. Les membres invités ne votent pas. En cas d'égalité, la voix du Coordinateur départage les votes. Chaque réunion du Comité Scientifique donne lieu à un compte rendu rédigé par le Coordinateur et transmis par mail à l'attention du secrétariat de direction et du responsable de chaque équipe. Les comptes rendus seront également adressés par mail pour information aux organismes financeurs, au titre de son soutien financier. Ces documents seront archivés au Centre hospitalier universitaire de Bordeaux

2.2.2 Commissions

Pour réaliser ces misions le conseil scientifique s'appuie sur quatre commissions dont il désigne les membres issus de son sein et/ou des équipes, à savoir

- Commission de l'organisation des soins
- Commission formation
- Commission recherche
- Commission valorisation

Chaque commission est animée par deux coordonnateurs (un clinicien et un chercheur pour les commissions formation, recherche, valorisation)

2.2.3 Comité de pilotage

Le coordonnateur du FHU et les coordonnateurs des commissions constituent le comité de pilotage du FHU

Réunions : 4 fois par an,

Au sein du Comité de Pilotage, les décisions sont prises à la majorité des voix. En cas d'égalité, la voix du Coordinateur départage les votes. Chaque réunion du Comité de Pilotage donne lieu à un compte rendu rédigé par le Coordinateur et transmis par mail à l'attention du secrétariat de direction, et du responsable scientifique de chaque équipe. Les comptes rendus seront également adressés par mail pour information aux organismes financeurs au titre de son soutien financier. Ces documents seront archivés au CHU de Bordeaux.

2.2.3 Strategic advisory board

Les trois personnalités scientifiques internationales membres du conseil scientifiques constituent l'advisory board. Elles évaluent la progression du projet scientifique du FHU et émettent des recommandations. Le board sera invité de façon annuelle lors de la journée scientifique du FHU.

Article – 2.3. Intégration des nouveaux Centres.

D'autres Centres pourront participer au Projet (cf politique nouvelle grande région). A cette fin, chaque demandeur devra adresser sa candidature écrite et argumentée au Coordinateur. L'acceptation d'un nouveau Centre devra recevoir l'accord des Centres déjà inclus, par le biais du Comité Directeur dans les conditions fixées à l'article 2.3., et devra être formalisée par voie d'avenant au présent Partenariat, signé de l'ensemble des Parties.

Article – 3. Conformité aux exigences légales et réglementaires.

La base de données « ACRONIM » a fait l'objet d'une déclaration CNIL sous le numéro : 0000000.

Chaque équipe est responsable de l'accomplissement des formalités légales et réglementaires relatives :

- à la collecte des données et à leur utilisation sur son site et dans son système d'information ;
- aux activités de préparation, conservation, et utilisation des collections d'échantillons biologiques sur son site (*notamment en application des articles L. 1243-3 et L. 1243-4 du CSP*).

Chaque équipe est responsable de l'information et du recueil du consentement des personnes dont les données médicales et personnelles sont issues et collectées au sein de la base «ACRONIM », et dont les échantillons biologiques forment la biocollection virtuelle partagée.

Les Responsables scientifiques de chaque équipe devront s'assurer de la réalité de l'information et du recueil du consentement des patients, avant d'enregistrer leurs données et ressources biologiques dans la base « ACRONIM ». Les données du patient seront codées à l'entrée dans la base afin de permettre le respect de l'anonymat. Les données circuleront sur le réseau informatique en mode crypté. Chaque équipe accédera à la base à l'aide d'un code personnalisé.

Article – 4. Alimentation de la base de données.

Les Centres s'engagent à remplir la base « ACRONIM » selon les modalités décrites au présent article 4.

Article – 4.1. Procédures de saisie des données.

A préciser

Article – 4.2. Normes qualité

A préciser

Article – 5. Formation de la Biocollection virtuelle.

La base **«** ACRONIM **»** permettra la formation d'une collection d'échantillons biologiques virtuelle à partir d'échantillons biologiques humains conservés au sein des collections locales des équipes. Ces échantillons doivent être préparés et conservés selon des modes opératoires communs afin de garantir une certaine homogénéïté de la biocollection virtuelle, selon les modalités techniques, de stockage et de transport détaillées dans l'Annexe 1.

Article – 6. Principes généraux

Article – 6.1. Droits sur la base «ACRONIM »

L'architecture de la base, son titre «ACRONIM », et son logo, dont le ou les auteurs sont XXXX, sont la propriété du CHU de Bordeaux, en application du régime applicable au droit d'auteur. A ce titre, le CHU de Bordeaux est seul titulaire des droits d'exploitation.

Le contenu de la base est une œuvre collective dont la propriété est attribuée aux équipes. En application du régime applicable au droit d'auteur, et du régime *sui generis* des producteurs de bases de données, chaque équipe participe au contrôle de l'extraction et de l'utilisation des données qu'il a lui-même collectées à partir des patients de l'équipe. Celles-ci s'effectuent dans les conditions prévues aux présentes, sous réserve que cette exploitation ne contrarie pas les ambitions scientifiques du Projet et ne nuise pas à la finalité du Partenariat. En leur qualité d'établissement Coordinateur et de Coordinateur scientifique, le CHU de Bordeaux et le Pr/Dr. XXXX ont la possibilité de s'opposer à toute piste d'exploitation combinée ou d'ensemble de la base envisagée par le Conseil scientifique qui serait de nature à contrevenir au Projet ou à le discréditer.

Article – 6.2. Principes de fonctionnement du Partenariat

Projets - Production scientifiques

Tout projet scientifique entrepris à partir des données de la base « ACRONIM », et le cas échéant de ressources biologiques issues de la biocollection virtuelle, doit faire l'objet d'un protocole méthodologique écrit, adressé au Coordonateur pour communication et évaluation du Conseil

scientifique, ainsi que pour détermination des conditions d'accès aux ressources biologiques et aux données (*article 2.4. des présentes*).

De plus, chaque équipe initiatrice devra fournir au Coordinateur un rapport scientifique annuel de son projet.

Accès aux ressources biologiques et aux données

Si cela n'est pas prévu dans le protocole méthodologique, l'équipe (ou le tiers) qui souhaite extraire ou utiliser les données d'un ou plusieurs équipes contenues dans la base « ACRONIM» doit en faire la demande écrite (*mail ou courrier*) au Coordinateur pour communication au Conseil scientifique.

L'extraction ou l'utilisation ne pourra intervenir qu'après l'accord écrit (*courrier ou e-mail*) du Comité scientifique, et du ou des équipes dont les données concernées proviennent. Les mêmes règles sont applicables en cas de recours à des ressources biologiques répertoriées dans la biocollection virtuelle. Dans ce cas, l'équipe initiateur est également tenu de compléter le formulaire présenté en Annexe 2, à l'appui de sa demande.

Qualité

Il est rappelé que chaque Centre est responsable de la qualité des données qu'il collecte et doit accepter de se soumettre aux audits de contrôle prévus à l'article 4.2 du présent Partenariat.

Ethique, législation, réglementation

Chaque équipe initiateur d'un projet scientifique s'engage à mettre en œuvre toutes les démarches requises afin d'en assurer la conformité à la législation/réglementation en vigueur, et ainsi solliciter tous les avis, déclarations, autorisations et décisions applicables. Le Centre initiateur sera également tenu de vérifier la compatibilité des mesures prises pour assurer l'information et le recueil du consentement des patients à la finalité du projet en cause.

Financement

Chaque équipe initiateur (ou tiers) d'un projet scientifique s'engage à trouver le financement nécessaire permettant de mener à bien son projet.

Contractualisation – Propriété intellectuelle

Pour tout projet scientifique entrepris dans le cadre du présent Partenariat, impliquant plusieurs équipes (*article 7.2*) et/ou des tiers (*article. 7.3*), un contrat particulier doit être rédigé et conclu entre les Centres concernés, et, le cas échéant, avec les tiers impliqués, afin d'en préciser les modalités de collaboration et de financement. Ces contrats doivent faire référence au présent Partenariat et doivent accorder une attention particulière à la sécurisation des données et des échantillons, à l'éthique et au respect de la réglementation, ainsi qu'aux droits de propriété intellectuelle, notamment au regard des règles fixées dans les présentes.

Les résultats obtenus par les Centres antérieurement à tout projet réalisé dans le cadre du Partenariat, restent leurs propriétés respectives. Les autres Équipes ne reçoivent sur les titres de propriété intellectuelle correspondants aucun droit du fait du présent Partenariat. Si l'exploitation de ces résultats était rendue nécessaire pour mener à bien un projet particulier du Partenariat ou sa valorisation, le Centre titulaire des droits d'exploitation s'engage à négocier les conditions d'exploitation des dits résultats avec le Coordinateur et le Conseil scientifique. Cette exploitation fera l'objet d'un avenant au présent Contrat.

Les Résultats issus d'un projet mené dans le cadre du Partenariat appartiennent conjointement aux Centres qui ont contribué à leur obtention, au prorata de leurs apports intellectuels respectifs sous réserve, le cas échéant, des droits du Coordinateur et du CHU de Bordeaux sur la base de données, et des droits éventuels des tiers.

La procédure et les actions relatives à la valorisation des résultats seront réalisées par un maître d'œuvre en charge de la valorisation désigné par le Comité Directeur. Le Comité Directeur devra définir les termes du mandat confié au maître d'œuvre par les Parties et encadrer ses missions par voie d'avenant au présent contrat.

Une copie de chaque contrat devra être adressée au Coordinateur pour information du Conseil scientifique.

Confidentialité - Communications - Publications

Dans le cadre des projets, les Centres s'engagent à observer les règles de confidentialité posées à l'article 9 des présentes. Le cas échéant, les Équipes veillent à ce que les tiers collaborateurs aux dits projets s'engagent selon les mêmes règles.

Toute communication ou publication intervenant dans le cadre ou en rapport avec le Partenariat, ou utilisant les ressources biologiques et/ou des données de la base ACRONIM doit faire mention de l'existence du Partenariat et de la base ACRONIM. Le contenu de ces mentions sera arrêté par le Conseil scientifique et réintroduits au sein des protocoles méthodologiques.

Toute communication ou publication d'un projet réalisé avec le concours d'une équipe de ressources biologiques (ci-après désigné « **CRB** ») de l'un des Équipes doit inclure des remerciements au dit CRB ou, le cas échéant, préciser le concours du CRB au sein de la section « matériel et méthodes » de la publication. Chaque communication/publication réalisée, ainsi que chaque brevet déposé en lien avec un CRB devra être notifié au Responsable du CRB en question pour suivi de son activité.

Article – 7. Règles particulières relatives à la configuration des projets

Les règles de fonctionnement particulières doivent être observées à la lumière des principes généraux du Partenariat (article 6) et de l'ensemble des stipulations des présentes.

Article - 7.1. Projet scientifique impliquant une seule Équipe

Les Équipes peuvent librement utiliser leurs propres données et échantillons biologiques pour leurs propres études et travaux, sous leur seule responsabilité.

Pour mémoire, une information préalable (*transmission du protocole*) du Conseil scientifique, par l'intermédiaire du Coordinateur est requise afin d'assurer le suivi de la production scientifique du Partenariat, sans que le Conseil n'ait toutefois la possibilité de s'opposer à l'étude ou à la publication qui en résulte.

Le Équipe initiateur adressera au Coordinateur un rapport scientifique annuel du projet, dans les mêmes conditions. Les publications se feront sous la signature du Équipe initiateur du projet scientifique.

Les droits de propriété sur les résultats des travaux appartiendront au Équipe initiateur, sous réserve des droits du Coordinateur et du CHU de Bordeaux sur la base de données, des droits antérieurs et des droits éventuels des tiers.

Article - 7.2. Etudes et travaux menés en collaboration entre plusieurs Équipes.

Un Équipe initiateur peut entreprendre un projet scientifique en collaboration avec d'autres Équipes, dans les conditions de l'article 6 des présentes.

Les publications réalisées grâce à l'utilisation des données de la base ACRONIM et/ou de la biocollection virtuelle, se feront sous la signature du Équipe initiateur de l'étude, suivi des Équipes collaborateurs au prorata du nombre de patients inclus dans la base par ordre décroissant et de la mention de l'existence de la base XXXX. L'accord écrit (*mail ou courrier*) préalable de toutes les Équipes participantes et du Coordonnateur devra intervenir avant la publication.

Article - 7.3. Etudes et travaux menées en collaboration avec d'autres partenaires publics ou privés.

Un Équipe initiateur peut entreprendre un projet scientifique en collaboration avec un ou des partenaires autres que les Parties. Par ailleurs, le Coordinateur et le Comité scientifique peuvent recevoir et instruire des propositions de projets scientifiques à l'initiative d'autres partenaires publics et privés. De tels projets sont soumis aux principes de fonctionnement prévus à l'article 6 des présentes.

Afin de permettre à de tels partenaires tiers d'anticiper la protection de leurs projets et éviter tout conflit relatif à la confidentialité, le Équipe approché par le dit tiers pour la réalisation d'une étude incluant des données et/ou échantillons provenant Partenariat, et/ou, selon le cas, le Coordinateur (*ou le Conseil scientifique*), doit l'informer du fait que, compte tenu de la gouvernance du Partenariat, le projet du tiers sera présenté à l'ensemble des Équipes via le Conseil scientifique.

Dans tous les cas, lorsque les travaux proposés par des tiers académiques ou privés nécessitent l'extraction ou l'utilisation de données de la base ACRONIM et/ou l'utilisation d'une partie des échantillons de la biocollection virtuelle, tous les Équipes seront informés préalablement de l'étude entreprise, et chaque Équipe dont seraient particulièrement originaires les données et les échantillons utilisés dans le cadre de l'étude en question, devra, préalablement à sa réalisation, donner son accord écrit (*mail ou courrier*).

Les publications réalisées grâce à l'utilisation des données de la base ACRONIM et/ou de la biocollection virtuelle, se feront sous la signature du Équipe initiateur de l'étude, sous réserve des règles particulières convenues avec les Équipes impliqués et les autres partenaires, au prorata du nombre de patients inclus dans la base par ordre décroissant et de la mention de l'existence de la base ACRONIM. L'accord écrit (*mail ou courrier*) préalable de tous les Équipes participants et du Coordonateur devra intervenir avant la publication.

Enfin, en cas de concurrence entre un projet proposé par un Équipe et un projet proposé à l'initiative d'un tiers, le Conseil scientifique arbitrera selon la qualité scientifique des projets en présence.

Article – 8. Dispositions financières relatives au fonctionnement du Partenariat

Par principe, chaque Partie fait son affaire du financement et de la gestion des moyens nécessaires à sa collaboration dans le cadre du Partenariat. Chaque Équipe décidera des modalités de recrutement ou d'affection, et de la gestion des personnels ainsi que de l'acquisition, l'entretien ou la gestion des matériels nécessaires à sa participation au Partenariat.

Le CHU de Bordeaux ne serait être tenu d'assumer, du fait de sa qualité de Équipe Coordinateur, une quelconque charge financière relative aux personnels et autres moyens matériels dont l'intervention est nécessaire au titre du fonctionnement du Partenariat dans les Équipes.

Le Équipe de Bordeaux est désigné récipiendaire des fonds obtenus dans le cadre de l'Appel à Projets Bases de Données Clinico-Biologiques versés par l'INCa. A ce titre, il assurera la gestion des moyens nécessaires au fonctionnement de la base dans la limite de la liste énumérée en annexe 3. Cette gestion est assurée au regard de chaque rapport d'activité annuel et des ressources obtenues dans le cadre Partenariat.

Afin de financier les coûts en personnel et matériels dédiés au Partenariat, les Parties pourront, par l'intermédiaire du Comité Directeur, définir une stratégie de recherche de financement approprié. Dans ce cas, le CHU de Bordeaux pourra être récipiendaire des fonds des appels d'offres, subventions ou dons octroyés dans ce cadre.
De plus, le Comité Directeur procèdera à une estimation financière annuelle et évaluera les modalités de financement envisageables, au regard des ressources disponibles.
Le CHU de Bordeaux ne saurait poursuivre l'acquisition, l'entretien et/ou la gestion des matériels, ou autres moyens pour lesquels il ne dispose pas de sources de financement spécifiques. En cas d'absence de financement, les Parties se concerteront afin de déterminer les modalités de poursuite du Partenariat. L'absence de financement dans les conditions précitées, est de nature à entraîner la résiliation anticipée du présent Partenariat.

Pour mémoire, chaque Équipe est responsable du financement des projets et études qu'il souhaite conduire dans le cadre du Partenariat.

Article – 9. Confidentialité

Il est rappelé, afin de permettre aux tiers académiques ou privés d'anticiper la protection de leurs projets et éviter tout conflit relatif à la confidentialité, que le Équipe approché par le dit tiers en vue de la réalisation d'une étude incluant des données et/ou ressources biologiques provenant de la base ACRONIM, doit l'informer du fait que, compte tenu de la gouvernance du Partenariat, le projet du tiers sera présenté à l'ensemble des Équipes via le Conseil scientifique.

D'autre part, chaque Partie s'engage à prendre toute mesure nécessaire à la protection des informations de nature confidentielle relatives aux autres Parties et dont la divulgation serait rendue nécessaire afin de satisfaire à l'exécution du présent Partenariat. Au terme des présentes, les Parties conviennent que ces informations peuvent être écrites, orales, numériques ou graphiques, quel que soit leur support ou leur mode de transmission et sont considérées comme non publiquement et légitimement disponibles.

Ces informations sont désignées ci après « Informations Confidentielles ». Elles incluent toute information, connaissance, savoir faire ou donnée de nature intellectuelle, technique, scientifique, commerciale, financière ou industrielle, ainsi que toute information relative à l'organisation d'un Équipe, sa politique, sa gestion administrative et financière, mais également toute information interne, comptable, sociale ou juridique comprise soit dans un document écrit ou électronique, soit transmise oralement ou visuellement, par inspection des pièces ou équipement. Les « Informations Confidentielles » incluent a fortiori les divers comptes rendus, ainsi que l'ensemble des informations afférentes aux études et travaux, et les résultats encore non publiés issus de ceux-ci.

Chaque Partie s'engage à (i) ne pas divulguer, discuter, fournir, transmettre, copier, rendre disponible ou communiquer d'une manière ou d'une autre, directement ou indirectement, tout ou partie des Informations Confidentielles d'une ou plusieurs Parties au présent Partenariat à un tiers, sans obtenir au préalable le consentement des Parties concernées et (ii) ne pas utiliser les Informations Confidentielles de cette ou ces Parties dans un but autre que celui d'exercer ses droits et d'exécuter ses obligations en vertu du présent Partenariat.

Nonobstant ces stipulations, chaque Partie peut communiquer les Informations Confidentielles dont elle peut apporter la preuve :

- qu'elles étaient disponibles publiquement préalablement à leur communication ou postérieurement à celle-ci, mais en l'absence de toute faute qui lui soit imputable ;
- qu'elles ont été reçues d'un tiers de manière licite ;
- qu'elles étaient déjà en sa possession avant la conclusion du Partenariat mais en l'absence de toute faute qui lui soit imputable;
- qu'elles ont été développées de manière indépendante et de bonne foi par des membres de son personnel n'ayant pas eu accès à ces Informations Confidentielles.

Toutefois, la Partie qui se trouve en possession d'Informations Confidentielles du fait des circonstances précitées, s'engage à en informer la Partie concernée, et sur la demande de cette dernière, à réserver la communication/publication de telles Informations confidentielles selon ses indications.

D'autre part, chaque Partie s'engage à :

- prendre toutes les mesures et précautions nécessaires et raisonnables afin d'éviter que ne soient divulguées à un tiers les Informations Confidentielles des autres Parties échangées entre elles ;
- ne transmettre les Informations Confidentielles communiquées par l'autre Partie qu'aux membres de son personnel ou à ses sous-traitants seulement si ces derniers sont amenés à en avoir besoin pour l'accomplissement de leur mission afférente au présent Partenariat, et sous réserve que ces personnels soient soumis au secret professionnel, et que ces sous-traitants soient soumis à un accord de confidentialité, reprenant les obligations stipulées aux présentes et garantissant le secret et la confidentialité des Informations Confidentielles des Parties ;
- prendre toutes les mesures raisonnables pour éviter que le personnel n'utilise les Informations Confidentielles des autres Parties à des fins autres que l'objet du présent Partenariat ;
- avertir les Parties concernées sans délai de la réalisation de tout évènement ou la constatation d'une quelconque activité qui serait de nature à porter atteinte à la confidentialité des Informations confidentielles, afin que ces Parties puissent convenir actes conservatoires ou autres mesures de prévention à diligenter afin de maintenir le secret des Informations Confidentielles.

L'obligation de confidentialité faisant l'objet du présent article doit être respectée réciproquement par les Parties pendant toute la durée du présent Partenariat et pendant une durée de dix (*10*) ans à compter à compter du terme définitif du Partenariat (*c'est-à-dire la date d'anéantissement pour toutes les Parties, quelle que soit l'état des éventuelles résiliations ou exclusions antérieures pour un Équipe*), à l'exception des Données à caractère personnel issues des patients qui sont gardées confidentielles sans limitation de durée. A l'expiration du Partenariat, chaque Partie s'engage à restituer aux autres Parties l'intégralité des Informations Confidentielles qui lui auront été communiquées ou échangées, sans en garder copie, ce à la demande simple d'une Partie concerné, et dans tous les cas, dans les trente (*30*) jours qui suivront le terme, la résiliation ou l'exclusion d'une Partie. Les Parties s'engagent à se fournir mutuellement des certificats de destruction. Toutefois, chaque Partie peut conserver les Informations Confidentielles nécessaires à l'accomplissement de ses obligations réglementaires de suivi et d'archivage. Dans ce cas, lesdites Informations confidentielles sont conservées dans des conditions garantissant leur stricte confidentialité.

A titre indicatif, il est rappelé que XXXX (*ex. Financeur Public ou Fondation*) peuvent avoir accès à certaines Informations Confidentielles au titre leur soutien médical, scientifique et/ou financier, notamment aux comptes rendus.

Dans tous les cas, les Équipes s'engagent à respecter les principes relatifs à la protection des personnes, notamment l'article L. 1110-4 du CSP, et la loi dite « Informatique et Libertés » du 6 janvier 1978 notamment modifiée par la loi n° 2004-801 du 6 août 2004 et ses textes d'application, et ce, quelque soit le lieu d'exécution du présent Partenariat ou encore le lieu d'utilisation des données à caractère personnel. Ainsi, « *Toute personne prise en charge par un professionnel, un établissement, un réseau de santé ou tout autre organisme participant à la prévention et aux soins a droit au respect de sa vie privée et du secret des informations la concernant. Excepté dans les cas de dérogation, expressément prévus par la loi, ce secret couvre l'ensemble des informations concernant la personne venues à la connaissance du professionnel de santé, de tout membre du personnel de ces établissements ou organismes et de toute autre personne en relation, de par ses activités, avec ces établissements ou organismes. Il s'impose à tout professionnel de santé, ainsi qu'à tous les professionnels intervenant dans le système de santé. Afin de garantir la confidentialité des informations médicales mentionnées aux alinéas précédents, leur conservation sur support informatique, comme leur transmission par voie électronique entre professionnels, sont soumises à des règles définies par décret en Conseil d'Etat pris après avis public et motivé de la Commission Nationale de l'Informatique et des Libertés* ».

Article – 10. Résiliation, exclusion.

Chaque Partie peut mettre fin aux présentes pour ce qui le lie respectivement et individuellement aux autres Parties, sous réserve de l'observation d'un préavis de trois (*3*) mois à compter de la date de réception de la notification adressée aux Parties
Une Partie peut être exclue du Partenariat, en raison de l'inexécution des obligations stipulées aux présentes. Cette exclusion devra être prononcée à la majorité des voix du Comité Directeur. La décision prononçant l'exclusion de la dite Partie devra faire l'objet d'une notification argumentée et signée de l'ensemble des autres Équipes à ce dernier. Les données de ce Équipe lui seront rétrocédées dans les mêmes conditions qu'en cas de résiliation.

En cas de résiliation ou d'exclusion, les Équipes perdront leur accès à la base ACRONIM.

Le Équipe qui souhaite se résilier sa participation au Partenariat ou qui est en est exclu ou Les données collectées de la Partie mettant un terme à sa collaboration seront extraites de la base ACRONIM et communiquées au Équipe selon ses directives expresses. Elles pourront également être maintenues dans la base ACRONIM pour des raisons réglementaires de suivi et d'archivage, sans que les Parties maintenues dans le Partenariat ne puissent en disposer à des fins d'études ou autres projets scientifiques.

Les décisions modificatives du présent Partenariat devront être prises à l'unanimité et faire l'objet d'un avenant exprès.

Article – 11. Durée

Le présent Partenariat est conclu pour une durée de trois 3 ans à compter du (date de mise en application). Il peut être renouvelé à la fin de cette période par un avenant conclu entre les Parties.

Nonobstant l'échéance du présent accord, sa résiliation anticipée dans les cas prévus à l'article 10"Résiliation - exclusion", les dispositions prévues aux articles 6, 7, 8 et 9 restent en vigueur.

A l'expiration du présent Partenariat et comme stipulé à l'article 9 de la présente Convention, chaque Partie prend l'engagement de restituer aux autres Partie ou détruire, dans le mois suivant ladite expiration, tous les documents et divers matériels qu'un Équipe aurait transmis à un autre Équipe, sans pouvoir en conserver de reproduction. Cette destruction ou restitution se fera sur simple demande écrite du Équipe divulgateur. Les Équipes s'engagent à fournir un certificat de destruction.

Article – 12. Cession

Le présent accord est **incessible**.

Article – 13. Intégralité et limite du contrat

Le présent Partenariat, assorti de ses annexes, exprime l'intégralité des obligations des Équipes. Aucune des dispositions des présentes ne peut être modifiée, altérée, complétée, modifiée, ni aménagée, que ce soit en totalité ou en partie, sauf par un écrit signé par les représentants régulièrement mandatés des Parties.

Article – 14. Invalidité d'une clause

Si une ou plusieurs stipulations du présent Accord étaient tenues pour non valides ou déclarées telles en application d'un traité, d'une loi ou d'un règlement, ou encore à la suite d'une décision définitive d'une juridiction compétente, les autres stipulations garderont toute leur force et leur portée. Les Parties

procéderont alors sans délai aux modifications nécessaires en respectant, dans toute la mesure du possible, l'accord de volonté existant au moment de la signature du présent Partenariat.

Article – 15. Litiges

Le présent Partenariat est soumis aux lois et règlements français. En cas de difficulté sur l'interprétation ou l'exécution des présentes, les Parties s'efforceront de résoudre leur différend à l'amiable. En cas de désaccord persistant au delà de quarante cinq (45) jours à compter de la première notification adressée par la Partie plaignante à la Partie Défaillante, les tribunaux compétents du lieu du siège du défendeur pourront être saisis sous réserve de l'application du décret n°2009-1205 du 09 octobre 2009 fixant le siège et le ressort des juridictions en matière de propriété intellectuelle.

Article – 16. Notification.

Toute notification concernant le présent Partenariat devant être adressée par une Partie à l'autre Partie se fera par Lettre Recommandée avec Avis de Réception. La date de réception fait foi. Pour rappel, la notification doit être adressée à l'adresse suivante, à savoir :

- Pour le Équipe Hospitalier Universitaire de Bordeaux :

- CHU de Bordeaux, Hôpital XXXX, Service XXXX, *à l'intention du Professeur / Docteur XXXX* 12 rue Dubernat – 33404 TALENCE Cedex
- Copie : CHU de Bordeaux, Direction de la Recherche et de l'Innovation, *à l'intention de Monsieur le Directeur Joaquin Martinez*, 12 rue Dubernat – 33404 TALENCE Cedex

- Pour XXXX:
  - _____ _____à l'intention de _____
  - Copie à XXXX
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  - _____ _____à l'intention de _____
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- Pour XXXX:
  - _____ _____à l'intention de _____
  - Copie à XXXX

Fait à Bordeaux en XX exemplaires, le ____/____/____

Pour le CHU de Bordeaux	
Pour le Directeur Général Monsieur Philippe Vigouroux **Et par délégation** Monsieur Joaquin Martinez **Directeur de la Recherche et de l'Innovation** **Bordeaux, le**	En présence du **Coordinateur/ Responsable scientifique** Professeur / Docteur