CRI - Centre de recherche sur l'inflammation

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of research units

AERES report on unit:

Center for Research on Inflammation

CRI

Under the supervision of the following institutions and research bodies:

Université Paris 7 - Denis Diderot

Institut National de la Santé Et de la Recherche Médicale

January 2013

agence d'évaluation de la recherche
et de l'enseignement supérieur

Research Units Department

President of AERES

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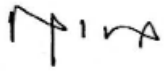


Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the following grades:

- Grading table of the unit: Centre de recherche sur l'inflammation

C1	C2	C3	C4	C5	C6
A	A	A+	A	A+	A

- Grading table of the team: Novel imaging biomarkers for inflammation, fibrosis and cancer

C1	C2	C3	C4	C5	C6
A	A+	A	A	A	A

- Grading table of the team: Innate immune responses in the child: role in viral infections and graft versus host reaction

C1	C2	C3	C4	C5	C6
A	B	NN	A	A	A

- Grading table of the team: Gastrointestinal & metabolic dysfunctions in Nutritional Pathologies

C1	C2	C3	C4	C5	C6
A	B	NN	A	A	A

- Grading table of the team: Mast cells and basophils in inflammation and remodeling

C1	C2	C3	C4	C5	C6
A	A+	A+	A	A+	A

- Grading table of the team: Phagocyte, NADPH odysases and immunogenetics in systemic inflammation

C1	C2	C3	C4	C5	C6
A	B	A+	A	A+	A

- Grading table of the team: Inflammatory and stress responses in chronic liver diseases

C1	C2	C3	C4	C5	C6
A	A+	NN	A	A+	A

- Grading table of the team: From inflammation to cancer in digestive diseases

C1	C2	C3	C4	C5	C6
A	B	NN	A+	A+	A

- Grading table of the team: Intestinal Inflammation

C1	C2	C3	C4	C5	C6
A+	A	A+	A+	A+	A+

- Grading table of the team: Immunoreceptors and renal immunopathology

C1	C2	C3	C4	C5	C6
A+	A+	A+	A+	A+	A+

- Grading table of the team: Heme, iron and inflammatory diseases

C1	C2	C3	C4	C5	C6
A	B	A+	B	A	B

- Grading table of the team: Physiopathology and treatment of viral hepatitis

C1	C2	C3	C4	C5	C6
A	A	NN	B	A+	B

● Grading table of the team: Research and innovations in surgery and endoscopy of gastrointestinal and inflammatory diseases

C1	C2	C3	C4	C5	C6
B	C	NN	B	B	B

Evaluation report

Unit name:	Center for Research on Inflammation
Unit acronym:	CRI
Label requested:	UMR_S
Present no.:	
Name of Director (2012-2013):	
Name of Project Leader (2014-2018):	Mr Renato MONTEIRO

Expert committee members

Chair: Mr Angelo PARINI, University of Toulouse

Experts:

Mr Sandro ARDIZZONE, Università degli studi di Milano, Italy

Mr Patrice CANI, Université of Louvain, Belgium

Mr Loreto GESUALDO, University of Bari, Italy

Mr Juan IOVANNA, University of Aix Marseille
(CSS INSERM representative)

Mr Olivier LORÉAL, University of Rennes

Mr Thierry METENS, University of Bruxelles, Belgium

Ms Lucette PELLETIER, University of Toulouse

Mr Joel PESTEL, University Lille1 (CoNRS representative)

Mr Harald SCHMIDT, University of Maastricht, Netherlands

Scientific delegate representing the AERES:

Ms Sophie DE BENTZMANN

Representative(s) of the unit's supervising institutions and bodies:

Ms Christine CLERICI, Paris Denis Diderot University

Ms Laurence LOMME, INSERM

1 • Introduction

History and geographical location of the unit

The teams participating in the CRI project come from former research Units (UMR699, UMR773, UMR843, UMR986). The teams of the CRI are located on parts of 4 different floors of the Bichat Faculty Building (3390 m^2) and 478 m^2 at the Abrami Building of the Beaujon Hospital. One team is located at Hospital Robert Debré. 9 of the teams of the CRI project were included in the Centre de Recherche Biomédicale Bichat-Beaujon (CRB3) in the previous last five year period.

Management team

The CRI organization and management includes a Director (Renato Monteiro) and a General Manager (Margot Sauvadet). The CRI will be organized into two scientific departments: Nephrology & Immuno-Hematology (NIH) and Hepato-Gastroenterology (HGE). The NIH (lead by Ulrich Blank) and HGE (lead by Richard Moreau) departments will include 5 teams and 7 teams, respectively.

AERES nomenclature

SVE1_LS6, SVE1_LS7

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	40 (13.2)	69 (22.3)	39 (12.7)
N2: Permanent researchers from Institutions and similar positions	29 (29)	29 (29)	29 (29)
N3: Other permanent staff (without research duties)	-	-	-
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	-	-	-
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	25 (21.8)	32 (27.6)	25 (21.8)
N6: Other contractual staff (without research duties)	9 (2.9)	7 (2.3)	8 (2.6)
TOTAL N1 to N6	**103 (66.9)**	**137 (81.2)**	**101 (66.1)**

Note : Full time equivalent are ndicated into brackets

Percentage of producers	***98,90 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	46	
Theses defended	37	
Postdoctoral students having spent at least 12 months in the unit*	33	
Number of Research Supervisor Qualifications (HDR) taken	23	
Qualified research supervisors (with an HDR) or similar positions	45	80

2 • Assessment of the unit

Strengths and opportunities

The project of the CRI is original and competitive, feasible based on the quality of the teams. There are strong interactions between teams materialized by the LabEx Inflamex as illustrated in the detailed parts of the report. The CRI has access to various Core Facilities. There is a good organization of the CRI based on a solid management.

Weaknesses and threats

• The different geographical locations (4 different floors of the Bichat Faculty Building and part of the Unit located of the Beaujon Hospital) represent a threat for the cohesivity of the Unit.

• The relationship between the project of some of the teams and inflammation is not well defined.

Recommendations:

• A particular effort should be devoted to the localisation of all the research teams in a unique site.

• The project of some of the teams should be more focused on inflammation.

• Some platforms should be better organized and supported in term of both personnel and equipment.

3 • Detailed assessments

Assessment of scientific quality and outputs

The scientific project of the Centre for Research on Inflammation (CRI) focuses on the fundamental aspects of inflammatory processes and fibrosis in different organs and their impact on human diseases. The starting hypothesis is that chronic inflammatory diseases of renal, gastro-intestinal, hepatic systems as well as of joint and systemic diseases may share common basic mechanisms. The identification and characterization of such common mechanisms would allow designing novel "multi-targeted" diagnostic and therapeutical strategies. One of the major strenghts of the project is the translational approach of inflammatory diseases going from basic studies to clinical trials. Such approach is strongly facilitated by the competences and skills of the teams involved in the project including both basic scientists and clinicians. Most of the members of the teams are already collaborating in the framework of the LabEx Inflamex, led by the CRI project leader, and the Clinical Consortium DHU "Fibrosis, Inflammation and Remodeling" (FIRE) recently created at the Bichat Hospital. This is doubtless a great asset for the achievement of the CRI project. The possibility to gather scientists working on different fundamental and clinical aspects of inflammation will strongly facilitate scientific and technical interactions and, consequently, the efficiency and productivity of the teams.

Assessment of the unit's academic reputation and appeal

Based on the activities of the teams in their former scientific environments, most of the teams of the CRI project have a good to excellent academic reputation and appeal. In term of publications, more than 1000 papers have been published by the members of the teams in the last five years, 20% in journals with IF > 10 (Nat Med, Nat Immunol, New Engl J Med, J Exp Med, J Clin Inv, Lancet, Plos Biol, EMBO Mol Med) and 60% in journals with IF > 4. More than 400 invited lectures in foreign research institutes or in international meetings have been given by the members of the teams. As mentioned above, the Unit Director is the leader of the LabEx Inflamex and half of the teams of the CRI are part of this network. One team is also member of the LabEx GR-Ex "The red cells: from genesis to death". The teams of the CRI also participate in the Clinical Consortium DHU "Fibrosis, Inflammation and Remodeling". The members of the teams are principal investigators or participate in different national and international basic science or clinical networks (36 ANR, 6 FP7, 11 PHRC). Clinicians are also involved in 7 Reference Clinical Centres located within the Hospital Departments associated to the CRI project.

In term of appeal for young scientists, since 2007 36 postdocs have been trained and, at present, 25 are working within the CRI teams. Six established investigators with University, INSERM or CNRS permanent positions joined recently the CRI project from other research units. One ATIP-AVENIR team is part of the UMR 699 and will participate in the CRI project.

Assessment of the unit's interaction with the social, economic and cultural environment

Members of the teams are co-founders of three start up (Redoxilab, Iatherys and IBDNov) supported by ANR, OSEO, INSERM Transfert. 17 patents have been filed.

Assessment of the unit's organisation and life

The CRI project includes 234 persons: 29 established investigators from the INSERM (21) and CNRS (8), 74 established investigators from the University (Medical School and Faculty of Science), 38 technicians and Engineers, 12 technicians with a temporary position, 81 students and post-docs. The Unit will be organized into two departments (NIH and HGE) and such organisation is coherent with the scientific projects and objectives of the CRI. The clinical research will be carried out in 5 different Hospitals. However, this dichotomised organization of the CRI into departments and the different geographical locations may represent a limit to the scientific interactions of the teams. This risk may be minimized by the fact that teams from the two departments are already interacting in the framework of the LabEx Inflamex and of the DHU FIRE. In addition, as mentioned in the project, the interaction between teams will be promoted by the organization of weekly-based seminars, journal clubs and an annual CRI meeting organised outside Paris.

The possibility to add a Deputy Director should be considered. The scientific strategies of the CRI will be elaborated based on the Scientific Advisory Board (already formed), including 5 international and one national experts and the Internal Council advises. The first meeting is scheduled for spring 2014. The additional functions of the Internal Council are detailed in the Internal Rules. This document also describes in detail different aspects concerning the Centre management (choice and function of the Director; tasks of the General Manager; team composition, recruitment and evaluation; management of technicians, engineers and administrative staff ; follow-up of students and postdocs; budget and space allowance; safety).

Different Core Facilities are already well defined: firstly, an administrative platform including 9 persons in charge of grant and direction assistance, secretary, financial management, website administration, warehouse, health & safety and human resources. This personnel is issued from former research units. Secondly, several technological platforms include animal facilities, Cell Imaging, Flow Cytometry and Cell Sorting, Recombinant Protein, Electronic Microscopy. The CRI has also full access to Biobanks and Clinical Database located at the Bichat or Beaujon Hospitals. All these platforms have at least one Engineer or Technician in charge of the platform management. However, as described in the project, additional recruitments are necessary to support the technological development of the platforms (in particular for Cell Imaging and Animal Facilities.

Assessment of the unit's involvement in training through research

The members of the CRI teams have trained 234 PhD students since 2007 and 56 Master/PhD are undergoing training. The teams are associated with several Doctoral Schools (Gc2ID, B3MI,..) and the CRI will be part of the future Bio-Paris-Cité Doctoral School (2014). The creation of a new master dedicated to Inflammation and Medical Inflammation is in progress in the framework of the LabEx Inflamex. The analysis of the employment of PhD and post-docs trained by the CRI teams since 2007 shows that 11 persons have been recruited within the teams as University, INSERM or CNRS established investigators. Among the 41 PhD students (17 from foreign countries and 12 with a MD), 30 % are undergoing a post-doctoral training and 70 % have a temporary or permanent position (industry or academic).

Assessment of the five-year plan and strategy

The project of CRI for the next five years is to establish a “Center of Excellence” in the field of Inflammatory Diseases connecting basic research, translational research and clinical practice. This Centre will focus on two specific axes: Nephrology/Immuno-Hematology and Hepato-Gastroenterology. The CRI will represent a unique center in France developing a multidisciplinary, translational research program on cell and systemic mechanisms involved in renal, liver, gastrointestinal and immuno-hematological inflammatory diseases. This is an ambitious and exciting project that appears feasible based on the competence and excellence of most of the teams. It is important to underline that a large part of the CRI project has been already evaluated positively and granted in the framework of the “Initiative of Excellence” (LabEx Inflamex).

4 • Team-by-team analysis

Team 1 : Immunoreceptors and renal immunopathology

Name of team leader: Mr Renato MONTEIRO

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4 (1.2)	7 (2.3)	7 (2.3)
N2: Permanent EPST or EPIC researchers and similar positions	2 (2)	2 (2)	2 (2)
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4 (4)	5 (4.5)	5 (4.5)
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**10 (7.2)**	**14 (8.8)**	**14 (8.8)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	6	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	3	8

• Detailed assessments

Assessment of scientific quality and outputs

The team leader is a researcher, well known worldwide, for his elegant studies on the pathogenesis of IgA nephropathy (IgAN), one of the most frequent form of primary glomerulonephritis. His team has a strong background on immunoglobulins, their receptors and in immunoregulatory mechanisms. The team reported that the transferrin receptor 1 (TfR1) is the IgA1 mesangial receptor that is upregulated in IgAN and plays an important role in the mesangial profileration and production of inflammatory cytokines (J. Exp. Med. 2001; JASN 2003; Kidney Int. 2012). Most importantly they have developed a new humanized mouse model of IgAN and demonstrated that sCD89 plays a pivotal role in IgAN inducing the formation of mesangial nephritogenic deposits as well as mesangial TfR1 and transglutaminase 2 (TGase2) overexpression, showing for the first time the role played by TGase2 in IgAN (J. Exp. Med. 2012). Moreover, they also showed similarities between the mechanisms involved in celiac disease and IgAN (J. Exp. Med. 2008, Lab. Invest. 2012). Finally, the team in collaboration with team 2 of the CRI, in the last 5 years showed that CD89 is a switch molecule that can induce either inhibition or cell activation through formation of inhibisomes (Blood 2012, Nat. Medecine 2007, J. Immunol. 2008). In the last 5 years, the team published 132 original articles and 65 reviews, 21 of them published in journals with an impact factor >10. The team leader has a very good H factor (31) as well as his senior researchers.

Assessment of the unit's academic reputation and appeal

In the last 5 years, the team has obtained a national and international recognition as demonstrated by 22 invited international conferences, 10 oral communications and 14 posters at the international meetings. They contribute to national (ANR, INSERM, AERES) scientific evaluations. The group is well known in the IgAN international community and was founding member of an International Network on IgA nephropathy. The team leader is the coordinator of the laboratory of excellence named Institute of Inflammatory Disease "Inflamex" and was founding member of the DHU Fire. Three members of the group have received awards (Award for absolute best abstract in WCN congress in 2009); Award Jacques Oudin in Immunology (in 2010) and Award for best abstract in ERA-EDTA congress in 2012.

Assessment of the unit's interaction with the social, economic and cultural environment

The team is a founding member of the active start-up Inatherys. This company attempts to produce therapeutic monoclonal antibodies in inflammation and cancer and has received grants from the OSEO as well as ANR BiotecS. Moreover, the team has filed 3 patents and has had partnership with several industrial companies: Biomarin, CSL Behring, Bioxtal, Novimmune, Sanofi. One PI is a member of the committee of Rein Echos, a "magazine" for patients translating new discoveries in a didactic manner.

Assessment of the unit's organisation and life

The group is well structured and includes 9 senior researchers, 4 post-docs, 7 students, 3 engineers & technicians and is incubating an Atip-Avenir group constituted of 4 researchers. The team meeting is organized once a week to discuss ongoing projects, collaboration and critical aspects. Students and PhD are well integrated in the group and their feeling is very positive. In the last 5 years, funding was regularly obtained from various sources (ANR, INCA, FRM, ANR, Nephrochain, Novoimmune, CLS Behring, etc.) for a total of 3 million euros and this achievement underlines the potential of the group to self-sustain its research over the next 5 years.

Assessment of the unit's involvement in training through research

Team members have trained 12 PhD students and 14 Master students since 2007 and are involved in teaching activities either by directly supervising master and PhD students and/or giving lectures in Universities for medical students. More recently, the team leader within the frame of the Labex Inflamex has participated in the set-up of a new master.

Assessment of the five-year plan and strategy

The project focuses on the pathophysiologic mechanisms involved in IgA nephropathy and is divided in four workpackages. The project is original, coherent and would like to expand previous findings.

WP1 would like to search for biomarkers able to classify patients according to their susceptibility to progress to End stage kidney disease (ESKD). On the basis of their previous studies, they will examine the prognostic value of circulating hypogalactosylated IgA, sCD89/IgA, IgG/IgA immune complexes in HSP patients showing three different phenotypes (isolated cutaneous purpura or associated with minimal or severe renal disease). The access to the clinical cohort Nephrotest reinforces the strategy of this aim as it will allow validating the results in a larger cohort of patients with various stages (2 to 5) of CKD.

WP2 will focus on TGase2 as a major determinant of IgA related diseases. This hypothesis will be tested in the presence or absence of TGase2: they will generate α 1KI-CD89Tg mice crossed with TGase-/- mice or with transgenic mice overexpressing TGase2. This model will be used to test the implication of alimentary antigens in the breakdown of oral tolerance. The team has already developed the ¤1KI-CD89Tg mice and the committee is confident that they will be able to develop ¤1KI-CD89Tg mice crossed with TGase-/- mice or with a transgenic mice overexpressing TGase2 since the tools are available in the lab. The experimental design has been well constructed and may shed light on the role played by the intestinal-kidney axis in the pathogenesis of IgAN. Interestingly, in the same WP2, the team will evaluate the deleterious role of testosterone in IgAN since there is a male preponderance of this disease (75%). Finally, in this WP2 the team will study in the α1KI-CD89Tg mice the role played by infections (bacteria or virus) in the development of glomerulonephritis. Preliminary results showed that staphylococcal enterotoxin B (SEB) increases IgA deposits in this model and renal inflammation while influenza infection (H1N1) decreased them. This finding opens new avenues of investigation on the role played by different infections in IgAN and the strategies proposed by the team may help to understand this unresolved question.

WP3 will be developed by the Avenir group and will focus on the role played by miRs in the regulation of inflammation and their implication in inflammatory kidney diseases with a particular focus on epithelial cells. A weakness of this WP3 is that does not fit well with the other WPs. Indeed, it would be interesting to study miRs in the mouse models that will be used to test the role played by TGase2 and the implication of alimentary antigens in the breakdown of oral tolerance. It could strengthen the role played by TGase2 in the pathogenesis of IgAN.

The WP4 will deal with immunotyrosine activatory motif (ITAM) activation. The team in collaboration with team 2 of the CRI was able to show that the induction of ITAM signal with monomeric IgA decrease renal inflammation. The research plan proposed may open new therapeutic avenues in IgAN.

The team had a good performance in the last five years and has the potential and the expertise to perform even better in coming years. The group has developed a very good animal model of IgAN that, crossed with TGase-/- mice or with a transgenic mice overexpressing TGase2, may address many questions reported in the project. The team has all the cellular tools and the expertise to complete the task. However, in some parts, this project may be more focused on IgAN and small heterodimer partner (SHP) and on the role played by intestinal microbiota and mucosal infections (viral vs bacteria). The role played by the gut-kidney axis in the pathogenesis of IgAN and SHP is very challenging. Moreover, the Avenir-group should try to better integrate his research strategy on miRs with the main target of the project.

Conclusion

- Strengths and opportunities

The project, constructed on previous well-published data, is very interesting and challenging. The group is trying to address key research questions in the pathogenesis of IgAN. There is an excellent history of national and international contacts and productive collaborations, and the team is well integrated within the Center. There are many possibilities to strengthen collaborations inside and outside the center, and to engage in technological developments. The team is internationally recognized in the IgAN field and possesses all the expertise and the potential to achieve outstanding results in the next 5 years.

- Weaknesses and threats

The main weakness is that the broad and the ambitious program of activities proposed by the group will diminish the chances of in-depth research on the main topic, IgA nephropathy. Moreover, the Atip-Avenir group should focus more on IgAN and orchestrate WP3 among the other WPs.

- Recommendations

To conclude the project, based on previous well-published data, is ambitious, challenging and wants to address key research questions in the pathogenesis of IgAN, an inflammatory kidney disease. The team is encouraged to sort out the most pressing needs, to hierarchize the priorities and to propose a more focused work plan in line with the current interests of the group.

Team 2 : Mast cells and basophils in inflammation and remodeling

Name of team leader: Mr Ulrich BLANK / Mr Pierre LAUNAY

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3 (1.1)	4 (1.4)	3 (1.1)
N2: Permanent EPST or EPIC researchers and similar positions	4 (4)	4 (4)	4 (4)
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2 (2)	3 (2.3)	2 (2)
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**9**	**11**	**9**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	5	6

• Detailed assessments

Assessment of scientific quality and outputs

One of the team leaders is recognized as an expert in early and late phases of mast cell signaling and led this theme of research with two Blood and recently 1 Kidney Int published as a first or last author. He was also strongly involved in the impact of signaling through IgAFc receptors and co-signed with the team 1 leader as the penultimate author 1 Blood, 1 Eur J Immunol, 1 J Immunol. He wrote numerous reviews including two Immunological Reviews, a major review in the field of immunology. He contributed to several good papers (1 Blood, 1 J. Exp. Med, 1 J. Clin Invest, 1 J Biol Chem) among others. The second team leader is an expert in calcium signaling with a focus on the role of the TRPM4 channel . He published 1 Nat Immunol in 2008 after coming back from his post-doctoral training period; he also contributed to a Nat. Med (2010). He was awarded an Avenir group.

The two other permanent researchers have also a very good publication record.

Assessment of the unit's academic reputation and appeal

Members gave 28 invited conferences in international Meetings. They were members of organizing committees of three meetings. They contribute to national (ANR) scientific evaluations.

The group demonstrated its strong implication in international science regarding autoimmune lupus and mast cell basophil functions. Indeed, they were founding members of an European network on mast cell/basophil biology, of a national network on lupus, and the Labex Inflamex. They are founding members and animate the DHU Fire They recruited 2 post-doctorants. This demonstrates the important role of the group at both national and international levels in this field with important implications in the treatment of autoimmune and allergic diseases.

Assessment of the unit's interaction with the social, economic and cultural environment

The team is a founding member of the active startup Inatheris and got 2 patents and 4 licensing contracts.

Assessment of the unit's organisation and life

Team 2 includes 4 permanent scientists, 1 MCF, 4 PUPH/PH/PHU, 2 postdocs and 8 students, and two engineers. Two groups lead by the team leaders respectively will constitute the team.

It is difficult to evaluate the managing potential of the entity that did not exist previously. However all the researchers and some students participated actively in the discussion. It seems clear that leaders jointly decide to focus their research to strengthen the coherence of their areas of research.

Assessment of the unit's involvement in training through research

The leaders trained 6 PhD and 10 masters. 5 PhD students and 3 Msc are enrolled in the new research program. The members are also strongly implicated in teaching activities. They are co-organizers of a new master in inflammation, which is in accordance with the Labex and the theme of the CRI.

Assessment of the five-year plan and strategy

The projects deal with the biology of mast cell/basophils; the implication of basophils in lupus and of mast cells in inflammation related to the expression of the chymase MCP4. This project is original, coherent and relies on previous findings of the staff. They constructed mice in which mast cells and basophils express the Tomato marker and therefore can be tracked. In addition, the administration of diphtheria toxin allows the depletion of these cells and with differential time-lapse for the reconstitution of these cell subsets. These animals represent an invaluable tool for studying the trafficking and the role of these cells in lupus and nephropathies. However, the team leaders propose to use these mice in a large number of experimental models of nephropathies, which rationale is not always well defined. They will also use numerous other knockout mice.

Regarding the mast cell biology, the group is interested by both early and late signaling events implicated in cell degranulation with an emphasis on both PLSCR1 in LAT and calcium dependent signaling and the role of SNARE/ SNARE regulators on granule fusion and degranulation (WP1). The tools have been constructed and are available in the lab. The experimental design appears interesting, promising and well done. The committee is convinced that the team skills will be useful in this part. However, this group decided to focus on the potential role of STIM, ORAI and TRPM4 in mast-cell basophil calcium increase using the appropriate conditional Knock Out. This group has access to the animal models, the cellular tools and has all the expertise to complete the task. However, this project is presented as one of the numerous questions to be solved. The team has also access to PLSCR1KO mice and can reconstitute KO mast cells with wild type or mutated PLSCR1 in order to demonstrate how the enzyme interferes with mast cell signaling. They also plan to use animal models for testing the role of PLSCR1 in allergy. A miRNA putatively important for basophil mast cell functions will also be explored.

The WP2 deals with the role of basophils in lupus nephritis and of mast cells in tissue modeling while the WP3 investigates the role of mast cells and basophils in the sepsis and skin inflammation. Once more, the questions are pertinent and the group has the competence, the expertise, and the means for solving them. However, each question is a full project needing a lot of investment and focusing on some parts would be more productive.

Conclusion

- Strengths and opportunities:

The projects are ambitious, well constructed, with financial funding and experts in the field. They rely on data obtained and already published by the group. They are well integrated in the scientific politics of the CRI. The senior scientists of this new team have already published together, are experienced and used to coordinate their efforts. They succeed to create the original cellular and animal tools required to complete the work.

- Weaknesses and threats:

The members want to explore the role of mast cells and or basophils in inflammation and remodeling using numerous models (partial ureteral obstruction, anti-GBM, ischemia reperfusion, lupus,…), various (although pertinent) knockout models. The strategy might be improved with a focus on some models at least in a first time. Perhaps a more hierarchized strategy would be more powerful. In addition, to define more precisely who does what could allow reinforcing the projects and the links between the members of the group.

- Recommendations:

To conclude: the project is interesting, multi-focused, well conducted, useful, with therapeutic implications in inflammatory diseases, the main topic of the CRI. It will benefit from the important and diverse scientific cultures of the partners. It will need to hierarchize the priorities and perhaps to better integrate the skills of each partner in the different tasks.

Team 3 : Phagocyte, NADPH odysases and immunogenetics in systemic inflammation

Name of team leader: Mr Jamel EL BENNA

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1 (0.5)	3 (1.5)	3 (1.5)
N2: Permanent EPST or EPIC researchers and similar positions	5 (5)	5 (5)	5 (5)
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2 (1.5)	2 (1.5)	2 (1.5)
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**8 (7)**	**10 (8)**	**10 (8)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	6	8

• Detailed assessments

Assessment of scientific quality and outputs

This team has a large experience in the molecular and cellular mechanisms involved in reactive oxygen species production by NADPH oxidases (NOX) and their impact on inflammatory diseases. Its work has been mainly focused on the regulation of NOX2 in neutrophils and its epithelial homologue NOX1. Very interesting and solid results have been obtained concerning the molecular mechanisms of NOX activation by proinflammatory cytokines, the role of phagocyte NOX2 in ROS production in RA patients and the identification of novel mechanisms of regulation of NOX2. In addition, the team developed novel antibodies recognizing low levels of phosphorylated $p47^{PHOX}$ that could facilitate the characterisation of the mechanisms of regulation of NOX in physiological situation and in inflammatory diseases. Team members have published good to very good papers in the field of NADPH oxidases in the physiopathology of systemic inflammatory diseases(SID): since 2007, 180 original article and 30 reviews (27 articles with IF > 9, Nat Cell Biol, J Immunol, J Hepatol, J Exp Med, PNAS, FASEB J, Blood, EMBO JJ, Diabetes,..). Very solid mechanistic studies, e.g. on the interesting inhibitors interaction of PIN1/p47 have been performed.

Assessment of the unit's academic reputation and appeal

The members of the team have given 33 invited conferences, 50 oral communications and 130 posters. The team participate to different networks including the Labex INFLAMEX, le DHU FIRE, the National Network on CGD and RA and the European COST on ROS. The members of the team are part of national and international evaluation boards (ANR, AERES, FRM, Swiss Science Foundation, Belgium FNRS,..).

Assessment of the unit's interaction with the social, economic and cultural environment

1 patent and the team leader is co-founder of the start-up “Redoxylab”.

Assessment of the unit's organisation and life

The team has been renewed in 2009 under the direction of J. El Benna at the UMR773. At present, the team includes 2 DR2 CNRS, 2 CR1 INSERM, 1 CR1 CNRS, 4 MD-PhD, 1 postdoctoral fellow, 4 PhD students and master students and 2 technicians. All the members interact for the six projects of the team. The team has collaboration with 7 teams of the CRI.

Assessment of the unit's involvement in training through research

Since 2007, the team has trained 11 PhD students and 10 Master students. The members are involved in various teaching activities.

Assessment of the five-year plan and strategy

This project focus on NADPH oxidases, the only known dedicated reactive oxygen forming enzyme family. This team aims at understanding the role of phagocytes and NADPH oxidases (NOX) in the physiopathology of systemic inflammatory diseases (SID). Immunogenetic approaches will be considered in autoimmune SID such as rheumatoid arthritis (RA) and systemic sclerosis (SSc) with the aim to better define the genotype-phenotype association. Production of reactive oxygen species (ROS) by NOX2 and NOX1 is required for host defence and cell signalling. However, excessive ROS production (by NOX?) is claimed to induce severe tissue injury that may contribute to physiopathology; whether SID is part of that is however not really clear and proven. The majority of their work now focuses in great detail on deciphering mechanisms underlying the activation of NOX, with the conviction that this would be essential for identifying novel therapeutic targets in SID. The project aims to understand the regulation of a single isoform, NOX2, in neutrophils, monocytes, macrophages, dendritic cells and epithelial cells by pro- and anti-inflammatory agents and to translate basic findings to animal models of inflammation, human phagocytic disorders and human SID. The team also plans to study gene polymorphism of NOX and a selected subset of regulators in RA and SSc. It is unclear whether the cohorts are sufficiently well designed to be used for this purpose and unbiased. The project aims to combine basic and clinical research by involving collaborations with teams in the CRI and hospital divisions, particularly on the role of IgA in neutrophil homeostasis. Evidence that one of these five (or – when including DUOX1/2- seven) genes is involved in RA or IBD, thus a real therapeutic target is lacking. The very solid mechanistic studies performed on the interesting inhibitors interaction of PIN1/p47 but translational issue and what the next steps are in this axis remains unclear. KO approaches are not proposed, other NOX isoforms are not considered, and the drug discovery part remains fuzzy.

Conclusion

- Strengths and opportunities:

The team has a strong know-how in the field of investigation.

Both pre-clinical (in vivo and in vitro) studies and clinical studies will be performed.

• The association between MDs and PhDs is a good opportunity to exchange specific points of view or strategies of intervention.

• The technical approaches and the models are in general original and up to date.

- Weaknesses and threats:

• The projet is large and should be more focused.

• More post-doctorants should be recruited.

- Recommendations:

• The team has to recruit highly qualified and productive international post-docs or specialists in one of the field of investigation; only when this is achieved the team is really an international top lab.

Team 4 : Heme, iron and inflammatory diseases

Name of team leader: Mr Laurent GOUYA

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	9 (2.9)	7 (2.3)	8 (2.6)
N2: Permanent EPST or EPIC researchers and similar positions	2(2)	1(1)	1 (1)
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3 (2.3)	5 (4.3)	2 (2.0)
N6: Other contractual staff (without research duties)	9 (2.9)	7 (2.3)	8 (2.6)
TOTAL N1 to N6	**23 (10.1)**	**20 (9.9)**	**19 (8.2)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	6	7

• Detailed assessments

Assessment of scientific quality and outputs

The proposed team follows the way of the previous team, from the CRB3, which was entitled iron and heme synthesis: genetics, physiology and pathology. The team has a long history in research on heme, iron metabolism, and related diseases. This includes especially porphyria, microcytic anemia and genetic hemochromatosis. Strong links exist between researchers and clinicians involved in diagnostic of rare anemia and other hematological disorders. The team has published several important papers in journals with high IF as main investigators (Gastroenterology, Blood, Am J Hum Genet, Lancet).

Assessment of the unit's academic reputation and appeal

Senior members of the team were invited to give a large number of conferences in international meetings. In addition team members are associated to the GR-Ex laboratory of excellence. They also previously created the European Porphyria Network and are in charge of the Network responsibility. The team also coordinates a European network for rare and congenital anaemia. Two post docs were involved in the team.

Assessment of the unit's interaction with the social, economic and cultural environment

A start-up emerged recently from two members of the previous team, in collaboration with another team of the Centre de Recherche Biomédicale Bichat-Beaujon (CRB3).

Funding was obtained from companies for specific studies.

The team interacts strongly with the French association of patients with porphyrias.

Members of the team have an internationally recognized expertise.

Assessment of the unit's organisation and life

The permanent core of the team implicates mainly 8 medical (HU and H) researchers, two full time permanent researchers (one emeritus), two assistant professors and one technician. One post doc and 4 PhD students are participating also. It is noteworthy that funding was regularly obtained from various sources (Europe, ANR, PHRC). However, for the next years, there is no mention of major funding obtained by the team leader.

Assessment of the unit's involvement in training through research

Members of team have directed 7 thesis and 15 Master 2. In addition they are also strongly involved in erythropoiesis and iron courses within the European School of Haematology. Members of the team are involved in the teaching and in the teaching organisation of master courses (Master Sciences de la vie et de la Santé).

Assessment of the five-year plan and strategy

The main objective of the proposed team deals with the characterization of relationships between heme, erythropoiesis, iron metabolism, and inflammation, with tasks devoted to characterization of: i) the impact of kidney inflammation/infection on iron and hepcidin (the iron regulator) metabolism, and their influence on erythropoiesis, ii) the impact of erythropoiesis on hepcidin, by taking advantage of rare genetic diseases, including Blackfon Diamond anemia and porphyria, especially acute intermittent porphyria leading to oxidative stress and inflammation; iii) the relationship between heme supplementation during acute intermittent porphyria and crisis recurrence in a context of inflammation, aiming to identify new therapeutic molecules.

Regarding scientific objectives of the team in the presented centre, hepcidin which is modulated by inflammation as well as its impact on erythropoiesis, appears as an essential target for the project and new original hypothesis will be explored. Regarding the relationship with heme and erythropoiesis, the project is based on a very strong clinical and biological expertise. The study of a large number of scientific questions is planned. This will require a large panel of cellular and animal models, specific methods and high throughput technologies. Despite the fact that they are accessible within the team or through collaborations, part of this project could perhaps be more centered on inflammation, regarding the focus of the CRI and the low number of full time researchers.

Conclusion

- Strengths and opportunities:

The team has a very strong recognised expertise in the field of iron metabolism and related disorders, especially in rare genetic anaemias. They already engaged researches on inflammation, hepcidin and iron metabolism thus dealing with a scientific question of major interest.

They benefit of large cohorts of patients with databases and biological samples for rare anaemias and collaboration with other teams of the CRI regarding patients with inflammation.

They have well established collaborations useful for the project both with clinical and basic teams especially in Europe.

They have already developed models useful for the project.

- Weaknesses and threats:

The team leader has a low rate of publications during the last years. To date, the proposed team leader is associated to 4 publications from 2007 with one as first author, thus illustrating the current lack of positioning of the proposed team leader as a key opinion leader in the field.

The focus of the project on inflammation could be improved especially for rare anemias.

The full time researcher number is very low.

- Recommendations:

The team has to better define the strategy for the team leadership.

Regarding the size of the team compared to the objectives as well as the global objectives of the CRI, it could be useful to focus efforts on inflammation. Interactions with other teams of the CRI involved in characterization of inflammatory processes could be emphazised.

It could be also useful to reinforce the team with at least one young full time researcher.

Team 5 : Innate immune responses in the child: role in viral infections and graft versus host reaction

Name of team leader: Ms Sophie CAILLAT-ZUCMAN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	None (creation)	7 (2.1)	7 (2.1)
N2: Permanent EPST or EPIC researchers and similar positions	None (creation)		
N3: Other permanent staff (without research duties)	None (creation)		
N4: Other professors (PREM, ECC, etc.)	None (creation)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	None (creation)	2 (2)	2 (2)
N6: Other contractual staff (without research duties)	None (creation)		
TOTAL N1 to N6	**None (creation)**	**9 (4.1)**	**9 (4.1)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	None (creation)	
Theses defended	None (creation)	
Postdoctoral students having spent at least 12 months in the unit	None (creation)	
Number of Research Supervisor Qualifications (HDR) taken	None (creation)	
Qualified research supervisors (with an HDR) or similar positions	None (creation)	5

• Detailed assessments

Assessment of scientific quality and outputs

The team leader has a strong experience in the innate immune responses especially in children during infections and graft-versus-host disease. The group focused on the ability of pathogens to down-modulate NKG2D-mediated signaling and NK functions leading to publications of good quality (two PloS Pathogens, 1 Arthritis Rheum, 1 Journal of Autoimmunity, 1 Transplantation). The team also contributed to publications in Immunity, Gastroenterology, 2 Blood, 2 Plos Pathogens.

Assessment of the unit's academic reputation and appeal

The leader of the team was recruited as PUPH in Robert Debré Hospital in 2011. Members of the team gave 13 invited presentations in International conferences. The team is member of the French Network on Graft-Versus-Host Disease and has recruited 1 national post-doc.

Assessment of the unit's interaction with the social, economic and cultural environment

The team is a member of the Labex Inflammex and got one patent with an exclusive USA licence.

Assessment of the unit's organisation and life

Team 5 composed of 7 PUPH/PH/PHU, 1 post doc and 2 students, and two assistant engineers Is located in Hôpital Robert Debré with a strong implication in Clinical Research. The team has strong expertise in the innate immune response in infected and transplanted children and will continue on this path. Four pediatricians interested in immunology will further strengthen the group. The team also plans to recruit a scientist, a point important for effectively completing the projects.

Assessment of the unit's involvement in training through research

The leader trained 5 PhD and 5 masters. 1 PhD student and 1 Msc are enrolled in the new research program. The members are also strongly implicated in teaching activities.

Assessment of the five-year plan and strategy

The project deals with three axes of research. The first one is logical and aims to understand how NKG2D, IL-15 and PGE2 interact in NK cells since the team demonstrated that chronic viral infection can impair NKG2D signaling, IL-15-induced NKG2D expression and IL-15-mediated survival and proliferation of NK cells through PGE2 and TGF production. The approaches are quite systematic phosflow, signaling pathway finder, phospho-immunoreceptor arrays. All cellular models are available, the funding is obtained and the team established appropriate collaborations. The team has recently shown that viruses may cause PD1 expression on NK cells leading to an exhausted phenotype (NK cells are activated but hypofunctional). They now propose the identification of viral sequences involved, to characterize how PD1 impacts signaling in NK cells based on the analysis of phosphosignaling in NK cells transduced with PD1 transfectants and to determine if anti-PD1 treatment can restore NK functions which would have obvious clinical implications especially in patients transplanted with bone marrows.

The second project is more risky with the underlying idea to investigate the mucosal associated innate cell ontogeny by extensive phenotypic analysis in the blood of neonates (according to the gestational age, the use of antibiotics and the microbiota composition). The use of blood for studying Mucosal-Associated Invariant T (MAIT) , which marker to be used and the determination of the composition of the intestinal flora and its eventual relationship with the numbers of MAIT may cause problems of interpretation and risks to be inconclusive. The team leader is in charge of large cohorts of children suffering from graft versus host disease (GVHD) and the analysis of MAIT in mucosa can be more promising than the former study. However, how will be performed the analysis of the flora needs to be clearly anticipated. The third project is ambitious, novel and exciting. It aims to explore the potential involvement of autophagy in GVHD. The team has access to patient samples but also to animal models of GVH (by using mice KO or not for ATG8) to decipher if macroautophagy is enhanced during GVHD, which cells are implicated, the consequences on the alloreactive response and on the inflammatory response. If autophagy participates to GVHD outcome, the manipulation of this process based on the use of rapamycin or other drugs would be of interest in therapy.

Conclusion

- Strengths and opportunities:

The projects are ambitious, partially based on previous results. The projects obviously deal with inflammation the main topic of the CRI. The team has access to large cohorts of patients, is well-funded, and has a very good expertise in the analysis of the innate immune response. The analysis of MAIT ontogeny and of its association with inflammatory diseases as such GVH is challenging but may increase our knowledge about GVH associated inflammation.

- Weaknesses and threats:

Team 5 is located in Robert Debré Hospital far away from the CRI. The members need to find a convincing way for successful integration in the CRI (effective collaborations, participation to animation and life of the CRI). The members want to recruit a top scientist to reinforce their research strength and the committee thinks that it is important especially for completing the third work package dealing with autophagy.

- Recommendations:

To conclude: the project is interesting, solid, based on strong past data, with potential implication in therapy of the GVHD. An effort is needed for better shaping the analysis of MAIT ontogeny /functions and its association with the gut flora composition. An expert will be needed to manage the third project.

Team 6 : Intestinal Inflammation

Name of team leader: Mr Eric OGIER-DENIS / Mr Jean-Pierre HUGOT

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4 (1.8)	7 (3.2)	4 (1.8)
N2: Permanent EPST or EPIC researchers and similar positions	3 (3)	3 (3)	3 (3)
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**7 (4.8)**	**10 (6.2)**	**7 (4.8)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	5	7

• Detailed assessments

Assessment of scientific quality and outputs

The team consists of researchers who, because of their long experience and high scientific profile, are well known in the field. In particular, some of them are well known for their research on the genetics of inflammatory bowel disease (see discovery of NOD2 mutation in Crohn's disease). Their scientific production is of high quality. Over the past five years, they published 128 original peer-reviewed articles, including 28 articles as first or last author (J Hepatol, Mol Cell Biol, Cell Death Diff, Gastroenterology), and 4 reviews articles.

Assessment of the unit's academic reputation and appeal

The team has a high national and international visibility, both in terms of presence in important meetings (15 invitations to international conferences) and publication of a number of original papers. In addition, the team is also known for its prestigious collaborations and well-harmonized collaborations in the project with the other groups of the CRI.

Assessment of the unit's interaction with the social, economic and cultural environment

Given the goal of the project with the aim to clarify some important aspects of inflammatory bowel disease (IBD) (pathogenesis and drug discovery), the results of this research can have a significant impact on both the scientific community and the media. The team has already obtained 3 patents and is involved in a start-up.

Assessment of the unit's organisation and life

The team is well organized and includes several profiles including basic research and clinical/university PIs. This combined basic research and clinical environment would represent excellent fertile ground for training young doctors and researchers.

Assessment of the unit's involvement in training through research

Several members of the team have important teaching activities. This should promote an adequate and qualified training of young researchers already included in the team. In addition, the high scientific profile of the team itself and of the present project, should attract other young researchers.

Assessment of the five-year plan and strategy

The project is deliberately multidisciplinary with a multi-scale approach from molecular level to patients. Its aim at identifying the genetic and environmental risk factors involved in IBD and to define their interactions.

The aims of the projects are ambitious, whose possible results could have a significant impact both in terms of basic science and clinical relevance. It is split into 4 main sub-projects (interaction between genetic and environmental risk factors in IBD; new animal models for IBD; dissecting the molecular mechanism of gut inflammation; exploration of new therapeutic options).

Moreover, they are perfectly integrated and further supported by an existing IBD BioBank containing colonic and intestinal samples. Finally, particularly significant is the fact that it is a translational research project from bench top to bedside and vice-versa.

Conclusion

- Strengths and opportunities:

The experience in this field, the variety of activities played by each team member, the presence of students and young researchers, the completeness of the research project (from research to clinical practice), are the main strengths of the project. The technical approaches and the models are very original, up to date, and with a significant impact on research and clinical practice in the next years.

- Weaknesses and threats:

Only one post-doctorant has been recruited.

- Recommendations:

The committee welcomes and recognizes the high interest of the team's projects. It is suggested to increase the number of the post-doctorants, and researchers in training.

Team 7 : Inflammatory and stress responses in chronic liver diseases

Name of team leader: Mr Richard MOREAU

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4 (1.2)	4 (1.2)	4 (1.2)
N2: Permanent EPST or EPIC researchers and similar positions	7 (7)	6 (6)	7 (7)
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4 (2.0)	4 (2.0)	4 (2.0)
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**15 (10.2)**	**14 (9.2)**	**15 (10.2)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	7	7

•Detailed assessments

The team program is in the continuity of the previous team, member of the CRB3, which was dealing with the study of complications of cirrhosis and vascular diseases of the liver.

The project is motivated by results obtained during the last years, demonstrating the role of innate immunity and inflammation in the development and prognosis of cirrhosis. It fits very well with the objective of the centre for research on inflammation.

Assessment of scientific quality and outputs

The team published regularly during the past years including 67 original articles since 2007, 23% appearing in journals with IF>10 (Hepatology, J Hepatol, Blood, Gut, Gastroenterology, Ann Intern Med, N Engl J Med,..). Members of the team are most often present in key position such as first or last author. Publications also includes 32 reviews. There is no publication in very high impact factor journal with members of the team as principal investigator.

Publications of the team contribute to the development of new concepts on relationships between innate immunity, hepatic vascular disturbances and the development of hepatic lesions during chronic liver diseases.

Assessment of the unit's academic reputation and appeal

The team has an internationally recognized expertise.

Members of the team gave a large number of invited conferences both at international (85) and national levels. They are involved in a large number of multicenter research projects, including participation in the new laboratory of excellence Labex Inflamex. They are also members of the new DHU Unity devoted to hepatology and gastroenterology.

The team has been involved in the organisation of international meetings in Europe and in the USA. They are also involved in the board of Scientific Societies and of Journals in the hepatology field. They are involved in the European network of hepatic vascular diseases.

During the past years 2 Post-docs were trained in the team.

Assessment of the unit's interaction with the social, economic and cultural environment

Members of the team are involved in the coordination of large studies on cirrhotic patients at the european level, with both basic and clinical aspects. They are also in charge of the French reference network for vascular disorders of the liver. Moreover, several team members are involved in the review panels of national agencies (e.g., ANR, PHRC, HAS) and international agencies (Welcome Trust UK, FNRS, FWO,…).

They have relationships with patient associations.

The team has also filed one patent.

Assessment of the unit's organisation and life

The team already exists and organisation of the team allowed good publications. Funding has been obtained by different full time researchers of the team, thus facilitating the development of the proposed research thematics.

It is noteworthy that during the past years, there was no major renewal of the team staff, although some people have now retired.

Assessment of the unit's involvement in training through research

The members of the unit trained 7 PhD students and 19 Master 1 or 2 students. The PhD students/HDR ratio is not very high. Members of the team have also teaching activities in Master courses and in advanced courses in hepatology, including European courses.

Assessment of the five-year plan and strategy

The five-year strategy is focused on the characterization between innate immunity, inflammation and the development/complications of liver diseases. In addition, studies on relationship between hepatic vascularization and hepatic lesions are also planned in the context of cirrhosis on the light of both new data on survival of cirrhotic patients under anticoagulants and the follow-up of patients with thrombosis of hepatic vessels. The project benefits of large cohorts of patients with annotated biobank.

The project includes the investigation of the innate immune reponse during cirrhosis, the hepatic tolerance during cirrhosis, when facing to immune challenge-with special regards on unfolded protein response (UPR). In addition, translational and clinical researchs plan to transfer results to patients, including the evaluation of anticoagulant therapies.

Regarding inflammation and immune response, most of the experiments are planned on peripheral blood cells and plasma. It could be valuable to also investigate whether or not the resident hepatic immune cells have similar profiles. This is likely of importance in a context of vascular disturbance and potential specific responses of Kupffer cells, for example. The panel of animal models used could be extended to more acute or immunodeficient ones. Knock-out models could be used, some genes of interest being already pointed.

Investigation of the relationship between anticogulant use, inflammatory status and hepatic lesions could be more strongly investigated.

Conclusion

- Strengths and opportunities:

The team has had a strong expertise for many years in the studied field and contributed to the development of new diagnostic and therapeutic approaches in hepatology. The proposed project deals with important questions regarding liver diseases and their complications, both having strong personal and economical impacts.

The team associates clinical and basic scientists, including 6 full time researchers. This is an opportunity to pursue and develop strong translational studies.

The members have access to large cohorts of patients, with biobanks and annotations. Members of the team are also involved in a large prospective study which open panels of possibilities.

Involvement of the team leader and senior members of the team in large French and European networks will facilitate the development of original studies involving patients.

- Weaknesses and threats:

No publication in top-notched journals (very high impact factor) has been gathered in.

The vascular part of the project is not very well connected with inflammation.

The team did not include a high number of external post-doctorants during the last years

Studies are mainly focused on PBMC's, it would be interesting to consider other cells (e.g., at the tissue level)

- Recommendations:

Improvement of the relationship between vascular thematic and inflammation has to be made.

The team has to plan to develop other animal models for innate immunity studies in inflammation.

The team has to think about the improvement of valorization.

Strategy to anticipate team leadership evolution in 5 years has to be considered.

Team 8 : Physiopathology and treatment of viral hepatitis

Name of team leader: Mr Patrick MARCELLIN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3 (0.9)	3 (0.9)	3 (0.9)
N2: Permanent EPST or EPIC researchers and similar positions	2 (2)	2 (2)	2 (2)
N3: Other permanent staff (without research duties)	-	-	-
N4: Other professors (PREM, ECC, etc.)	-	-	-
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7 (7)	6 (6)	8 (8)
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**12 (9.9)**	**11 (8.9)**	**13 (10.9)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	2	2

Detailed assessments

Assessment of scientific quality and outputs

The team is known for its national and international prestige of the highest level. Over the past five years, 106 original peer-reviewed articles (Gut, Hepatology, Ann Intern Med, J Hepatol, N Engl J Med, Hepatology, Gastroenterology, Lancet, Lancet Infect Dis) have been published including 74 articles as first or last author, and 36 reviews. Moreover, they have been invited in 34 (22 international and 12 national) conferences. The team follows large cohorts of patients with B and C hepatitis, and drives one of the largest international clinical trial center.

Assessment of the unit's academic reputation and appeal

The team has a high national and international visibility, both in terms of presence in important meetings and publication of a number of original papers. On the contrary, the characteristics of the proposed project does not seem to blend well with the other groups of the CRI.

Assessment of the unit's interaction with the social, economic and cultural environment

Despite the high scientific reputation of some of its members, the team is self-referential and disconnected in comparison to the other groups of the CRI. Some members had been involved in panels for clinical practice guidelines on management of Hepatitis B or in Hepatitis Network Ile de France Nord. The team has obtained several contracts from ANRS, Sidaction, Medicen or from foreign ministry through cooperation with China.

Assessment of the unit's organisation and life

The number of permanent professors and researchers is too small, even if the team includes three post-docs. It should be noted that the team is potentially attractive to young doctors in training.

Assessment of the unit's involvement in training through research

The members of the team have important teaching activities. This will promote an adequate and qualified training of young researchers already included in the team. However, the number of young permanent researchers should be increased.

Assessment of the five-year plan and strategy

The aim of the project is to continue to develop a strong activity in clinical trials of new drugs and reinforce translational research for a better understanding of the physiopathology and the response to new therapies in chronic hepatitis B and C.

The project is feasible and splitted in 4 sub-works (clinical trials of new antivirals; new markers for monitoring antiviral therapy with viral kinetics and predictors of response; HCV resistance to new drect antiviral agents; clinical application of molecular markers). The major drawback is that the team proposal delivers a project that appears in some way disconnected from the general purpose of the CRI.

Conclusion

- Strengths and opportunities:

The long and prestigious clinical experience in the field is the main strength of the project.

- Weaknesses and threats:

The project did not explore in depth the inflammation associated with chronic hepatitis and, therefore, relates poorly with the projects and groups of the CRI.

- Recommendations:

The committee welcomes and recognizes the interest of the team's projects. However, it is suggested to deepen research about the inflammatory processes associated with chronic hepatitis B and C. It is strongly suggested to increase the number of permanent researchers and training, and to improve crosstalk with the other team members of the CRI.

Team 9 : From inflammation to cancer in digestive diseases

Name of team leader: Ms Valérie PARADIS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	8 (2.4)	12 (3.6)	12 (3.6)
N2: Permanent EPST or EPIC researchers and similar positions	2 (2)	2 (2)	2 (2)
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	12	15	15

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	8	12

• Detailed assessments

Assessment of scientific quality and outputs

This team results from a merger of three research teams, which have made numerous important contributions to their respective fields during recent years. They have published their major breakthroughs in several very good disciplinary journals (Hepatology, Gastroenterology, J Hepatol, Clin Cancer Res, ...) and beyond (NEJM).

The team has published more than 200 papers in basic and translational research in 5 years and among them 40 were published in journal with an impact factor higher than 10. Moreover, they have contributed to more than 250 articles in clinical research.

Assessment of the unit's academic reputation and appeal

The team is part of the Labex Inflamex, several team members are involved in EU projects (4) and other multicenter research projects (ANR, PHRC). Several team members are experts for several national (AERES, INSERM, ANRS, CSS) and international funding agencies or committees and are members of editorial boards of top journals in their fields.

Within the future centre, the team has developed additional collaborative work between other teams.

The active recruitment of post-docs or international scientists has not been achieved (only two post-docs during the past period of 5 years).

It is noted that the participation in international congresses as invited speaker is quite high.

Assessment of the unit's interaction with the social, economic and cultural environment

Two patents have been obtained during the past 5 years. Several team members are in the advisory board or have collaborative work with pharmaceutical companies or biotechs. Moreover, several team members are involved in the review panels of national agencies (e.g., ANR, INCA, ANRS). Altogether the teams (previous) have obtained numerous grants for a total of more than 2.55 million euros.

Assessment of the unit's organisation and life

The organisation of the team is clear, including the leaders involved in each project and sub-projects. This team is mainly composed of PU-PH members, 1 DR Inserm and 1 CR Inserm. Whether the interactions between the different team members is adequate is unclear at this stage. However, given the organization of the previous team as well as the collaborative work that has been valorized (i.e., publications), one may anticipate that the expertise of each collaborator will strongly contribute to development of this novel team.

Assessment of the unit's involvement in training through research

The members of the team engage in important research training activities including 12 PhD thesis, 21 Master students. Moreover they have numerous teaching duties for medical and Master students, specialised modules or European scholarships.

Assessment of the five-year plan and strategy

This novel joint team will deal with basic, translational and clinical research in the field of inflammation, liver fibrosis and cancer in the digestive system. A key part of the project will be focused on the mechanisms or investigation of targets (OX1R, CXCR4) that they have recently identified. The main project is divided into 3 main work packages with specific aims and focus on inflammation, fibrosis, liver cancer in metabolic syndrome (WP1), G protein-coupled receptors (GPCR) and digestive diseases (WP2) and Clinical research trials (WP3). The project is ambitious and with a high risk / high gain profile. In general, the project is clear, timely, dealing with state of the art technical approaches or innovative models and they have a high potential for the valorization of their findings. Moreover, the projects are based on solid preliminary data. However, specific attention should be paid to the strategy focusing on the visceral adipose tissue and FABP4 which is less clear in this context. Although the panel of experiments and the animal model used in the context of the OX1R are evident, the animal models or the development of animal models coupling metabolic syndrome with liver carcinogenesis is less clear. The contribution of the visceral fat depots on the liver carcinogenesis (other than simple correlations) and finally acts as a key mechanism will be difficult to prove in this experimental settings. The combination of *in vitro*, pre-clinical *in vivo* and human studies is highly appreciated.

Conclusion

- Strengths and opportunities:

The team has a strong know-how in the field of investigation.

Both pre-clinical (*in vivo* and *in vitro*) studies and clinical studies will be performed.

The association between MDs and PhDs is a good opportunity to exchange specific point of views or strategies of interventions.

The technical approaches and the models are in general original and up to date (e.g. liver slices).

- Weaknesses and threats:

There are not novel post-docs recruited.

The strategy to investigate the link between fat depots and liver cancer is not clear; it is of utmost importance to urgently decide on the strategy that will be adopted and why.

Although most team members have published in the best journals in their fields, it would be interesting to think about the strategy of publication in order to publish in broad readership / interdisciplinary journals, including top-ranked journals. Both the novel team and the expertises (human and animal models) proposed here should contribute to achieve this goal.

- Recommendations:

The team has to recruit highly qualified and productive international post-docs or specialist in one of the field of investigation; only when this is achieved, the team is really an international top lab.

The strategy has to be clearly defined particularly regarding the way to investigate the putative role of the visceral adipose tissue and FABP4 with back-up strategies in case of failure.

The team has to focus on specific mechanisms both in animals and humans in order to avoid descriptive studies or correlative findings in the field of metabolic syndrome and cancer

The team has to outline a specific translation strategy (diagnostics, therapeutics) and back-up plans.

Team 10 : Gastrointestinal & metabolic dysfunctions in Nutritional Pathologies

Name of team leader: Mr André BADO

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4 (1.2)	6 (2)	4 (1.2)
N2: Permanent EPST or EPIC researchers and similar positions	2 (2,0)	3 (3)	2 (2)
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1 (1)	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**6 (3.2)**	**10 (6)**	**6 (3.2)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	5	7

• Detailed assessments

Assessment of scientific quality and outputs:

The team is known for its expertise in the field of gastrointestinal peptides, as shown by the publication in the last years of 122 original peer-review articles, of which as first or last author. Moreover, they published 15 original articles with IF above 10 (Diabetes, Gastroenterology, Lancet, N Engl J Med, Lancet Oncol,..).

Assessment of the unit's academic reputation and appeal

The team is composed of members whose national and international visibility is confirmed by a high-level scientific output, as well as their presence in many international conferences as experts. The composition of the team (many researchers, engineers, technicians, and students) also reflects the lively scientific activity, as well as their collaborations with other teams of the CRI or research groups outside.

Assessment of the unit's interaction with the social, economic and cultural environment

Considering the importance and popularity of the topic (obesity), a special interest from the media can be expected. Furthermore, the results potentially obtainable from this research can have a strong impact on lifestyle habits.

Assessment of the unit's organisation and life

The number of members constituting the team, as well as the complementarities in term of skills are assets to potentiate their research activities.

Assessment of the unit's involvement in training through research

The team members are experts in various areas of the topic in question. Both basic research and clinical PI allowed the team to train 10 Master1 and Master 2 students and 7 PhD students and to host 2 post docs.

Assessment of the five-year plan and strategy

The originality of the projects presented resides in the realization of a process by which experimental model leads to the clinical application, aiming to understand the physiological, cellular, and molecular basis of intestinal adaptation. The project aims at deciphering physiological, cellular and molecular basis of intestinal adaptation with combination of basic research approaches (animal and cellular models) and clinical and translational studies. The project has three workpackages: WP1/ studying intestinal adaptation in response to gastrointestinal surgery during obesity and massive small intestinal resection such as in short bowel syndrome (SBS); WP2/ studying the role played by the metabolic hormones leptin and insulin in intestinal adaptation in response to nutrients and metabolic status; WP3/ studying the temporal course and specific roles of diet-induced intestinal inflammatory change in mediating obesity ; WP4/ determining the intestinal adaptive responses to nutritional changes over liver and specific brain areas controlling feeding behavior.

The team will develop an experimental animal model of bariatric surgeries and SBS .The projects are ambitious, and potential results could have a significant impact both in terms of basic science and clinical relevance. For this reason, particular importance has the combination of *in vitro*, pre-clinical *in vivo* and human studies. Moreover, the variety of activities carried out by different members of the team, may facilitate further collaborations with other teams of the CRI and with other research groups.

Conclusions

- Strengths and opportunities:

The experience in this field, the variety of activities of each team member, the presence of students and young researchers, the completeness of the research project (from research to clinical practice), are the main strengths of the project.

- Weaknesses and threats:

The team lacks post-docs

Moreover, it is not clear how to the team will study the interaction between intestinal flora and intestinal inflammation.

- Recommendations:

The committee of experts appreciates and recognizes the interest of the team's projects. It is suggested to increase the number of post-docs, and researchers in training, as well as to improve the research about the role of intestinal microbiota as a link between intestinal inflammation and obesity.

Team 11 : Novel imaging biomarkers for inflammation, fibrosis and cancer

Name of team leader: Mr Ralph SINKUS / Mr Bernard VAN BEERS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	None (creation)	4 (1.2)	4 (1.2)
N2: Permanent EPST or EPIC researchers and similar positions	None (creation)	1 (1)	1 (1)
N3: Other permanent staff (without research duties)	None (creation)		
N4: Other professors (PREM, ECC, etc.)	None (creation)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	None (creation)	4 (4)	4 (4)
N6: Other contractual staff (without research duties)	None (creation)		
TOTAL N1 to N6	**None (creation)**	**9 (6.2)**	**9 (6.2)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	5

• Detailed assessments

Assessment of scientific quality and outputs

The team has published 160 peer reviewed articles over the last 5 year period, 57 first or last authors, 3 review articles all first or last authors This is an excellent balance taking into account the small size of the team, most of the publications were accepted in top journals of the sub speciality (i.e. for imaging: Radiology, Magnetic resonance in Medicine, but also Gastroenterology and PNAS).

Assessment of the unit's academic reputation and appeal

The group participated in 70 international meetings, with several invitations as plenary session speakers. One of the team leaders has been elected member of the prestigious Royal Academy of Medicine in Belgium. Other permanent members of the team have been elected in several national and international societies.

Assessment of the unit's interaction with the social, economic and cultural environment

The team has 1 patent, contributes to a start-up and has numerous contracts with industrial major partners in medical imaging (Philips, GE) or in contrast material for human or animal *in vivo* studies (Bayer Guerbet) including agreement for use of WIP molecular imaging new contrast agents.

Assessment of the unit's organisation and life

The Unit consists of a medical and a fundamental wing including Imaging Physicists and Pharmacokinetics experts. The organization of the team allows them a smooth and integrated process of working on animal model, phantoms, and *in vivo* human medical imaging.

Assessment of the unit's involvement in training through research

The team has attracted several young researchers most of them are already authors of a major paper.

Assessment of the five-year plan and strategy

The group aims at the development of new imaging biomarkers in the context of the study of inflammation, fibrosis and cancer and constitutes the imaging pole of the new center for research on inflammation CRI. In recent times this team has developed a widely recognized expertise in translational research i.e. physics based new imaging, and engineering novelties have been proposed tested and validated with the purpose of visualizing on macroscopic images features that are related to microscopic relevant physio-pathologic events, the ultimate human clinical stage being involved directly from the early research of this group. In the present project the research effort, quoted as multi-wave multi-scale approach, will combine MRI, acoustics, optics and targeted contrast agents combined with the relevant pharmacokinetic modelling. The method deals with the core inflammatory processes including fibrogenesis, endothelial cell activation as early inflammation marker, change in spatial vasculature architecture, cell membranes including aberrant nucleus to cell diameter ratio in cancer and metastasis and finally attempts to new therapeutics based on mechano-transduction. The common objective of this imaging project is to provide insight and understanding of the interaction between the dynamics of angiogenesis, inflammation fibrogenesis and cancer development. The strategy is unique in that it covers both physical and methodological fundamental developments in imaging, animal modelling and human *in-vivo* medical progress, with a great care for translation between these different operational levels inside the team but also in cooperation with other teams of the CRI. The general approach is multi wave and multi-scale and makes use of different imaging modalities or even a same modality (Magnetic Resonance Imaging) that will be made sensitive to various scales: intracellular, endothelial, interstitial, and organic levels. Also new human hepatocyte targeted contrast agent as well as molecular imaging animal stage specific agent targeting metalloproteinase will be used in a carefully prepared research strategy relying on results previously obtained by the group.

Conclusion

- Strengths and opportunities:

The strength of this team is the presence of both fundamentalists (Imaging physicists and biologists) and medical experts, closely cooperating within the team and with several other teams of the CRI consortium. The translational nature of their research has been emphasized in their scientific publications dealing with physical, physiological and clinical aspects. In conclusion the project has been carefully designed and involves all necessary testing allowing to progress towards clinical use. The very strong point in favour of the CRI initiative is the existing collaboration with other teams of the future CRI, that should provide the imaging team direct feeding from the fundamentalists and conversely the imaging team will enable a vital access to relevant imaging studies to all other groups.

- Weaknesses and threats:

Considering the size of the group compared to the broad objectives, the committee would recommend the team a reasonable phasing of the research effort, starting from basic essential parts and upsizing progressively the effort to full scale.

As one of the team leaders is going to reduce his activities in the team, the need of enlarging the number of senior scientists of the team, including full time researcher, should be emphasized. Also taking into account the quite large number of different elements of this project, the inclusion of several new PhD students or post doctoral researchers would be desirable.

- Recommendations:

The presence of an imaging team represents a considerable scientific asset for the future CRI. The major objective , should focus on the definition of well controlled and documented imaging biomarkers of the onset, the development and the organic functional impact of inflammation. The team should also remained open to direct collaborations with other teams of the CRI.

Team 12 :

Research and innovations in surgery and endoscopy of gastrointestinal and inflammatory diseases

Name of team leader: Mr Xavier DRAY

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	None (creation)	5 (1.5)	5 (1.5)
N2: Permanent EPST or EPIC researchers and similar positions	None (creation)	0	0
N3: Other permanent staff (without research duties)	None (creation)	0	0
N4: Other professors (PREM, ECC, etc.)	None (creation)	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	None (creation)	0	0
N6: Other contractual staff (without research duties)	None (creation)	1 (0.7)	0
TOTAL N1 to N6	**None (creation)**	**6 (2.2)**	**5 (1.5)**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	None (creation)	
Theses defended	None (creation)	
Postdoctoral students having spent at least 12 months in the unit	None (creation)	
Number of Research Supervisor Qualifications (HDR) taken	None (creation)	
Qualified research supervisors (with an HDR) or similar positions	None (creation)	4

• Detailed assessments

Assessment of scientific quality and outputs

The team is known for its expertise in endoscopy of the gastrointestinal tract. In particular, in previous years, it was marked by the introduction of innovative endoscopic techniques for diagnosis and for treatment of various gastrointestinal disorders. In addition, the team has developed two experimental models such as porcine model and in cadavers on the diagnostic capabilities of transumbilical single-access flexible endoscopy. Moreover, the team has developed animal models for training and research in various diseases of the digestive tract. They published 101 peer reviewed articles (Endoscopy, Dig Liver Dis, Clin Gastroenterol Hepatol, Eur Radiol,..), 29 first or last authors, including 23 review articles with 12 first or last authors.

Assessment of the unit's academic reputation and appeal

The team is composed of members whose national and international visibility is confirmed by a high-level scientific output, as well as their presence in many international conferences as experts. However, there is a relatively small number of young researchers or doctors in training. Finally, the members of the team have developed collaborations for opto-electronics and tissue engineering.

Assessment of the unit's interaction with the social, economic and cultural environment

The collaboration with opto-electronics and tissue engineering certainly create further relationships with other teams and can have a considerable impact on the media. The introduction of new techniques for endoscopic therapy for esophageal atresia of the newborn is a major step forward, and also a good example of translational medicine.

Assessment of the unit's organisation and life

The number of members of the team is small and can limit the progression of the projects. This is counterbalanced by close interaction with other teams such Team 6.

Assessment of the unit's involvement in training through research

The impact of new endoscopic techniques that will be evaluated in the projects presented by the team can have a potentially significant impact for the young doctors in training. However, this will depend on the results of these projects.

Assessment of the five-year plan and strategy

The team is involved in the development of a new generation of endoscopes with real time analysis and classification of digestive lesions (mainly colonic polyps) with the aim to introduce in endoscopes active stereoscopic (3D) systems, autofluorescence, image segmentation, and machine learning meta-algorithm (boosting). The team has also the project to use interventional endoscopy for the treatment of esophageal atresia. The main strength of the two projects, though quite different, lies in improving the endoscopic techniques in order to make more 'accurate diagnosis and treatment of various digestive diseases (cancer, IBD, esophageal atresia).

The main strength of the two projects, though quite different, lies in improving the endoscopic techniques in order to make more 'accurate diagnosis and treatment of various digestive diseases (cancer, IBD, esophageal atresia). However, although stimulants, the projects are relatively unrelated to each other and to the CRI project.

Conclusion

- Strengths and opportunities:

The main strength of the two projects, though quite different, lies in improving the endoscopic techniques in order to make more accurate diagnosis and treatment of various digestive diseases (cancer, IBD, esophageal atresia).

- Weaknesses and threats:

Although stimulant, the projects are relatively unrelated to each other and to the CRI project. In addition, the number of members dedicated to their execution, as well as the number of researchers and doctors in training is very limited.

- Recommendations:

The committee of experts appreciates and recognizes the interest of the team's projects. However, it is suggested to investigate aspects more closely related to the study of inflammation, in order to improve the coherence of the project with the purposes of the CRI. An increase in the number of young doctors and researchers in training would be desirable.

5 • Conduct of the visit

Visit dates:

Start: Monday 21 january 2013, at 8h30"

End: Tuesday 22 january 2013, at 18h00 "

Visit site(s): Faculty of Medecine Bichat,

Institution: Paris 7

Address: 16 rue Huchard, 75018 Paris

Conduct or programme of visit:

Monday 21 january 2013

8:30	Welcome (closed-door) Visiting committee with the AERES Scientific advisor
8:45	AERES representative: the role and procedures of AERES
9:00	Director of the Unit : Presentation of the past activities and project
10:00	Team 1 – Immunoreceptors and renal immunopathology Mr Renato MONTEIRO
11:00	Team 2 – Mast cells and basophils in inflammation and remodeling Mr Ulrich BLANK / Mr Pierre LAUNAY
12:00	Lunch
13:00	Parallel meetings with personnel: Discussions with engineers, technicians, administrative Discussions with staff scientists Discussions with students and post-docs
14:00	Team 3 – Phagocyte, NOX and immunogenetics in systemic inflammation Mr Jamel EL BENNA
15:00	Team 4 – Heme, Iron and inflammatory diseases Mr Laurent GOUYA
16:00	Coffee break
16:15	Team 5 –Innate immune responses in the child : role in viral infections and graft versus host re action Ms Sophie CAILLAT-ZUCMAN
17:15	Discussion with the representatives of the managing bodies
18:15	Debriefing on the team presentations

Tuesday 22 january 2013

8:15	Team 6 – Intestinal inflammation
	Mr Eric OGIER/Mr Jean-Pierre HUGOT
9:15	Team 7 – Inflammatory and stress responses in chronic liver diseases
	Mr Richard MOREAU
10:15	Coffee break
10:30	Team 8 – Viral hepatitis
	Mr Patrick MARCELLIN
11:30	Team 9 – From inflammation to cancer in digestive diseases
	Ms Valérie PARADIS
12:30	Lunch coupled to Discussion with the head of the Unit
13:15	Team 10 – Gastrointestinal dysfunctions in nutritional pathologies
	Mr André BADO
14:15	Team 11 – Novel imaging biomarkers for inflammation, fibrosis and cancer
	Mr Ralph SINKUS/Mr Bernard VAN BEERS
15:15	Team 12 – Research and innovations in surgery and endoscopy
	Mr Xavier DRAY
16:15	Private meeting of the visiting committee (in presence of the AERES scientific advisor)
18:00	End of the visit

6 • Statistics by field: SVE on 10/06/2013

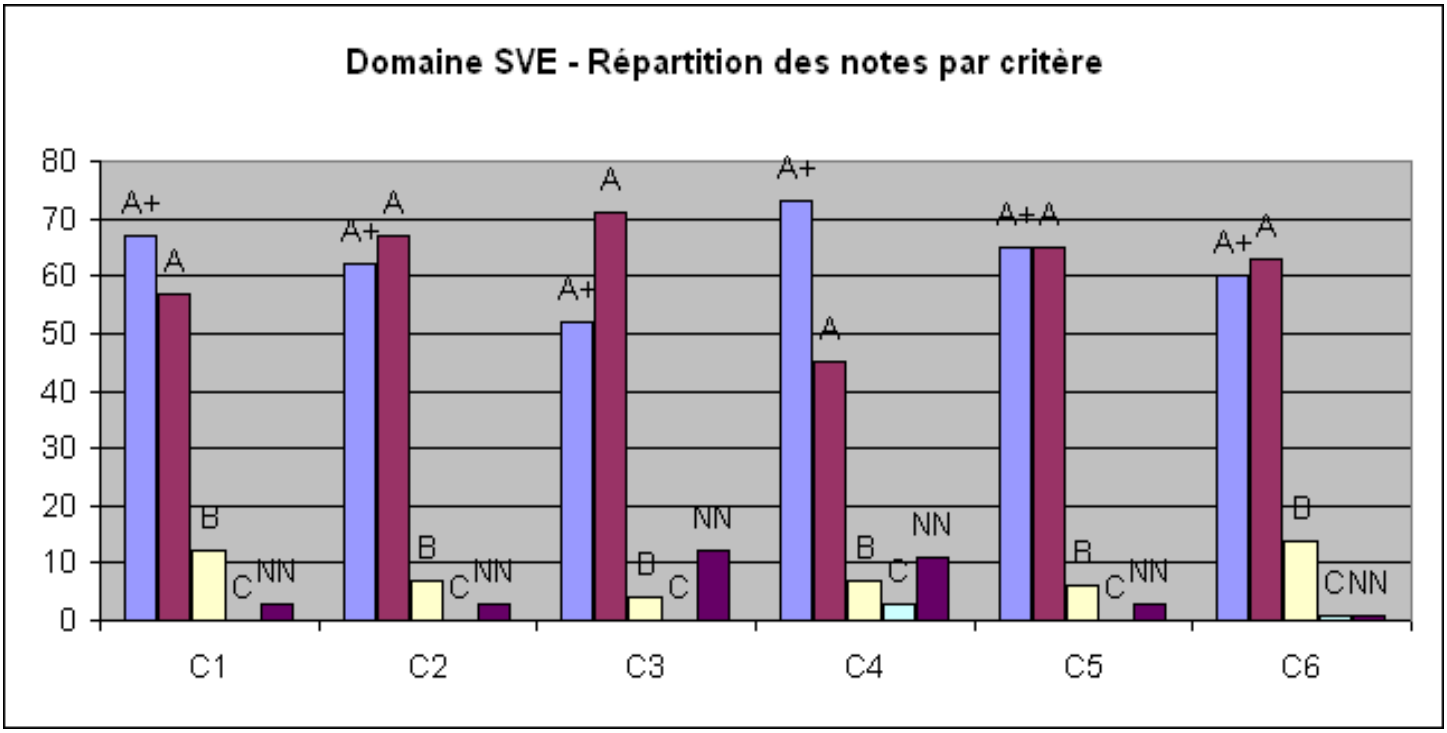
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

Le Président

P/VB/LB/NC/YM – 2013 - 087
Paris, le 22 avril 2013

M. Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

S2PUR140006412 - Centre de recherche sur l'inflammation - 0751723R

Monsieur le Directeur,

Je tiens, en premier lieu, à remercier les membres du comité de visite de l'AERES pour l'analyse très détaillée de la situation du « Center for Research on Inflammation », unité dont le comité souligne les bonnes organisation et management malgré sa taille et les localisations géographiques différentes.

Le directeur et chacun des responsables d'équipes ont argumenté et répondu en détails aux recommandations du comité, ce qui est signe d'une forte prise en compte de cette évaluation.

Le comité a relevé la position de leader de cette unité dans le champ des maladies inflammatoires, mis en évidence tant par le très bon niveau de publication, que part l'excellente capacité à faire de la recherche translationnelle, grâce au partenariat étroit entre cliniciens et chercheur.e.s et enseignant.e.s-chercheur.e.s, base de notre association avec IINSERM. Je me réjouis que le comité note que l'obtention du Labex Inflamex constituait déjà un gage d'excellente évaluation de cette unité.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de toute ma considération.

Vincent Berger

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SORBONNE PARIS CITÉ
RECHERCHE ENSEIGNEMENT SUPÉRIEUR

Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

Unités de Recherche U699 and U773

Paris, April 9th, 2013

Answer to AERES Report of the Center for Research on Inflammation (CRI)
Reference # D2014-EV-0751723R-S2PUR140006412-003205-RT

Evaluation of the Unit:

We thank the AERES committee for the constructive criticisms. As suggested by the committee and after approval by the CRI scientific council on April 5th, **Richard Moreau** (DR1 Inserm) was designated as candidate **Deputy Director of the CRI**. R. Moreau will provide a strong support to CRI management notably by his experience as head of U773.

Recommendation 1:

• **A particular effort should be devoted to the localisation of all the research teams in a unique site.**

Answer: We agree that having all research teams at a unique site (Bichat site) would be optimal. Yet, there are two strong reasons supporting the maintenance of the current multisite research proposal.

1- A major effort has already been made by the CRB3 during the last period (2006-2013). The animal facility of the Abrami building was closed down and several labs were transferred from Beaujon to Bichat (Pessayre, Moreau, Marcellin). Three teams remained, however, located at the Abrami building: Teams 8 (Marcellin), 9 (Paradis) and 11 (van Beers). The past five years' experience at the CRB3 has demonstrated that these teams were fully integrated in the Bichat-Beaujon research center with common seminars (Mercredis de Bichat-Beaujon and journal clubs). They have shown to be both complementary and synergistic with other teams located in the Bichat building (common publications between Beaujon and Bichat teams). **Importantly**, all Beaujon teams have also lab spaces at the Bichat site: one lab for the team 8, two labs and one office for team 9 (group of A. Couvineau), a MRI platform for team 11 at the Bichat -2 level. This dual location allowed full integration of these teams within the CRB3 unit eliminating any costly duplication of platforms, animal facilities…. Moreover all major platforms are located at Bichat and researchers move easily from one site to the other. Beaujon and Bichat are only 10 minutes away from each other and well-connected by public transportation and parking spaces are well available at both sites. Of note, team 5 (Caillat-Zucman) and team 12 (Dray) will also benefit of such dual location strategy having lab space at the Bichat site to facilitate their integration into the CRI. Regular meetings "Challenge in inflammation" organized by the Inflamex LabEx will also provide a continuing opportunity to reflect on common research strategies within the CRI.

2- Beaujon is the leading site for hepato-gastroenterology (HGE) in France and strong connections have been established between clinicians and researchers, especially in translational research. Recently the DHU UNITY has been created, which reinforces the need of maintenance of lab space at the Beaujon site. The teams located at Beaujon are heavily dependent on immediate access to patient material for their research. This includes blood and tissue samples for team 8 (Marcellin) and team 9 (Paradis). Team 9 also needs to immediately process cells isolated from fresh tissue samples for tissue culture, or team 11 (Van Beers) for MRI research on patients. In addition, the tissue bank of liver, pancreatic and GI human samples represents a strong asset for the HGE department of the CRI. This biobank has been established and is maintained at Beaujon hospital because of its close proximity with operative and endoscopic rooms and is under the leadership of team 9 (Paradis).

Nevertheless, we wish to point out that a future project for a new "hôpital Nord" (fusion between several hospitals of "Hôpitaux Universitaires Paris Nord Val de Seine" including Bichat and Beaujon, which is underway) may allow to establish the CRI at a unique site in the future.

Recommendation 2:

• **The project of some of the teams should be more focused on inflammation.**

Answer: As this suggestion involves only some teams, this point will be addressed individually by the respective teams (teams 4, 8, 10 and 12). All of these teams in their comments propose to strengthen their research axis on inflammation and the inflammatory processes.

Recommendation 3:

• **Some platforms should be better organized and supported in term of both personnel and equipment.**

Answer: The current organization of the platforms is inherited from past development of the research units. Creation of the research center will be an opportunity to rationally and globally organize and reinforce platforms with personnel and equipments, in particular cell Imaging and animal facilities. A session devoted to coordination of the platforms is already planned during each annual scientific retreat of the future Center. Of note, funding to buy a Biacore X100 has recently been obtained for the CRI at the CORDDIM, which will be annexed to the existing biochemistry platform piloted by an Inserm technician.

Evaluation of each team:

Team 1 (Monteiro): We thank the AERES committee for their positive evaluation.

"Assessment of scientific quality and outputs". Comments: Among the papers (first and/or last authors) in journal with IF>10 were not mentioned 2 Nature Medicine in 2011 and 1 Cell Host & Microbes. The first Nat. Med. paper was signed as co-first author by M. Flamant and the second was signed as co-last author by R. Monteiro. They describe new pathogenic mechanism of GN and new function of the IgA1 receptor TfR1, respectively.

Weaknesses and threats :

• The main weakness is that the broad and the ambitious program of activities proposed by the group will diminish the chances of in-depth research on the main topic, IgA nephropathy.

Answer: We agree that one main goal is the understanding of IgA nephropathy. However, we disagree that we lack to perform in-depth research in this topic. In fact, since many years our strategy is to combine fundamental and applied research to better understand the physiopathology of IgA nephropathy. Our team is well recognized at the international level for its contributions on the role of IgA and IgA receptors in immune regulation. We have pioneered a new concept of ITAM/ITAMi regulation explaining IgA anti-inflammatory functions, and have extended this to other Ig isotypes. We believe that progress in understanding the IgA (and the immune) system will give fundamental clues to the onset/development and treatment of IgA nephropathy. Thus although seemingly broad, our research program that includes study on the IgA system is a guarantee to in-depth progress on the disease.

• The Atip-Avenir group should focus more on IgAN and orchestrate WP3 among the other WPs.

Answer: The Atip-Avenir group has presented orally exactly along these recommendations, including IgA nephropathy in most WPs.

Recommendations: The team is encouraged to sort out the most pressing needs, to hierarchize the priorities and to propose a more focused work plan in line with the current interests of the group.

Answer: same as to the first point above. Also note that the team will be joined by 4 new investigators (2 senior scientists from CNRS and University as well as 2 post-docs supported by the labex Inflamex).

Team 2 (Blank/Launay): We appreciate the positive evaluation of our team by the committee, which recognizes a well-constructed and ambitious project that is based on original cellular and animal models.

Weaknesses and threats: The strategy might be improved with a focus on some (animal) models at least in a first time. Perhaps a more hierarchized strategy would be more powerful. In addition, to define more precisely who does what could allow reinforcing the projects and the links between the members of the group.

Answer: These suggestions seem contradictory to the statement of a "well constructed project" that is based on original cellular and animal models. It should be noted that we presented during our oral presentation an already further hierarchized research program reducing the initial 4 WPs to 3 WPs stating for each one who does what. It should be noted that: 1) a new postdoc (L. Danielli, Italy) will join the team in June, (I. Madera) 2) team members already share authorship in 18 publications, 3) the team holds weekly meetings where work progress of each member is discussed in-depth, 4) most projects associate at least two senior team members.

Recommendations: It will need to hierarchize the priorities and perhaps to better integrate the skills of each partner in the different tasks.

Answer: As above.

Other points: Publications cosigned as a penultimate author with team 1. Rather two publications (JI and Sci Signaling) co-signed as senior authors.

Team 3 (El Benna): We thank the AERES committee for their positive evaluation

Weaknesses and threats : The project is large and should be more focused.

Answer : Because the team has a solid and recognized expertise in NOX2 and NOX1 and a new member of the team is the head of the rheumatology department in Bichat hospital, we have now chosen to focus our project only on studying NOX2 and NOX1 in rheumatoid arthritis.

Recommendation : More post-doctorants should be recruited.

Answer: One post-doc candidate from Italy with a solid experience in inflammation working in Ireland and Germany for several years has recently been selected by the Labex-Inflamex postdoctoral program and will start to work in early june 2013. A second post-doc will be recruited in january 2014.

Team 4 (Puy & Gouya): We thank the AERES committee for their constructive criticisms. All recommendations suggested were taken into consideration:

Recommendation 1: The team has to better define the strategy for the team leadership

Answer: Following the Expert committee evaluation report, we propose a joint-management for team 4 by Hervé Puy and Laurent Gouya. This will allow maturation of Laurent Gouya's leadership for the next period. Hervé Puy is an MD-PhD, 52 yr-old senior researcher, full Professor at Paris Diderot University in Biochemistry and Molecular Biology, involved since 1991 in the field of heme, inflammation and iron metabolism. He is internationally well recognized in the field and has several major contributions as senior author during the 5 past years as follows:

1) Discovery of a new disease and physiopathology mechanism with an original mode of inheritance in erythropoietic protoporphyria. (Am J Hum Genet 2008, Lancet 2010, Blood 2011, J Invest Dermatol 2012, Hum Mol Genet 2013).

2) Highlight on hepato-biliary inflammatory cholestasis in the rare disease models. (Cell Metab 2010 collaboration with the EMBL Prof Hentze; Gastroenterology 2011).

3) Involvement of ABC family in mitochondrial and plasmic porphyrins and heme transport. (2 Nature Genet 2012 in collaboration)

H. Puy's output and indicators *(please see also Hervé Puy "fiche individuelle")*

98 publications referred in Pubmed from 1990 to date. H index > 23; 17 as first author (JCI, Lancet, 2 Am J Hum Genet,…), 30 as second author (NEJM, Nature Genet, 2 Am J Hum Genet, Blood, Hum Mol Genet, 2 J Internal Med, 2 J Hepatol, …), and 22 as last author (Gastroenterology, 2 Blood, Am J Hum Genet, Hum Mol Genet, ….).

Selected publications as a corresponding author (last 5 years):

1. Lyoumi, et al ***Blood*** 2007, 109(2) :811-18.
2. Whatley et al. ***Am J Hum Genet*** 2008, 83(3):408-14.
3. Puy et al. ***The Lancet*** 2010, 375(9718):924-37.
4. Lyoumi et al. ***Gastroenterology*** 2011,141(4):1509-19.
5. To-Figueras et al. ***Blood*** 2011, 118(6):1443-51.
6. Ducamp et al. ***Hum Mol Genet*** 2013, 22 (7); 1280-8.

Grants coordinated by H. Puy during the 5 past years:

- 2008-2010: ANR, Autosomal dominant erythropoietic protoporphyria.
- 2011-2013: European Porphyria Network, (European Porphyria Network, IG Sanco, 17 countries participants).
- 2013-2015: National PHRC Obesity and heme and iron metabolism: FORBES.
- 2011-2014: APHP and Waters international partnership in Mass spectrometry for heme, porphyrins and hepcidin.
- 2013-2015: P-STIC Innovant technology : Hepcidin assay by quantitative mass spectrometry in inflammatory anaemia.

National and International position and responsabilities:

H. Puy is a partner of the LABEX Gr-Ex, a founding member of the "European Porphyria Initiative », an ssociate Director of the Centre Français des Porphyries, head of Biology section ("pole PUI") of Hôpitaux Universitaires Paris Nord Val de Seine APHP - University Paris Diderot (2010-2015), a contributor to the DHU UNITY: "Unmet needs in Hepato Gastroenterology" and an elected member of the National Council of University CNU (sous section 44-01 Biochimie et Biologie Moléculaire). H. Puy was invited to several meetings as plenary speaker and Chair: Gordon research conferences, Tetrapyrrol Group, European Society Haematology London 2012, Bioiron, and recently to talk about "heme related disorders and inflammation" in the next ASH meeting in New Orleans December 7-10th 2013.

Recommendation 2: Regarding the size of the team compared to the objectives as well as the global objectives of the CRI, it could be useful to focus efforts on inflammation. Interactions with other teams of the CRI involved in characterization of inflammatory process could be emphasized.

Answer: As raised by the experts, our projects on liver and/or renal hepcidin function and regulation are already built around inflammatory processes (Z. Karim's WP). However, in the other projects, the team will prioritize to enhance the inflammation research axis in agreement with the CRI objectives as follows:

- The pro-inflammatory properties of heme in Acute Intermittent Porphyria (AIP): preliminary studies in the AIP mouse model shows that heme-arginate treatment (Normosang®) induced inflammation and oxidative stress in liver and on endothelial cells explaining many complications during AIP patient treatment (Gouya et al., submitted). We develop now a cellular hepatic model of AIP to study the inflammatory properties of heme arginate and to optimize treatment by heme limiting the inflammatory side effect.
- We will also focus on heme and hemoglobin clearance mechanisms in congenital erythropoietic porphyria (CEP, Gunther disease) that is associated with hemolysis using a new mouse model and clinical studies to evaluate heme, hemoglobin exhibited proinflammatory properties. Of note, we showed that the liver compared to spleen is the preferential site of iron overload with macrophage recruitment (Puy et al, submitted).
- Heme overproduction can lead to oxidative stress and inflammation, which may be responsible, at least in part, for the apoptosis observed in Blackfan Diamond Anaemia. Da Costa will study the role of heme in apoptosis, inflammation and subsequently erythropoiesis defect in DBA.
- Our expertise in heme, porphyrins, iron, hemolysis, hemoproteins and related disorders is useful for many if not all the CRI teams involved in hepatology, nephrology and macrophage functions. The best indicator of our integration in the CRI and UNITY partners are current and future collaborations as follows: 1-Team 10 on anemia associated with inflammation in Obesity, 2- Team 7 for inflammation in hepatic porphyrias, 4-Team 3 on the di-heminic NOX enzyme and erythrophagocytosis by macrophages, 5-Team 2 on exosomes and iron clearance by the kidney and finally 6-Team 1 on the role of hepcidin/iron cross-talk through transferrin receptors in macrophages and mesangial cells using a humanized mouse model for IgA nephropathy.

Recommendation 3: Its could be also useful to reinforce the team with at least one young full time researcher

Answer: We plan to strengthen the team by three full time positions within the next 3 years:

-1) Sarah Ducamp, ex-PHD student of Hervé Puy holding actually a post-doc position in another lab with 8 publications so far in Am J Hum Genet, Blood, JID, Hum Mut,…as a first author. She will apply for a CR1 position next year.
- 2) Hana Manceau, post-doc with L. Gouya, will apply for a MCF-P7 position next year.
- 3) Katell Peoc'h, MCUPH in Paris Descartes Univ. will join us and apply for a "Contrat d'interface INSERM" shortly.

Assessment of the unit's organisation and life: The permanent core … for the next years, there is no mention of major funding obtained by the team leader.

Answer: 9 new grants with a total of **1.067 million €** funding will be coordinated by team 4 during next years: **1-** AFM, Therapeutic strategy adapted to erythropoietic protoporphyria (34.5 K€, Gouya) in 2013; **2-**PHRC Forbes, Bariatric surgery, iron metabolism and inflammation (184 K€, Msika & Puy); **3-**Fondation maladies rares, Traitement des Porphyries Hépatiques (Gouya 15 K€); **4-**P-STIC DGOS, Innovation in technology: Hepcidin assay by quantitative mass spectrometry in inflammatory anaemia (Puy, 81.1 K€); **5-**Labex GrEx, Exome sequencing in patients with microcytic anemia and in DBA patients (123 K€, Gouya, Da Costa & Karim); **6-**e-RARE, 225 K€, L. Da Costa; **7-**PHRC national, 115 K€, Da Costa; **8-**Pres Sorbonne Paris Cité, Iron handling by the kidney: role of hepcidin and physiology (150 K€, Karim); **9-**IDEX-Pres Sorbonne Paris Cité, Heme, Microparticles & Red blood cells : Actors of vascular injury (140 K€, Blanc-Brude & Gouya).

Team 5 (Caillat-Zucman): We thank the AERES committee for their positive evaluation.

Weaknesses and threats:

• **The members need to find a convincing way for successful integration in the CRI (effective collaborations, participation to animation and life of the CRI).**
Answer: We have already started effective collaborations with team 6 (JP Hugot) on 2 of our 3 sub-projects: in autophagy (provide autophagy-deficient mice) and with MAIT cells and intestinal inflammatory diseases. We will participate in other CRI projects through the proposal of pediatric/adult translational research projects. Moreover, other members joining our team (i.e. Pr Michel Peuchmaur) have a long-standing tradition of collaborative research projects with CRI teams (i.e. Team 1, 2 & 6), which has resulted in multiple publications.

• **The members want to recruit a top scientist to reinforce their research strength and the committee thinks that it is important especially for completing the third work package dealing with autophagy.**
Answer: We agree with the committee and as already stated during our oral presentation we plan to recruit Dr. Monique Gannagé, currently completing a post-doc in Switzerland to develop autophagy projects.

Recommendation: An effort is needed for better shaping the analysis of MAIT ontogeny /functions and its association with the gut flora composition.
Answer: This study is already in progress. A technician has been recruited for the analysis of MAIT cell ontogeny in the neonate and in stem cell recipients (patient samples routinely analyzed since February 2013). A collaboration with a research group at INRA (Marion Leclerc) has been established for a parallel analysis of the gut microbiota on swabs taken longitudinally in the neonates and transplant patients (deep sequencing and metagenomics).

Team 6 (Hugot/Ogier-Denis): We thank the AERES committee for their positive evaluation.

Assessment of scientific quality and outputs. Comments: The scientific production does not correspond to the mentioned list. Among the papers (first and/or last authors) in journal with IF>10 were not mentioned 1 Journal of Clinical Investigation and 1 Cell Host and Microbes in 2012 as well as 3 *Gut*, 2 *Gastroenterology*. Team members were also co-authors of 7 *Gut*, 10 *Gastroenterology*, 2 *Hepatology*, 3 *Blood*, 1 *American Journal of Human Genetics*, 1 *Journal of Experimental Medicine*, 1 *Journal of Clinical Oncology*, 1 *Journal of Clinical Investigation*, 1 *Immunity*, 1 *Lancet*, 4 *Nature Genetics*. Team members have contributed to several book chapters.

Assessment of the unit's academic reputation and appeal. Comment: We want to mention that the team is member of the Labex Inflamex. Team leaders received several awards including a French National Academy of Science award. The clinicians are coordinators of reference centres for rare diseases and they founders or active members of the French research networks on Inflammatory bowel disease (GETAID, GETAID Pédiatrique and REMIND). The team is member of the Département Hospitalo-Universitaire "UNITY" recently labeled.

Assessment of the unit's interaction with the social, economic and cultural environment. Comment: We want to mention that we have developed a strong interaction with several patient associations. JP Hugot has been administrator of the "Association François Aupetit" during the last 6 years and contributing in the association for more than 15 years. Team members also contributed to several European clinical guidelines (see the ECCO web site).

Weaknesses and Threats section. Only one post-doctorant has been recruited. Answer: We thank the committee for their recommendations. One post-doc will be recruited in September 2013 and another one in January 2014, both funded by the Labex Inflamex. Furthermore, the team has applied to several ANR funding in which a post-doc position is requested for each of them (answer May 2013). We also want to mention that a young researcher (U Meinzer) has recently applied for an AVENIR team. We are thus confident in our ability to further recruit young scientists in the close future.

Team 7 (Moreau): We thank the committee for their recommendations.

Before addressing recommandations made by the Visiting Committee we would like to comment on two points raised in the section entitled "Weaknesses and threats". First, we were surprised to read: "No publication in top-notched journals (very high impact factor) has been gathered in". It should be emphasized that there are 74 journals classified by Web of Science in our specialty, i.e., "Gastroenterology and Hepatology". Among 100 articles published by our team during the period, 67 were published in journals of the specialty. Among these 8 were published in the Top 1% Journals (i.e., Gastroenterology, IF 11.675) and 59 in the Top 10% (including 4 journals with IF ranging from 11.675 to 9.264). Of note the team leader is the first author of an original article which is in press in Gastroenterology and already cited in PubMed. Finally, 3 members of Team 7 have an "h-index" above 40. In addition, 4 team members are among the 20,000 scientists who are classified worldwide according to citation rankings by ISI Web of Knowledge/Essential Science Indicators.
Second, the Committee stated that "The team did not include a high number of external post-doctorants during the last years". We agree with this. Nevertheless it should be noted that we have engaged a strategy designed to recruit Indian post-docs. Indeed, in October 2012, a research project (which associated our Lab with the Institute for Liver and Biliary Sciences (ILBS, New Delhi, India)) has been selected for funding by the Indo-French Centre for the Promotion of Advanced Research (IFCPAR). One of the goals of this project is to raise funding to allow recruitment of an Indian post-doc. Moreover, in February 2013 the ILBS has been endorsed by Inserm as an International Laboratory associated with our team. The development of these projects rely on the integration of Indian post-docs in our group. Moreover, the recruitment of one post-doc funded by the Labex Inflamex is planned in January 2014.

Recommendation 1: Improvement of the relationship between vascular thematic and inflammation has to be made. Answer: Dominique Valla who is in charge of the vascular thematic in Team 7 has recently shown that patients with cirrhosis have a pro-coagulant state related to systemic inflammation (Gastroenterology 2012,143:1253-60). Studies using genetically modified mice investigating the role of translocation of intestinal Gram-negative bacteria in cirrhosis-associated pro-inflammatory and pro-coagulant states are ongoing involving Team 7 and the team directed by Ms Chantal Boulanger (Paris Centre de Recherche Cardiovasculaire, PARCC, Hôpital Georges Pompidou).

Recommendation 2: The team has to plan to develop other animal models for innate immunity studies in inflammation. Answer: Please see our answer to recommendation 4.

Recommendation 3: The team has to think about the improvement of valorization.
Answer: We would like to draw attention to the fact that two team members were inventors of two pharmacological therapies in the context of severe complications of cirrhosis, i.e. one for the prevention of hemorrhage (beta-blockers), the other for the treatment of renal failure (terlipressin). These therapies are now used worldwide in patients with cirrhosis. Of note, a new therapeutic approach (the use of long-term antibiotic therapy) is under evaluation in a large randomized double-blind trial. We are also thinking to valorize our recent findings that alcoholic cirrhosis is associated with a marked defect in the induction of interferon-stimulated genes by environmental stimuli.

Recommendation 4: Strategy to anticipate team leadership evolution in 5 years has to be considered.
Answer 4: This is a very important point. We can state now that Dr. Sophie Lotersztajn (Research Director at Inserm) will join Team 7 at the end of 2013. Dr. Lotersztajn is currently team leader in the Inserm Unit U955 (Hôpital Henri Mondor). During the next five years she will be co-leader of this team with the objective of becoming team leader in 2018. She is an internationally recognized expert for basic research in the field of liver inflammation. Her studies, in genetically modified mice led to several publications in prestigious journals (Nature Medicine, Nature, Journal of Clinical Investigation) and in top 1% journals of the specialty (Gastroenterology, Hepatology). Therefore, team 7 will greatly benefit from the arrival of Dr. Lotersztajn not only in terms of renewal of leadership but also in terms of research. She is currently developing new animal models for the study of innate immunity in inflammation that will be shared with all the members of team 7 and allow team 7 to comply with recommendation #2 made by the Committee.
The Visiting Committee was not aware of the fact that Dr. Lotersztajn will join Team 7 because her decision to leave her current site was not yet taken. Discussions with Dr. Lotersztajn and the current Team 7 leader (and other members of Team 7) have been initiated in September 2012 and a final agreement was found in March 2013. Please see below a summary of Dr. Lotersztajn's projects for 2014-2018 and her selected publications as follows:

Sophie Lotersztajn (DR1 Inserm) – Co-leader of Team 7

Summary of Achievements and highlights (since 2008)
Alcohol abuse, non-alcoholic fatty liver disease and viral hepatitis are the major causes of chronic liver injury, and result in progressive accumulation of fibrosis within the liver parenchyma. Progression to cirrhosis is accelerated by genetic and environmental factors and exposes patients to life-threatening complications and to a high risk of hepatocellular carcinoma. Overall, chronic liver diseases represent a major health problem with an estimated rate of death in the range of 1,400 000 per year worldwide. Over the past 5 years, our main interest has been to understand the mechanisms underlying progression of chronic liver diseases, with major emphasis on the identification of therapeutic targets that control liver inflammation and fibrosis. During this period, we have uncovered the key role of the endocannabinoid system in the pathogenesis of several key steps of acute and chronic liver injury. Our findings have identified pharmacological modulation of cannabinoid receptors as an attractive strategy for the management of chronic liver diseases, and served as the basis of three patents registered with Inserm-Transfert. We also identified new pathways controlling liver inflammation and fibrosis and developed novel macrophage imaging strategies. The projects have been developed together with industrial partners and with numerous national and international collaborations. Besides funding from Inserm and UPEC, our research has been supported by public contracts (ANR), associations (FRM) and industry (Abbott, Sanofi-Aventis) for more than 2 M€.

Research projects 2014-2018:
Our main goal is to provide a better understanding of the mechanisms underlying progression of chronic liver disease, with major emphasis on the identification of therapeutic targets that control liver inflammation, fibrosis and liver regeneration, focusing on the interplay between immune cells, fibrogenic cells and hepatocytes. Our objectives are in perfect line with the projects developed within the CRI. Because of the common interests in the field of innate immunity, inflammation and the development/complications of liver diseases, I will join team 7 of the CRI with part of my group by the end of 2013, as a co-leader together with R. Moreau. Our projects are to investigate whether manipulating monocyte/macrophage phenotype prevents fatty liver disease progression to fibrosis, and to identify novel anti-inflammatory candidate molecules with antifibrogenic properties. This translational project will benefit from recognized complementary expertises of my group, that of R Moreau and other CRI liver groups in the field of hepatic inflammation and fibrosis, and from all the anticipated interactions with the other CRI teams. The project will combine preclinical and clinical studies, using multidisciplinary approaches, molecular tools, original models of mice bearing specific invalidation of genes of interest in macrophages, cell cultures and human studies. Specific aims are to characterize the mechanisms and mediators that control monocyte/macrophage phenotype, focusing on how lipid metabolism in macrophages may impact on their phenotype. We will i) study how the components of the endocannabinoid system may reprogram macrophage metabolism and its consequences on inflammation, liver injury and fibrosis. ii) define an immunometabolic signature characteristic of an anti-inflammatory and antifibrogenic macrophage. Given the major role of macrophage in the progression of hepatocellular carcinoma, strong interactions with the group of V Paradis are also anticipated. We also wish to develop novel models of fatty liver disease with more severe forms of ALD and NAFLD, which better reflect the pathogenesis in humans. Our project is likely to pave the way for the development of more effective therapeutic strategies to target monocyte/macrophages in vivo with beneficial consequences on fatty progression towards fibrosis and hepatocellular carcinoma.

6 selected publications since 2006:
1.Adipose tissue macrophages: MR tracking to monitor obesity-associated inflammation. Luciani *et al.*, ***Radiology***, 2012, 263(3):786-793. Higlighted by a News and Views
2.Cannabinoid CB2 receptors protect against alcoholic liver disease by regulating Kupffer cell polarization. Louvet *et al.*, ***Hepatology*** 2011, 54:1217-26

3.Hyperactivation of anandamide synthesis and regulation of cell cycle progression via CB1 receptors in the regenerating liver. Mukhopadhyay *et al.*, ***PNAS*** 2011, 108(15):6323-8 Higlighted by an associated News and Views
4.Beneficial paracrine effects of Cannabinoid receptors on liver injury and regeneration, Teixeira-Clerc *et al.*, ***Hepatology*** 2010, 52(3):1046-59.
5. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis. C. Hézode *et al.*, ***Gastroenterology***. 2008, 134(2):432-9.
6.CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. Teixeira-Clerc *et al.*, **Nat. Med.** 2006, 12(6):671-6.
- 3 patents have been registered since 2008 with Inserm-Transfert
(please see below in the annex the CV of Dr Lotersztajn).

Team 8 (Marcellin):

Recommendation 1: The committee welcomes and recognizes the interest of the team's projects. However, it is suggested to deepen research about the inflammatory processes associated with chronic hepatitis B and C.
Answer: We welcome the recommendation to investigate more deeply the link between inflammation and chronic hepatitis. In fact, we have already started to explore this relationship and this has resulted in several original articles on HCV and inflammation, immune response, gene expression, interferon stimulated genes (ISG), and we have been invited for review or conference on this topic (including J Interferon Cytokine Res. 2012, 32:557-62; J Hepatol. 2012, 57:1110-25; Eur J Immunol. 2012, 42:447-57; J Hepatol. 2012, 56:527-32; J. Hepatol. 2012, 56:726-8). Also, we developed several biomarkers associated with fibrosis progression or response to treatment. Interestingly, these biomarkers belong mainly to inflammatory response and ISG (Gut 2008, 57:516-24). We are leader for future genetic studies involving inflammatory response and HCV infection. Thanks to an ANRS grant, a project on inflammation, fibrosis and HCV has started this year (with a doctorant Kevin Arpouchaux).

Recommendation 2: and to improve crosstalk with the other team members of the CRI.
Answer: We have already developed crosstalk with the other team members of the CRI, in particular the team of R. Moreau by investigating endoplasmic reticulum stress, autophagy, and HCV, which are linked to inflammation (J. Pathol. 2010, 177:1791-7; Am J Pathol. 2011, 178:2708-15), and furthermore with Bernard Van Beers on fibrosis imaging diagnosis (Radiology, 2010, 256:135-42). Also, our team has long term strong collaboration with Pierre Bedossa and with strong expertise on fibrosis associated with HCV infection (Gastroenterology 2008, 135:821-9; Gastroenterology 2008, 134:416-23). In particular, our team has demonstrated long-term HCV cure after treatment (Gastroenterology 2008, 135:821-9).

Recommendation 3: It is strongly suggested to increase the number of permanent researchers and training,
Answer: We agree with the committee that increasing the number of permanent researchers will be beneficial. Among existing post-docs we wish to recruit Emilie Estrabaud working on cell biology, gene expression and HCV and Olivier Lada working on HBV virology.

Team 9 (Paradis):

Recommendation 1: The team has to recruit highly qualified and productive international post-docs or specialist in one of the field of investigation; only when this is achieved, the team is really an international top lab.
Answer: One post-doc will be recruited in January 2014 on the TEDAC project already funded by OSEO. As a partner of the Labex INFLAMEX, the team will recruit a second post-doc at the next call of offer to start in January 2014.

Recommendation 2 and 3: The strategy has to be clearly defined particularly regarding the way to investigate the putative role of the visceral adipose tissue (VAT) and FABP4 with back-up strategies in case of failure. The team has to focus on specific mechanisms both in animals and humans in order to avoid descriptive studies or correlative findings in the field of metabolic syndrome and cancer
Answer: We thank the committee for their positive evaluation. This concerns one of the 3 sub-projects within WP1. Nevertheless, we wish to point out that the working hypothesis of FABP4 as a putative mediator linking Visceral adipose tissue to liver carcinogenesis is scientifically sound. The oncogenic role of FABP4 is supported by data from literature (Nat Med. 2011, 17:1498-503) and by our preliminary results showing that it increases lipid availability to fuel rapid growth of cancer cells. Importantly, we will benefit from the input of S. Lotersztajn who will join the CRI.
Our 4 step strategy is as follows: **1-**The oncogenic effect of FABP4 in liver cancer will be established by using hepatocancer cell (HCC) lines with adipocytes from Fabp4−/− mice and markers of cell cycle, apoptosis, proliferation and invasiveness as readout. Other approaches will include injection of liver cancer cells intraperitoneally in Fabp4−/− and evaluation of tumor burden. **2-** FABP4 oncogenicity mechanism through differential transcriptomic and proteomic approaches will be performed in order to identify specific genes or pathways with oncogenic relevance. **3-**FABP4 small-molecule inhibitors in hepatoma/adipocyte cocultures and in the model of DEN-induced HCC in obese mice (in collaboration with institute Cochin) will be evaluated. **4-**Relevance in human HCC associated with MS will benefit from our tissue biobank, which includes multiple frozen samples of HCC associated with MS. FABP4 expression and lipid content will be investigated in tumoral cells.
Backup strategy: We will perform differential analysis of the secretome of ex vivo cultured VAT of patients with and without HCC. This approach will serve either as a confirmatory experiment for FABP4 or as a backup strategy since it represents a global approach which will reveal other secreted molecules differentially expressed in the presence/absence of HCC.

Recommendation 4: The team has to outline a specific translation strategy (diagnostics, therapeutics) and back-up plans. Answer: We will assess whether FABP4 or other markers obtained in the previous experiment may serve as diagnostic biomarkers of HCC in patients with MS using serum samples of patients with MS and HCC from our biobank. We will collaborate with other teams of the CRI for development of monoclonal antibodies to establish new ELISA.

Team 10 (Bado): We thank the AERES evaluation committee for its appreciation and interest in our projects. We will pay attention to all their recommendations (see below).

Recommendation 1: It is suggested to increase the number of post-docs, and researchers in training.
Answer: Concerning the current absence of postdoc fellows in our team: as noted by the committee, during the last 5 years, we have trained 2 postdocs (S. Guilmeau now Associate Professor at University Paris 5 and V. Jarrousse currently in Postdoc position at CEA Fontenay-aux Roses). In 2013, we applied for numerous financial grants within postdoc fellowships (Ile de France Region (CORDDIM) and ANR). We have already identified a candidate that we would like in the long-term to recruit as full time researcher (Inserm or CNRS) and who is willing to join our team in January 2014. We are very sensitive to the future of the PhD students and postdoc fellows we trained.
Recommendation 2: …improve the research about the role of intestinal microbiota as a link between intestinal inflammation and obesity.
Answer: The study of intestinal microbiota in our experimental models of gastrointestinal weight-loss surgeries will benefit from our longstanding and fruitful collaboration with various members of INRA Micalis (PLoS One. 2013; 8:e54335; Gut 2012 doi: 10.1136.; Biochimie 2010, 92:753-61; Am J Physiol Gastrointest Liver Physiol. 2009;297:G116-23). The analysis of the role of intestinal microbiota as a link between intestinal inflammation and obesity will be facilitated by our integration within the CRI allowing easy collaborations with other teams specialized in intestinal inflammation with whom we already have successfully collaborated (Mol Cell Biol. 2010, 11:2636-50).

Team 11 (van Beers): We thank the committee for the positive evaluation.

Weaknesses and threats: …The need of enlarging the number of senior scientists of the team, including full time researcher, should be emphasized. Also taking into account the quite large number of different elements of this project, the inclusion of several new PhD students or post doctoral researchers would be desirable. Answer: One university researcher (Catherine Pastor who heads the "laboratoire de physiopathologie hépatique et imagerie moléculaire" in the University Hospital of Geneva) will join our team part-time starting this year, being nominated as invited professor at the Paris Diderot University. Philippe Garteiser who currently is post-doc in our lab applies this year as CR2 researcher at Inserm. We also have recruited an additional post-doc (Benjamin Leporcq) and a M2 student (Wassef Khaled) this year. Finally, we have started intensive consulting with a DR of INRIA about future collaboration, including possible joining our research team.

Recommendation 1: The major objective, should focus on the definition of well controlled and documented imaging biomarkers of the onset, the development and the organic functional impact of inflammation.
Answer: Quantitative imaging of inflammation is indeed the major objective of our research group. As explained, besides our functional multiwave/multiscale approach for the development of inflammation biomarkers, we will also focus on a molecular approach with targeted imaging probes, including markers of macrophage subtypes during inflammatory processes.

Recommendation 2: The team should also remained open to direct collaborations with other teams of the CRI.
Answer: We are well aware of the opportunities of collaborations within the CRI. We have already collaborative projects with teams 1, 2, 3, 6, 7 and 9 on tissue inflammation and fibrosis, as indicated in our report and mentioned during the oral presentation. We are convinced that the arrival of Sophie Lotersztajn will further increase our collaborations within the CRI.

Team 12 (Dray): We thank the committee for their recommendations.

Recommendation 1: The committee of experts appreciates and recognizes the interest of the team's projects. However, it is suggested to investigate aspects more closely related to the study of inflammation, in order to improve the coherence of the project with the purposes of the CRI.
Answer: Technology for health can definitely serve / grow from research on inflammation. It is of paramount importance that innovative imaging systems (such as MRI in team 11 and endoscopy in team 12) are embedded in the CRI. Regarding endoscopy, many potential developments are considered (confocal microendoscopy, endoscopic biomarkers) in addition to current advanced projects in optoelectronics (image processing for polyps and IBD) and in therapeutics (preventing tracheal inflammation and oesophageal fibrosis by treating esophageal atresia with natural orifice endoscopic surgery).

Recommendation 2: An increase in the number of young doctors and researchers in training would be desirable.
Answer: Our small but unique team has been most recently created. MSc and PhD students are enrolled starting November 2013. Our developmental strategy is to enroll researchers in biology (to study tracheal inflammation in esophageal atresia) and in optoelectronics (to build endoscopic systems for detection and classification of polyps and IBD lesions). The study of inflammatory processes involved will be performed in close collaboration with CRI teams in particular with team 6.

Finally in the name of all the teams, I want to thank the members of the visiting committee for their careful evaluation and precious suggestions.

Sincerely yours,

Professor Renato Monteiro
Candidate director of the CRI

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ANNEX:

CV and publications of
Sophie LOTERSZTAJN
27/09/1958

Education background :

- Master of Science in human biology/ Master of Science in Physiology, University Paris 7, 1979
- Ph.D in biochemistry, University Paris 6 1982.
- Doctorat es Sciences, University Paris 6, 1985

Professional Experience :

1983-1992	INSERM Research scientist (INSERM U99).
1984	Visiting scientist, Mc Master University, Hamilton, Canada
1990 and 1991	Visiting scientist, University of Liverpool, Liverpool, England
1992- 2002:	Director of research (INSERM U99).
2003-2006	Director of research (INSERM U581)
2007-	Director of research (Institut Mondor de Recherche Biomédicale, INSERM U955)
2004-2009, and since 2009	Contrat d'Interface with AP-HP
Since 2010	Prime d'excellence scientifique

Editorial activity/Consulting

- Associate Editor American Journal of Physiology-Cell Physiology since 2008
- Editorial Board member of American Journal of Physiology (Cell Physiology) 1999-2008.
- Editorial Board member of American Journal of Physiology (Gastrointestinal-Liver) since 2009
- Editorial Board member of Molecular Pharmacology since 2003
- Editorial Board member of the Journal of Hepatology since 2012
- Member of the Advisory Board of Biorion (targeting of antifibrogenic molecules) .

Scientific expertise

French scientific committes

- Member of the Scientific Inserm section CSS9 (2003-2006)
- Member of the Scientific Inserm section CSS5 (1995-1999)
- Expertise for Avenir INSERM position (2002)
- Membre of the scientific section for CDD INSERM position (2004, 2009)
- Chairman of the National Program of research in Hepatology (2005-2007)
- Member of the scientific section CSS 4 of the French agency for research on AIDS and viral hepatitis 2007-2010
- Expert for AERES, ANR
- Member of the administrative committee of the french association for the study of the liver (2008-2011)
- Chairman of the Inserm study section CSS5 (2012-2016)

International committees

- Scientific expertise for Groningen University and american University of Beirut (2003)
- Expertise for the Israelian Scientific Foundation, 2005, 2009
- CEE expert, 6ème PCRDT, 2005 7ème PCRDT, 2009
- Expertise for the Spanish ministry of research (NBRC/ANEP) (2008-2010)
- Expertise for the belgium association Walbio (2012)
- Member of the scientific committee for EASL abstracts evaluation (EASL, 2003 et 2011-2015)
- Member of the scientific council of the International Society for hepatic Sinusoidal research (ISHSR) since 2011
- Member of the scientific advisory board of Ciberehd, (Centro de investigacion biomedica en red enfermaded hepaticas y digestivas, Espagne) since 2009

Meeting organization

- « COX-2 and cell growth: new insights », Symposium :at the joint meeting of the American Society of Pharmacology and experimental Therapeutics (ASPET) and the American Society of Biochemistry and Molecular Biology (ASBMB), June 2000, Boston USA
- Coorganisation of the 2ème European Club for Liver Cell Biology, Abbaye de Fontevraud, 2003
- Coorganization of the meeting « Steatohepatitis, from bench to bedsite », Paris 2004
- « Fibroblasts and myofibroblasts in tissue repair », symposium at the Experimental Biology meeting, San Francisco, 2006
- Early morning workshop on NAFLD, International Liver congress (EASL), Milan 2008
- Early morning workshop on liver fibrosis, International Liver congress (EASL), Copenhagen, 2009
- "Nuclear Receptors: role in liver pathophysiology", AFEF symposium, 2009
- « Nouveaux outils diagnostiques et thérapeutiques dans le CHC », AFEF symposium 2010
- « Pathophysiological mechanisms of alcoholic liver disease » International Society for Biomedical Reseach on Alcoholism, Paris 2010
- « Polymorphismes génétiques » AFEF symposium 2011

- Basic Science Seminar on liver fibrosis International Liver Congress, EASL London 2014, Co organization with C Trautwein and M Pinzani
- EASL monothematic conference on liver fibrosis, 2016, Co organization with C Trautwein and M Pinzani (approved by EASL, Italy, location to be determined)

Selected invitations since 2005

- Cannabinoid symposium, New York, 2005
- Experimental Biology meeting, San Francisco, 2006
- NIAAA, Bethesda, 2006
- Inserm NIAAA joint meeting, Paris 2007
- Inserm Imperial College joint symposium, 2007
- Cannabinoid receptor 2 meeting, Banf, Canada, 2007
- AFERO-ALFEDIAM meeting, Brussels 2008
- 6th Meeting of the International Chair on Cardiometabolic Risk (ICCR), Quebec City, 2008
- Meeting "Roles of cannabinoids in nutrition and digestive diseases" Lille, ,2008
- International Cannabinoid Reasearch Society meeting, Chicago, USA 2009
- International Symposium on Hepatic Encephalopathy, Valencia, Spain 2009
- Réunion franco-suisse de diabétologie, Chamonix, 2010
- EASL Monothematic Conference on "Signaling in the Liver", Amsterdam, Netherlands 2010
- EASL meeting, "Liver fibrosis" symposium, Vienna, Austria, 2010
- International Society for Biomedical Research on Alcoholism (ISBRA), Paris 2010
- Cannabinoids in biology and medicine, Jerusalem, Israel, 2010
- Symposium « obésité et syndrome métabolique», St Denis de La Reunion, 2010
- EASL Monothematic conference on alcoholic liver disease, Athens, 2010
- Joint symposium on alcoholic liver disease EASL-ISBRA, Berlin, 2011
- EASL Monothematic conference on liver fibrosis, St Petersberg, Germany 2011
- UEGW, UEGF Teaching Activity on Basic Science, Fibrosis in the GI Tract, Spineto, Italy, 2011
- International Association for Cannabinoid Medicines and the European Workshop on Cannabinoids Joint Meeting: Cannabinoid Conference, 2011, Bonn
- Mount Sinaï School of Medicine, New York, 2011
- International congress on hepatic glycogen storage diseases, Lyon, 2012
- 17th EASD-Hagedorn Oxford Workshop on Liver Metabolism and Steatosis, Oxford, 2012.
- EASL 2012, post graduate course, conference on "novel mechanisms of alcoholic steatohepatitis", Barcelona 2012
- FASEB Summer Research Conference. "Liver Biology, Fundamental Mechanisms&Translational Applications", Snowmass Colorado, USA 2012
- Meeting of the International Society for Biomedical Research on Alcoholism (ISBRA), annual meeting, Sapporo 2012,
- Meeting of the NAFLD study group, Finland 2013
- Meeting of the International society for hepatic sinusoid research, Osaka, 2013

PUBLICATIONS AND PATENTS SINCE 2008

1) Marra F and Lotersztajn S (2013), Pathophysiology of NASH: perspectives and targeted treatments **Current Pharmaceutical Design,** 19, In press
2) Mallat A, Teixeira-Clerc F and Lotersztajn S, Cannabinoid signaling and liver therapeutics (2013), **J Hepatol,** In press
3) Mallat A and Lotersztajn S Reversion of hepatic stellate cell to a quiescent phenotype: from myth to reality? (2013), **J Hepatol,** In press
4) Deveaux V, Poirier-Quinot M, Luciani N, Levy M, Ballet S, Manin S, Pechoux C, Autret G, Clement O, Rahmouni A, Mallat A, Wilhem C, Lotersztajn S, Gazeau F, **Radiology**, **2012**, 263, 3, 786-793
Article highlighted by an editorial « Science to practice : Why follow the track of macrophages in obesity ? » Roos A. Radiology, 263, 3
5) Louvet, Teixeira-Clerc, Chobert, Deveaux, Pavoine, Zimmer, Pecker, Mallat, Lotersztajn Cannabinoid CB2 receptors protect against alcoholic liver disease by regulating Kupffer cell polarization, (**2011**) **Hepatology,** 54, 4, 1217-26
6) Hyperactivation of anandamide synthesis and regulation of cell cycle progression via CB1 receptors in the regenerating liver. Mukhopadhyay B, Cinar R, Yin S, Liu J, Tam J, Godlewski G, Harvey-White J, Mordi I, Cravatt B, Lotersztajn S, Gao B, Yuan Q, Schuebel K, Goldman D, Kunos G (**2011), PNAS**, 108(15):6323-8
Article « from the cover » and highlighted by an editorial (« Unique pathway for anadamide synthesis and liver regeneration » , Izzo AA and Deutsch DG, PNAS 2011, 16 (108) 6339)
7) Long term in vivo biotransformation of iron oxide nanoparticles. Levy M, Luciani N, Alloyeau D, Elgrabli D, Deveaux V, Pechoux C, Chat S, Wang G, Vats N, Gendron F, Factor C, Lotersztajn S, Luciani A, Wilhelm C, Gazeau F. **Biomaterials. 2011 Jun** ; 32(16):3988-99
8) A Mallat and S Lotersztajn The liver X receptor: in hepatic stellate cells: a novel antifibrogenic target? **(2011), J Hepatol,** 55, 1452-54
9) A. Mallat, F. Teixeira-Clerc, V. Deveaux, S. Manin and S. Lotersztajn The endocannabinoid system as a key mediator during liver diseases : new insights and therapeutic openings **(2011), Br J Pharmacol**, 163,1432-40.

10) Teixeira-Clerc F. Belot MP, Manin S, Deveaux V, Cadoudal , T, Chobert MN, Louvet A, Body-Malapel M, Zimmer A, Tordjmann T Mallat A and Lotersztajn S, Beneficial paracrine effects of Cannabinoid receptors on liver injury and regeneration, **Hepatology, 2010** sept 52(3) : 1046-59.

11) Mallat A and Lotersztajn S, Endocannabinoids in the pathophysiology of obesity-the liver (2010) **, Drug Discovery today**, 7(3-4) e185-e190

12) Endocannabinoids and their role in fatty liver disease. Mallat A, Lotersztajn S. Dig Dis. 2010;28(1):261-6.

13) Latasa MU, Gil-Puig C, Fernández-Barrena MG, Rodríguez-Ortigosa CM, Banales JM, Urtasun R, Goñi S, Méndez M, Arcelus S, Juanarena N, Recio JA, Lotersztajn S, Prieto J, Berasain C, Corrales FJ, Lecanda J, Avila MA. Oral methylthioadenosine administration attenuates fibrosis and chronic liver disease progression in mdr2-/- mice. **PLoS One**. **2010** Dec 29;5(12):e15690.

14) Servettaz A, Kavian N, Nicco C, Deveaux V, Chereau C, Wang, Zimmer A, Lotersztajn S, Weil B, and Batteux F, Targeting the cannabinoid pathway limits the development of fibrosis and autoimmunity in a mouse model of systemic sclerosis, **Am J Pathol, 2010,** 177(1):187-96.

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16) The cannabinoid receptor type 2 promotes cardiac myocyte and fibroblast survival and protects against ischemia/reperfusion-induced cardiomyopathy. Defer N, Wan J, Souktani R, Escoubet B, Perier M, Caramelle P, Manin S, Deveaux V, Bourin MC, Zimmer A, Lotersztajn S, Pecker F, Pavoine C. **FASEB J. 2009** Feb 26.

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3. Lotersztajn S, Mallat, A, Louvet, A Teixeira-Clerc F . Use of agonists of the CB2 receptor for the manufacture of a composition useful for the treatment of alcoholic liver disease, european application EP09305700.8 23/07/ 2009. International application in 2010

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