2IC - Infection et inflammation chronique

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Cell death, Inflammation, Infection

CD2I

Under the supervision of the following institutions and research bodies:

Université de Versailles Saint-Quentin en Yvelines - UVSQ

Institut National de la Sante Et de la Recherche Médicale - INSERM

École Pratique des Hautes Études - EPHE

February 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Ms Carmen GARRIDO, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the expert committee, the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Cell death, Inflammation, Infection
Unit acronym:	CD2I
Label requested:	INSERM, UVSQ
Present no.:	
Name of Director (2013-2014):	
Name of Project Leader (2015-2019):	Mr Gilles CHIOCCHIA

Expert committee members

Chair:

Ms Carmen GARRIDO, Université Dijon

Experts:

Mr Hafid AIT-OUFELLA, Université Paris-Descartes

Ms Martine GILLERON, Université de Toulouse

Mr Dominique HEYMANN, Université de Nantes (representative of CSS INSERM)

Mr Jean-Claude MARTINOU, University of Genève, Switzerland

Mr Ulrich MAUS, Hannover Medical School, Germany

Mr Georg SCHETT, University of Erlangen, Germany

Scientific delegate representing the AERES:

Ms Sophie DE BENTZMANN

Representatives of the unit's supervising institutions and bodies:

Ms France GONNET (representative of Doctoral School n°423)

Ms Anne ROCHAT, INSERM

Mr Giovanni STEVANIN, EPHE

Mr Jean-Luc VERSIERE, UVSQ

1 • Introduction

History and geographical location of the unit

The research teams of this future unit ("Cell death, Inflammation and Infection") are all located in the same building (Simone Veil) within the Faculty of Health Sciences, Université de Versailles St-Quentin. The proposed unit gathers four university teams and one Inserm group (initially at the Institute Cochin, Paris). These five teams have different thematics but many possibilities for collaborations because of their different known-hows. Most scientists involved in the project are academic (professors or assistant professors), some are medical doctors and very few full researchers (2).

Management team

The future unit will have a director Mr Gilles CHIOCCHIA who is also co-director of the team 3, and a co-director and will be composed of 80 staff members. Some more thought is needed about how the unit will be managed/directed. For instance, a unit council does not exist yet and there is not a clear policy about money issues. The future unit has already proposed to have a technology transfer committee directed by on PI that will gather together team leaders and representants of the intellectual property institutions.

AERES nomenclature

SVE1_LS4 Physiologie, physiopathologie, biologie systémique médicale

SVE1_LS3 Biologie cellulaire, Biologie du développement animal

SVE1_LS2 Génétique, génomique, bioinformatique

SVE1_LS6 Immunologie, microbiologie, virologie, parasitologie

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	36	37
N2: Permanent researchers from Institutions and similar positions	2	2
N3: Other permanent staff (without research duties)	10	12
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	2	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	7
N6: Other contractual staff (without research duties)		1
TOTAL N1 to N6	**55**	**60**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	21	
Theses defended	20	
Postdoctoral students having spent at least 12 months in the unit	8	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	24	24

2 • Assessment of the unit

Overall opinion about the unit

The research activity of the unit is broadly centered on inflammation studies. The different teams seem to have made an effort so their heterogeneicity (both between teams but also, for team 4, within the group) might be an advantage. Some of their projects clearly reflect their strong will to strengthen and expand further their collaboration and develop new projects at the interface of their different domains.

In-house facilities are very good and include classic technical services but also different platforms dedicated to mass spectrometry, cellular imaging, confocal microscopy, animal houses, FACS, P3, etc.

In general, the experts committee has appreciated the different know-how among the teams and the multidisciplinary approaches. The potential for becoming a reference in translational research for some inflammatory disorders is impressive. The dynamism of some of the team leaders, including the future unit director, has been remarked.

Strengths and opportunities related to the context

The unit will be clearly visible in the French and international research landscape, as each of the future constituting teams is well known in their repective fileds.

All the teams are physically close (within the same building).

A good scientific environment is already established in terms of facilities and platforms very well equipped.

The future unit gathers groups with different themes and know-how. A convincing effort has been made to build on the different expertises.

The future unit has very good connections with master and medical students. The unit members are deeply involved in teaching and training actions. The teams of the future research unit benefited from a regular recruitment of assistant professors (both from the university and the EPHE).

The high percentage of young scientists in the research teams results in a very dynamic atmosphere.

Several of the unit teams leaders have a very good to excellent international visibility and reputation.

The amount of contracts with private companies is impressive.

The different protagonists of the future unit have been able to raise excellent funding from National agencies, but also from European calls.

An effort is being made to encourage the teams to patent.

Weaknesses and threats related to the context

Among the 5 teams, there are only two full time researchers and one will be the director of the future unit. There is, therefore, a strong need for reinforcing the pool of full time researchers.

There is also need of more engineers/techicians. The EPHE (team 1) has engaged to give one position to the unit.

There is a lack of post-doctoral fellows in most teams. Recruitment of post-doctoral fellows should be increased, particularly because this is a first step for the recruitment of future researchers.

It will be necessary to provide actions for maintaining the scientific cohesion. Since this is a unit creation, although collaborative projects have been started already, there is not yet any publication, patent or accepted grant for strenghtening these collaborative works.

There are few international contracts.

The number of high ranked publications, at least in some teams, is quite low.

Only team 4 has patents.

Recommendations

The unit will have to work in order to be more attractive for young researchers (foreigners and French post-doctoral fellows).

Some teams should try to publish in higher impact journals even if that means to publish less.

The emergence of a new generation of young scientists as group leaders should provide the required momentum for new perspectives. This is particularly true for team 2. This team is actually leaded by a PU-PH with many duties (ministry, dean, hospital and teaching duties) and will require to strenghten its research activity. The experts committee strongly advices that a permanent professor or researcher with less duties co-directs the team.

The Microbiology team (team 4) appears dispersed in different sub-projects not related one to the other. An effort should be made to have less but more focused projects (host inflammation/infection).

The scientists should be ambitious enough to push their own research in the front line by initiating and coordinating national and european networks and competing at the highest level for prestigious grants.

The future unit would benefit from the recruitment of an immunology team.

An unit council should be formed, composed not only by the team leaders but also by at least one representant of each unit workforce. The financial aspects for the unit management should be clearly and rapidly discussed within the unit council.

3 • Detailed assessments

Assessment of scientific quality and outputs

Excepting team 1, all future teams have a strong expertise in translational research. The relevance and the originality of the research conducted is attested by the individual scientific records of teams and the research they carry on has a strong echo in their respective communities. This is true for the peer-reviewed articles (i.e. several JAMA published in team 2; Immunity, PLOS Genet, etc for team 3), but also for the valorisation work of team 4 (5 patents). The scientific quality, although unequal among the teams, in general is very good.

Concerning the synergy, and how their being together will result in an improvement of the collaborative productions, it is too early to conclude but they already propose some interesting collaborative works and the fact they are located within the same building must undoubtedly favor these collaborative works.

Assessment of the unit's academic reputation and appeal

The academic reputation and appeal is good as attested by the presence of foreigner post-doctoral fellows (for teams 2 and 3). Future unit members are regularly solicited as referrees for journals, jury members of thesis, HDR, committees, for collaborations (as seen for ANR, publications and their belonging to study groups such as: CORTICUS, APPOCHES Trial investigators, etc.). They are regularly invited to national and international meetings and have organized workshops/meetings. Team leaders have been involved as advisors in different national and international scientific councils. The 5 team leaders are recognized leaders and invited speakers in international conferences in their respective fields.

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

The teams have excellent connections with the pharmaceutical industry at different levels and abundant contracts with privates societies. 5 patents have been obtained for team 4, of which members are consultants for one biotechnology company and shareholders of another one.

The different teams are all engaged in actions beyond their academic environment.

Assessment of the unit's organisation and life

The strong point of the research unit lies on the fact that constitutive teams are all in the same building and this physical proximity is evident when discussing with the students of the different teams. Another strong point is the impressive facilities, all also within the same building. At its turn, team 1 is the coordinator for most academic activities and seems at the center of all the collaborations within the unit.

The different team leaders have already started to organize this new unit. However, they still need to constitute a unit council and to decide how the money will be shared among the different teams and whether some money will be reserved, for instance, to fund collaborative projects within the unit.

They already proposed to have a technology transfer committee directed by one PI of team 4, teams leaders and representants of the intellectual property institutions that will meet every three months.

For communication, they are putting efforts to develop a website.

Assessment of the unit's involvement in training through research

Future unit members are strongly implicated in teaching and master programs and have contributed to a wide ranging of teaching initiatives and teaching supports. The researchers of the unit are largely involved in training PhD and M2 students (supervision, publications). Most of the researchers have a professorship or assistant professorship position directly involved with university educational tasks. The participation of the unit to the doctoral school is very good through the leader of team 1 who is director of this doctoral school (shared by the universities of Versailles St-Quentin and Evry Val-d'Essonne) but also responsible for the master Cellular Biology (155 PhD students, 185 HDR, 45 associated teams). The team 1 leader is an active organizer of the different activities of the doctoral

school i.e. “journées de l’École Doctorale“ to which participate many members of the 5 teams. The participation of the PhD students is mandatory (either with poster or oral presentation for the 3rd year PhD students). The PhD students of the teams that belong to the future unit have an average time for the thesis of 42 months and do not have any requirement in terms of publications to get their PhD. The experts committee felt very surprised that some HDR in the unit can take as much as 6 students in co-direction. As this doctoral school will disappear to be substituted by a new one that will be common to 10 different universities of the surroundings of Paris (including the Université de Versailles), this will be harmonized. The experts committee recommends that the unit will propose a Master program unique to their know-how.

Assessment of the strategy and the five-year plan

The projects are original, ambitious, timed and propose integrated approaches. Most proposed projects are relevant and feasible, with a few minor readjustments. Among the projects, several involve a collaboration between the teams. This inter-team collaborations and synergy mostly organized by the team 3 should be encouraged in order to pull all the teams at the excellence level of this team.

It is recommended that their theme remain focused on the main subjet of the unit: Inflammation/Infection/Sepsis. It is strongly recommended that an immunologist join the unit. It has to be noted that not all teams have reached the same level of excellence and therefore the collaborations and synergistic interactions should take into account the reinforcing or integration of the more fragile teams. The strength of the research unit resides more in its strong originality and visibility in the French and European scientific landscape than in the excellence of some of the teams.

4 • Team-by-team analysis

Team 1: Cell death and cellular stress

Name of team leader: Mr Bernard MIGNOTTE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	10	11
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	4*	1
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**15**	**13**

* : Among these 4 people, one person died in December 2013, two people in charge of whashing/prep medium will be affected to common facility of the unit.

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	7	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs

The team and the team leader have been active in the apoptosis field since the early 90s and have investigated various pathways involved in the control of apoptosis, including the role of mitochondria, the Bcl-2 family members and p53. Many of the results have been obtained using Drosophila as a model organism, for which the team has built up a strong expertise. The main results of the team during the past five years can be summarized as follows:

- p53 was shown to interact with OSCP, a subunit of the ATP synthase, thereby regulating oxidative phosphorylation (Cell Cycle, 2013);

- FGF1 inhibits p53-dependent apoptosis via an autocrine pathway involving its translocation to the nucleus (BBA, 2009);

- RBF, the Drosophila homologue of the human retinoblastoma protein, displays both pro- and anti-apoptotic activities depending on the proliferative or quiescent status of the cell (Cell cycle, 2010).

In addition, members of the team have participated in a study showing that Ref(2)P is required for protein aggregation in the Drosophila brain (JCB, 2008).

In the past five years the team has published 28 papers in peer-reviewed international journals, and most of these have been with medium impact factors. Of note, 13 papers have been published in collaboration with other teams. Members of the team have also been involved in producing two teaching books for medical students.

Assessment of the unit's academic reputation and appeal

The team has established a number of national and international collaborations (11 separate collaborations during the past five years). The team funding mainly comes from the university and to a lesser extent from a recurrent subsidy from the Ligue Contre le Cancer des Yvelines .

In May 2014, the team leader will be chairman of a session at an international meeting on apoptosis in La Baule.

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

The team leader has participated in a number of large public conferences on cell death and has been a member of the scientific committee of the Cosmetic Valley cluster from 2007 to 2012. The team has signed a contract a cosmetology group to evaluate the potential of cosmetic components to counter endogenous and exogenous mitochondrial oxidative stress.

Assessment of the unit's organisation and life

The group currently consists of 2 professors, 7 assistant-professors, four of whom have a HDR, 1 technician, 1 post-doctoral fellow and 5 PhD students. The team has regular lab meetings and the students appear to be well integrated.

Assessment of the unit's involvement in training through research

Five PhD students have defended their thesis between 2008 and 2013. Seven PhD students are currently at different stages of their thesis work. Moreover, it is important to mention that many members of the team are actively involved in teaching at the Master's level and in doctoral schools. The team leader is coordinator of the Master's programme on 'Biology-Health' at UVSQ and director of the Doctoral School ED n°423. During the past 5 years, the team has provided educational tutoring for 26 Master's students and 41 students preparing for the diploma of the EPHE.

Assessment of the strategy and the five-year plan

The plan for the next five years is based on previous findings by the team and can be divided into 3 parts:

1) the role of FGF1 in the control of p53-mediated apoptosis;

2) the role of Rbf1 protein in cell death;

3) mitochondrial and ER stress in Drosophila.

All projects are original and the programs are feasible.

- Project 1) The team members hypothesize that FGF1 and p53 interact and form part of a larger complex which they would like to characterize further by immuno-precipitation and mass spectrometry. They also hypothesize that FGF1 could act as a transcription factor and will perform chromatin IP studies. These hypotheses are reasonable

and the knowledge of the team on apoptosis will be an asset in understanding how FGF1 can counteract p53-induced cell death.

- Project 2) The team has shown that, depending on the cell context, Rbf1 can be either pro- or anti-apoptotic. The team proposes to build on their recent finding that the pro-apoptotic activity of Rb involves dE2F2-dependent down-regulation of dIAP1 and Buffy, leading to mitochondrial fission, ROS production and JNK activation (this work has been submitted for publication). The aim of the team is now to understand how Rbf1 controls these events. For this, they will investigate the role of the Rbf1-associated DREAM complex in the transcriptional regulation of Buffy expression. In addition, using a genetic approach, they will search for suppressors of Rbf1 action. The work seems interesting and could potentially lead to the identification of key regulators of Rbf1 pro- and anti-apoptotic functions.

- Project 3) The team has developed a model of ER and mitochondrial stress in Drosophila and is currently investigating the pathways that lead to cell death or survival through compensatory mechanisms.

It is important to point out that the team is also making their tools and expertise available to other research projects currently ongoing in the unit. For this, they have stopped working on several projects (e.g. p53 and mitochondria) and will focus on the dynamics of mitochondria in septic shock (interaction with team 2), HLA-B27-induced ER stress in Drosophila and mammalian cells (team 3) and on new modulators of the immune response in Drosophila (team 3).

Conclusion

- **Strengths and opportunities:**

The projects seem to be well focused and an effort has been made to integrate the research of the group into the global activities of the future unit. The team has an excellent knowledge of the mechanisms of apoptosis and a well-recognized expertise in the use of *Drosophila* as a model organism. Both will be of benefit to the other teams of the future unit. The expertise of the team is not limited to *Drosophila* but also includes experience with mammalian cells. This allows them to extend their findings in *Drosophila* and test their relevance to mammalian cell apoptosis. Importantly the team has access to the outstanding services and facilities that have been set up in the unit, which is a major asset for their research.

- **Weaknesses and threats:**

The publication record of the team is very good but yet not outstanding, and a greater effort should be made to publish more papers in high impact journals. Moreover, the group would be well advised to expand their experimental model systems to clinically relevant mouse models and to help the other teams that are more clinically oriented with their knowledge in apoptosis. Members of the team should also participate more widely in key scientific meetings to increase the national and international visibility of the team's work.

Many key members of the team are heavily involved in teaching responsibilities, and this inevitably reduces the amount of time spent on the team's research activities.

Finally the funding of research is mainly dependent on the UVSQ. The team should attempt to diversify its sources of financial support.

- **Recommendations:**

The projects are well constructed, the questions are relevant and there is no doubt that the *Drosophila* model can be useful in identifying new players in stress induced cell death. However, the projects can only be successful if more effort is put into research. This will require recruitment of additional post-doctoral fellows, or scientists involved in full time research, and able to mentor the PhD students on a day-to-day basis.

Team 2: Neuroendocrine response to sepsis

Name of team leader: Mr Djillali ANNANE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5	5
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (PREM, ECC, etc.)	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		1
TOTAL N1 to N6	**9**	**10**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

The main research goal of the team is to investigate the neuroendocrine response to sepsis, focusing on the hypothalamic-pituitary-adrenal axis and the noradrenergic system exploration. They also aim to characterize brain dysfunction following acute injury in critically ill patients. During the last campaign 2008-2013, the team has investigated different therapeutic approaches in septic shock patients based on corticosteroid (N Engl J Med 2008, JAMA 2009, JAMA 2010, Crit Care Med 2008, Intensive Care Med 2010 & 2011) and activated C protein (AJRCCM 2013) administration. In animal models, the team has reported an alteration of ACTH synthesis (Intensive care Med 2008, Plos One 2011) and Vasopressin secretion (Crit Care Med 2010) in sepsis context. More recently, they focused on the modulation of the noradrenergic system using B1-blockers (Intensive Care Med 2011). Finally, they developed a multimodal analysis of brain dysfunction in critically ill patients (Crit Care Med 2010, Crit Care Clin 2008) with clinical tools and anatomo-pathological analysis in collaboration with Pasteur Institute (Paris).

In the last five years, the team published 92 articles in international journals with 5 publications in high ranking journals (IF>10), 39 publications in good journals (5<IF<10) and 48 publications in others (IF<5). The main publications have been done on clinical multicenter studies. Based on its track record and the international recognition of the team leader, the team is clearly leader in Europe in the field of human septic shock management.

Assessment of the unit's academic reputation and appeal

The team leader is nationally and internationally recognized in the field of clinical management of sepsis as demonstrated by several invitations in national and international meetings (>50 presentations). The team leader is member of the editorial board of several journals (Intensive Care Med, J Crit Care) and recurring reviewer for seminal journals (N Engl J Med, Lancet, AJRCCM, British Med J). The team is involved in various societies (Société de Réanimation de langue française, Société française d'Anesthésie réanimation, The British Microcirculation Society).

In addition, the team leader chairs the "systemic review group of the European Society of Intensive Care Medicine", the group "initial fluid inotropic vasopressor therapy" of the international surviving sepsis campaign. One member of the team organizes since 2010 the "Versailles international neurocritical care symposium".

The team has developed an important international network and an exchange program for PhD student (Canada, England, Belgium).

In the last five years, funding was regularly obtained mainly from PHRC program CRC, ANR and DIM.

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

During the last 2 years, the team leader was the president of the "Société de Réanimation de langue française" that interacts with several patient care associations and is implicated in the communication on Intensive medicine. The team had research contracts with industrial partners.

Assessment of the unit's organisation and life

The team includes 6 permanent positions (3 PU-PH, 1 MCF, 1 PH, 1 AHU), 1 permanent research engineer, 6 PhD students and 1 Master student. The team is organized in 3 axis based on technical aspects: animal models of sepsis, anatomo-pathological analysis of samples from septic shock patients (plasma, adrenal glands and brain), and hemodynamic/brain function exploration in human and animals.

Assessment of the unit's involvement in training through research

The team leader is the dean of the UVSQ. He is strongly involved in teaching and promoting the development and the organization the new university.

During the last campaign, team members have trained 3 PhD students and 15 master 1 students/year. The team leaders are strongly involved in teaching activities: Master 1 "biologie-santé-UVSQ", Master 2 "Biologie Intégrative et moléculaire", medical school. One member of the team is in charge of a university degree in neurointensive care.

Assessment of the strategy and the five-year plan

In the next five years, the team will focus its research on experimental and human sepsis with 4 main parts:

1/ interactions between the adrenal-derived peptides and the immune system;

2/ mechanisms of vasopressin depletion during septic shock;

3/ effects of beta antagonists on metabolic and inflammatory responses during septic shock;

4/ exploration and characterization of brain dysfunction during injury.

They will develop mouse models of sepsis and adrenal deficiency and analyze human samples from international biobanks. They aim to investigate in details the immune system in sepsis and critically ill context and the impact of corticosteroids and beta-antagonists on the inflammatory response.

The team will also focus on the exploration of brain injury during severe injury with clinical and computer-assisted monitoring in patients. In addition, histological studies on a rare brain tissue biobank will be performed.

Overall, the funding obtained demonstrated the capacity of the team to self-sustain its research programs over the next 5 years.

Conclusion

- **Strengths and opportunities:**

The projects are proposed by experts internationally recognized in the field of sepsis. The goals are interesting and translational with experimental and clinical approaches supported by financial funding. They are highly feasible, based on the scientific background of the team, the biological cohorts already established and the technical skills available.

The project on the exploration of brain dysfunction during severe injury is original and adds novelty.

- **Weaknesses and threats:**

Mechanistical analysis in experimental and translational studies performed by the team requires additional cellular and molecular explorations.

The effects of corticosteroids during severe infections have been extensively studied and the originality of this project is questionable.

The team project and its integration in the new multidisciplinary group have to be emphasized.

The team has a weak expertise in fundamental research.

- **Recommendations:**

The projects proposed are interesting and translational. The integration in the CDI2 group will provide cellular and molecular skills.

An additional full time basic researcher would be necessary if the team decides to address more fundamental and mechanistic questions.

Team 3: Chronic Inflammation and immune system

Name of team leader: Mr Maxime BREBAN and Mr Gilles CHIOCCHIA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	5
N2: Permanent EPST or EPIC researchers and similar positions	2	1
N3: Other permanent staff (without research duties)		1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7**	**9**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	5	6

• Detailed assessments

Assessment of scientific quality and outputs

The main research goal of the team is to investigate the pathogenesis (mechanisms involved in the initiation, progression and perpetuation) of chronic inflammatory articular diseases, such as ankylosing spondylitis and rheumatoid arthritis. The team identified and characterized a new susceptibility locus in spondyloarthritis (PLoS Genet 2009, Nature Genet 2013, Arthritis Rheum 2011 and 2013, Ann Rheum Dis 2012 and 2013). The group has initiated the characterization of a functional defect in dendritic cells in this disease (Arthritis Rheum 2008, 2009, 2010, 2011, 2012, 2013) and defined the major implication of these cells in the TH17 cell differentiation and Treg function in the inflammatory process associated to spondyloarthritis (Immunity 2013; Arthritis Rheum 2011 and 2014). Using genomic approaches, they identified several molecular signatures in chronic spondyloarthritis and rheumatoid arthritis (Arthritis Ther 2009, Arthritis Rheum 2010 and 2011) and more recently, they identified the intra-cellular behavior of the HLA-B27 alleles in correlation with spondyloarthritis predisposition (Arthritis Rheum 2014). In the last five years, the team published 81 articles in international journals, 32 of them published in the top journal of

rheumatology (16 in Arthritis Rheumatism, IF 7.4 and 16 in The Annals of Rheumatic Diseases, IF 9.11). In addition, the team contribution is marked by one manuscript published in Nature Genetic (IF 35.2), 2 in PLoS Genetics (IF 8.5) and one in Immunity (IF 19.6). Based on its track record and the international recognition of the team leaders, the team is clearly leader in Europe in the field of arthritic diseases.

Assessment of the unit's academic reputation and appeal

The team is nationally and internationally recognized in the field of arthritic diseases, as demonstrated by 60 invitations to national and international meetings. One of the team leaders is co-coordinator of the labex « Inflamex ». This laboratory of excellence associates 10 internationally recognized scientific teams to address, through an interdisciplinary approach, the inflammatory mechanisms regulating main autoimmune inflammatory chronic diseases. The other team leader is the French coordinator of an international randomized control trial in axial spondyloarthritis and is coordinating an international multicenter trial in patients with active rheumatoid arthritis. The team leaders are members of several Editorial boards of international journals: Medical Immunology; Open Journal of Autoimmunity; Arthritis Rheumatism. In addition, they are active members of various scientific advisory boards (Arthritis Foundation, French Society of Rheumatology, ESPOIR cohort). The two team leaders organize the « Journées de Cochin de Rhumatologie» since 2007, the EULAR sonography course in 2008 and are in charge of the organization of the international meeting on Clusterin in 2014. They are on board of the International spondyloarthritis congress since 2000, of the IGAS meeting since 2009, of the EULAR meeting since 2011 and the OMERACT meeting since 2010.

In the last five years, funding was regularly obtained for a total of 1.8 million € (average/year: 300,000 €) from ANR, Foundations, Labex, industry and PHRC.

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

The team leaders are strongly involved in the patient's care associations. Indeed, they contribute to the scientific advisory board of the association ACS « Action Contre les Spondyloarthropathies » and participate to the annual meeting of the patient's association. They initiated a partnership with the patients association ACS, the UVSQ, the Ambroise Paré hospital and a private partner "BePatient" dedicated to patients information and follow up. One of the team leaders participates to the special day dedicated to the information for Rheumatoid arthritis affected patients and their families.

Assessment of the unit's organisation and life

The team is very well structured and includes 7 permanent positions (1 DR INSERM, 1 CR INSERM, 2 PU-PH, 1 MCU, 1 PH, 1 IR), 4 non-tenured technicians/engineers, 3 post doctoral fellows and 4 PhD students. The team is organized in 4 axis based on technical aspects: genomic analysis, functional and validation of the targets, animal models, clinical applications.

Assessment of the unit's involvement in training through research

Team members have trained 9 PhD students since 2008 and 4/5 master students per year. The team leaders are strongly involved in teaching activities. One of the team leaders has been head of a teaching unit in the Master 2 degree issued from the Labex (Univ. Paris Diderot) and is co-head of a teaching unit in Master 2 degree « Ostéoarticulaire et Orofacial » (Univ. Paris 13). In addition, he is external member of the Doctoral School Galilée (Paris 13). Since january 1st 2014, the team is part of the Paris-Saclay school: ED "Structure et Dynamique des Systèmes Vivants" (SDSV).

Assessment of the strategy and the five-year plan

In the next five years, the team will focus its research on sondyloarthritis using genomic, cellular biology and animal approaches. The various aspects studied will be the genetic susceptibility, the role of the antigen-presenting and T cells, the microbiome to gain insight into the interactions between host genetic background, immune system and environmental triggers. The team will start from a large body of data recently obtained by combining genetics, transcriptomics, proteomics, cellular biology and animal models. A new whole genome linkage study on the largest collection of multiple-cases families ever studied in spondyloarthritis and a dense marker panel (250,000 SNPs) was then conducted and identified two new loci with significant linkage threshold in 13q13. Based on these findings, the

working hypothesis is that a rare variant (or rare variants) is (are) contributing jointly with HLA-B27 to the high penetrance of the disease in these families. The team then proposes to identify the disease locus by deep-sequencing of the identified region of chromosome 13 in a collection of affected individuals belonging to the most linked families. Identification of significantly associated polymorphisms will be followed by functional in vitro and in vivo studies. The team also proposes to investigate, using high-throughput RNA sequencing, the differential expression of both long and small RNA in immune cells (CD14+ monocytes, macrophages, dendritic cells, CD4+ T cells, etc). This characterization will be followed by functional study of monocytes/macrophages and dendritic cells, both in rat model and patients. Finally, the team will study the role of three molecular targets (clusterin, FADD, CITED2) already identified in spondyloarthritis. In conclusion, this ambitious project articulates around two axes: 1) analysis of molecular signatures of the patients to determine new therapeutic and diagnostic targets, 2) establishing the role of already identified targets: the clusterin, FADD and CITED2; this should allow to connect genotype and phenotype of gene expression to the phenotype of the disease of interest. Overall, the funding obtained demonstrated the capacity of the team to self-sustain its research programs over the next 5 years.

Conclusion

- **Strengths and opportunities:**

The projects proposed by experts internationally recognized in the field are ambitious, well constructed, with financial funding. They are highly feasible based on the scientific background of the team, the biological cohorts already established and the technical skills available. These projects strongly focused in the pathophysiology of spondyloarthritis are major assets of the “Cell Death, Infection and Inflammation unit”.

- **Weaknesses and threats:**

In addition to the biological cohorts available, the team is developing rat model of spondyloarthritis. A mouse model would be very useful to develop preclinical approaches of this disease.

- **Recommendations:**

To conclude, the projects proposed are particularly interesting, very well focused, well conducted and show a strong added value for the better understanding of the pathophysiology of spondyloarthritis and for the future therapeutic developments. It is recommended to give a specific attention to reinforce the links with the other teams of the unit.

Team 4: Pathophysiology and diagnosis of microbial infections

Name of team leader: Mr Jean-Louis HERRMANN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	9	10
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	2	4
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**16**	**19**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

The team is organized into three subgroups, each of them headed by a principal investigator. The main topic of the team is the study of chronic infectious and inflammatory diseases. The research axes are:

I) fast growing mycobacteria, with a particular focus on *Mycobacterium abscessus* complex;

II) bone and joint infections by Staphylococcus;

III) the respiratory syncytial virus (RSV).

The major achievements of axis 1 are:

I) the analysis of the genome for understanding the complexity of *M. abscessus* isolates. The complete genome sequence of *M. abscessus* (sensu stricto) (Plos One 2009), highlighting horizontal gene transfer of virulence genes, from distantly related environmental bacteria, mostly actinobacteria and pseudomonads. They discovered extensive rearrangements between closely related species inside the *M. abscessus* complex (J. Clin. Microbiol. 2011);

II) the understanding of the hyper-inflammatory response occurring throughout the course of a pulmonary infection in cystic fibrosis patients. Inflammation in these patients is associated to the presence of a Rough (R) morphotype of M. abscessus that overproduces lipoproteins, key TLR2 ligands. This is of clinical importance as R morphotypes are associated with more severe and persistent infections (Cell. Microbiol. 2011);

III) the understanding of the transition observed in M. abscessus isolates from S to R morphotypes, at the genome and the transcriptome levels (Mol. Microbiol. 2013).

The major achievements of axis 2, focusing on osteo-articular prostheses infections, are:

I) the description for the first time of the clonal population of *Staphylococcus epidermidis* isolates (J. Clin. Microbiol. 2009 and 2013);

II) the set up of an infectious model in rabbit which reproduces nearly the events of early post-operative infections observed in humans, thereby contributing to a better understanding of the pathophysiology of infections by S. aureus, a major pathogen in humans (Plos One 2009 and 2012).

The team uses this model to develop new biomaterials inhibiting adhesion and/or bacterial multiplication during infections on prostheses (supported by ANR TECSAN).

As recommended by the previous AERES experts committee in 2009, the axis on RSV was promoted and experiments were initiated in March 2011. A new reverse genetic system for RSV has been set up and for the first time the RSV polymerase protein has been produced *in vitro*.

In the last 5 years, the team published 73 articles in international reviews (47 in basic research, 26 in clinical research) including 1 Plos Med. (2008), 2 Plos Pathog. (2008 and 2011), 1 PNAS (2014), 3 J. Virol. (2008 and 2009), 1 Cell Microbiol. (2011), 1 Nat. Immunol. (2010), 2 Clin. Inf. Dis. (2009 and 2011). Team members are authors of 2 important reviews, in Trends Microbiol. (2010) and in Annu. Rev. Microbiol. (2008). Team members are first and/or corresponding authors of 44 of these articles. In partnership with the Pasteur Institute, they also created a MLST (multi locus sequencing typing) *M. abscessus* website which is under their guardianship.

Assessment of the unit's academic reputation and appeal

The team is member of several networks (Azay-Mycobacteria network which enables surveillance of infections and resistance to antibiotics of Mycobacterium tuberculosis; the ISMABIOs regional network for the surveillance and treatment of bone and joint infection; “Paris National Reference Center for Bone and Joint Infections” which is part of a nine-center national network to improve the standard of care of complex bone and joint infections). Senior researchers of the group have been reviewers for several international journals and for funding agencies. Two researchers are Academic editors for PLoS One. One of them is a visiting scholar at The Wyss Institute at Harvard Medical School (Boston, USA) and part of the work is performed at UVSQ. In the last 5 years, one ANR was obtained, as well as an important financial support from ISMABIOs (573 K€) to buy mass spectrometers. Small regular funding came from VLM (Vaincre La Mucoviscidose), Legs Poix, eau de Paris.

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

One team member is consultant for a diagnostic company, for which he was one of the two creators. Moreover, this team member together with the team leader are shareholders in a company involved in identification of bacteria, fungi and mycobacteria by mass spectrometry. RSV subgroup collaborates with pharmaceutical industry for exploring the activity of new molecules in experimental models. The team has 5 patents, including 3 patents filed with the Wyss Institute.

Assessment of the unit's organisation and life

The team moved in September 2012 from Garches and Ambroise Paré hospitals to the new site of the Medical Faculty "Sciences of health - Simone Veil" at Montigny le Bretonneux. One laboratory has been maintained on the Garches site for the clinical research. The team is organized into 3 thematic clusters:

1) Mycobacterium abscessus and other rapidly growing Mycobacteria;

2) osteo-articular protheses infections;

3) respiratory viruses. It includes 14 senior researchers, 2 PhD students, 1 post-doctoral fellow, 2 engineers.

Assessment of the unit's involvement in training through research

Team members have trained 35 Master 1, 5 Master 2, 4 PhD students (2 of them defended their thesis during the period), 3 post-doctoral fellows during the period. They are involved in science and medical teaching activities. They are members of 2 doctoral schools. They also participate in the set-up of an inter university diploma about the management of complex joint infections.

Assessment of the strategy and the five-year plan

A specific project is described for each thematic cluster that is in the logical development of the previous work.

Projects of axis 1 are to decipher the intracellular behavior of Mycobacterium abscessus complex, by (I) assessing its virulence in 3 different models (APC, Amoeba and zebrafish) and a mutant library of R and S strains and (II) identifying new gene families that may explain the specific properties of M. abscessus (i.e. understanding M. abscessus speciation process, genomic history and genomic plasticity). These projects will be performed through national collaborations with Pasteur Institute (Paris) and CNRS (Montpellier). An ANR funding started in 2013 will support the program using the zebra fish model. This program will use the platforms "Cymages" and "2Care".

Implant infection is a 3-player game involving the bacterial biofilm, the implant surface chemistry and topology and the host response. The program of axis 2 addresses prosthetic joint infection in its prevention, immune modulation and optimized antibiotic treatment by integrating the biological capabilities currently in place in the laboratory and the assay of novel biomaterials and advanced chemical engineering performed by collaborators in France, Canada and USA in order to face the challenge of bacterial colonization of medical implants. Projects are to:

I) use Staphylococcus epidermidis as a model agent of implant biofilm infection;

II) develop biofilm resistant implant surfaces;

III) precise the biofilm specific antibiotic profiling.

RSV is a major health problem, for which there is no anti-viral drug and no vaccine. Projects of axis 3 aim at (I) characterizing viral-cell protein interactions at the molecular level (identifying cellular proteins playing a key role in RSV replication) (an ANR funding has been obtained for 2014-16) and (II) investigating the structure and composition of inclusion bodies where genome transcription and replication take place. These data are expected to help defining molecular targets for the development of antiviral drugs.

Conclusion

- **Strengths and opportunities:**

The expertise in mycobacterial infections as well as joint and bone infection is a strength of the team, in particular when participating in a future joint center dedicated to inflammation research. Since these kinds of infections are usually chronic and influenced by host responses, opportunities emerge for joint projects with researchers experiences in the immune system.

- **Weaknesses and threats:**

The global strategy and coherence of the team is weak. The RSV subgroup was created following the recommendation of previous AERES experts committee in 2009, but 5 years later, this subgroup did not develop research axes proving interactions with other subgroups of the team.

- **Recommendations:**

The head of the group should make all efforts to build a more coherent group. Moreover, all the actors of the team should work together on the same site. The project has to be a common project, not a sum of individual goals, as it is now. The principal investigators of this team should coordinate their efforts and publish together. The RSV subgroup needs to develop a project in a way to interact and to connect with team members working on host/pathogen interaction.

Team 5: Molecular mechansims and pharmacolgy of bronchial obstruction

Name of team leader: Mr Philippe DEVILLIER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	9	6
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	1	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**10**	**10**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	5

• Detailed assessments

Assessment of scientific quality and outputs

The research group has originally been established in 1998. The current location of the group is at the Foch hospital campus. The scientific activity of the group is largely dependent on supply of human lung explant tissue from Foch hospital, which is the largest lung transplant center in France, and which therefore, is of strategic importance to the group. Consequently, the main research activity of the team is almost exclusively focused on human cell-based and tissue-based models. It makes use of human lung explant tissue to address mechanisms of epithelial ion transport and permeability in the airways of healthy subjects and cystic fibrosis (CF) patients, the effects of β2-adrenergic agonists in stretching-induced bronchial hyper-responsiveness, as well as lung macrophage polarization.

The group has discovered that co-culture of 10 % of normal with 90 % of CF epithelial cells exhibiting perturbations in their CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) channel activity was enough to restore CFTR-dependent chloride secretion, while at the same time reducing Na^+ absorption by the ENaC channel, thereby normalizing mucus hydration in this system (Am J Respir Cell Mol Biol 2009), which is an important contribution to CF research. Similarly, they assessed the effect of NO on human proximal and distal airways from CF patients *versus* healthy donors (AJP Lung 2012). With regard to hyperresponsiveness and inflammation of conducting airways, the group explored the role of bronchial epithelium in airway hyperresponsiveness to β2 agonists (Pharmacol Res 2010). Further published work addressed the role of Wnt proteins in stretch-induced stress in human bronchi, for which the group established an *in vitro* bronchial explant stretch model. These data suggested a role for Wnt proteins in β2 agonist induced bronchial hyper responsiveness (Crit Care 2011). Such work dealing with bronchial hyperreactivity, vascular tone, epithelial ion transport issues appears to be quite congruent. In a parallel approach, the team also aims to characterize functional M1 (classical) and M2 (alternative) phenotypes of human macrophages. Again, the group approaches this area of research from a pulmonary-pharmacological point of view, by asking what effects adenosine, or phosphodiesterases, or 15-lipoxygenases, or nicotinic receptors etc. might have on M1/M2 human macrophage phenotypes (Br J Pharmacol 2010, 2012). It currently remains less clear how these two main streams of research are interconnected to each other.

Assessment of the unit's academic reputation and appeal

The team is nationally and internationally very well recognized in the field of pharmacological intervention of human bronchial hyperreactivity and inflammation. More than 45 topic-related scientific contributions to national and international congresses have been listed. The team leader has also been invited to numerous (73), mostly national symposia and congresses. Two doctoral theses of this team have been awarded by the French Society of Pharmacology and Therapeutics. Several scholarships have been granted to both doctoral students and Post-Doctoral fellows of the team. Privileged partnerships have been established with French institutions such as Pasteur Institute, the Université de Strasbourg and the Université de Rennes.

The funding of the team in 2012-2013 amounted to a total of 510 K€, which are composed in large part of scholarships (231 K€), but also as grants (190 K€) and some industrial contracts. Continued financial support (legs Poix, Vaincre la Mucoviscidose, Assoc. pour la Recherche sur les Nicotiniaées) has been granted to different team members during the past years.

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

There are several current contracts with different pharmaceutical companies. The will to receive extramural funding from pharmaceutical companies is very well established in this team, and the clinical relevance of the conducted research to successfully achieve this support is evident.

Assessment of the unit's organisation and life

This multidisciplinary team is composed of more than 10 clinicians, medical biologists, pharmacists, and scientists. A 50 % technical position is funded from the unit’s own resources. The team is presently organized in several sub-teams working on bronchial reactivity and pulmonary inflammation, stretch reactivity of bronchial vessels, and endothelial dysfunction of pulmonary vessels. There is no doubt that this multidisciplinary team collaborates perfectly with each other. The team is headed in a very integrating/enthusiastic manner.

Assessment of the unit's involvement in training through research

The head of the team coordinates a respiratory pharmacology module in which he and and other team members are teaching. 2 PhD theses have been completed during the period, 5 PhD students are still working on their thesis, 15 Master 2 students, 14 undergraduate students and 42 Master 1 students have been also trained. One joint PhD supervision with a foreign university, and supervision of a Spanish Post-Doctoral fellow (from 2008 to 2011) have to be mentioned.

Assessment of the strategy and the five-year plan

The team will focus its upcoming 5-year research on pharmacological interference with bronchial contraction/relaxation, using different model systems, as well as human macrophage polarization studies. As for

bronchial reactivity, the effect of bitter taste receptors and cannabinoids on bronchus contraction/relaxation will be explored in so-called organ bath cultures. Moreover, the team aims to characterize the airway response to acute mechanical stretch. Here, to mimic the human airway response to mechanical ventilation, isolated human bronchi are exposed to motorized mechanical stretch in an organ bath, which has been developed by the team. This motorized model system shall then be exploited to determine stretch-induced effects on airway tone and responsiveness to acetylcholine and elucidation of the underlying molecular pathways. This kind of research will be very important for future improvements of mechanical ventilation algorithms in critically diseased ICU patients, and as such is of great clinical relevance. Concerning human macrophage polarization studies, the team has performed genome-wide transcriptomic analysis of G-protein coupled receptors, and has performed chemokine arrays in M1 vs. M2 primed human macrophage cultures, which will result in interesting novel insights into inflammatory activation profiles of M1 vs M2 macrophages in different clinical settings. This part of research is far less developed as compared to the bronchus-related research, but will have a great chance for development within the requested 5-year funding period.

Conclusion

- **Strengths and opportunities:**

The major strength and opportunity of this team is its close scientific interaction with the leading human lung transplant center in France, hospital Foch, from where abundant and permanent access to human lung explant tissue has been established. This source of human lung material enables the researchers to focus on human-predictive *in vitro* model systems, which will be exploited for various clinically highly relevant pharmacological approaches, all of which are firmly established. They have over 20 years of experience with the isolated human bronchi model and the use of many related techniques (electrical field stimulation, cyclic stretching, etc). This positions team 5 as unique among the other teams in terms of supply with human explant tissue, and, from a methodological point of view, may have important implications for the translational research of all other teams.

- **Weaknesses and threats:**

Currently, the project of team 5 appears to be overambitious and the scientific aims require further adjustment to the main group's expertise. A lot of collaborations will be started with different research laboratories, which needs some focus. The entire team should come on the site. Mainly VLM grants and Leg Poix have been gathered, but no important research grants.

- **Recommendations:**

The project would profit from focusing its aims on the primary scientific and clinical expertise of the group related to pharmacological intervention of bronchial hyper-reactivity. A better scientific focus might help the team to aim at higher impact publications, which in turn may further improve their industrial funding success.

5 • Conduct of the visit

Visit dates:

Start: February 13th 2014 at 09.00 am

End: February 14th 2014 at 05.00 pm

Visit site: UFR des Sciences de la Santé Simone Veil

Institution:

Address: 2 avenue de la Source de la Bièvre, 78180 Montigny le Bretonneux

Conduct or programme of visit:

Day one – February 13th 2014	
09:00 am	Welcome (closed-door) experts committee with the AERES Scientific Delegate (DS)
09:15 am	DS: the role and procedures of AERES
09:30 am	Direction of the unit: past and future + discussion
10:15 am	Coffee break
10:30 am	Team cell death and cellular stress *(Talk + discussion with the team leader)* Name of the team leader: Mr Bernard MIGNOTTE
11:25 am	Team Neuroendocrine response to sepsis *(Talk + discussion with the team leader)* Name of the team leader: Mr Djillai ANNANE
12:20-12:30 pm	closed meeting
12:30 pm	Lunch
01:45 pm	Team Chronic Inflammation and immune system *(Talk + discussion with the team leader)* Name of the team leaders: Mr Maxime BREBAN and Mr Gilles CHIOCCHIA
02:40 pm	Team Pathophysiology and diagnosis of microbial infections *(Talk + discussion with the team leader)* Name of the team leader: Mr Jean-Louis HERRMANN
03:35 pm	Team Molecular mechansims and pharmacolgy of bronchial obstruction *(Talk + discussion with the team leader)* Name of the team leader: Mr Philippe DEVILLIER
04:30-04:45 pm	Direction of the unit : synthesis + discussion
04:45-05:00 pm	closed meeting
05:00 pm	Coffee break
05:30-06:00 pm	Discussion with the representatives of the managing bodies

Day two: February 14th 2014	
09:00 am	Discussion with doctoral school director
09:30 am	Parallel meetings with personnel: - Discussions with engineers, technicians, administrative; - Discussions with staff scientists; - Discussions with students and post-docs.
10:15-10:45 am	Visit of the unit and technological facilities
10:45-11:30 am	Discussion with the head of the center
11:30-05:00 pm	Private meeting of the experts committee (in presence of the DS), including lunch
05:00 pm	End of the visit

6 • Supervising bodies' general comments

UNIVERSITÉ DE VERSAILLES ST-QUENTIN-EN-YVELINES

Versailles, le mardi 14 mai 2014

Le président de l'Université de Versailles Saint-Quentin-en-Yvelines

à

Dossier suivi par :
Christian Delporte,
Vice-Président du conseil scientifique chargé de la recherche et du développement scientifique
Réf : JLV/CD/MC/DREDVal 14-192

Monsieur Didier Houssin
Président
Agence dévaluation de la Recherche et de l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

Réf. : S2PUR150008351 - Mort cellulaire, Infection, Inflammation - MCI2 - 0781944P

Objet : Evaluation des unités de recherche : Volet Observations de portée générale

Monsieur le Président,

Nous avons pris connaissance avec le plus grand intérêt du rapport d'évaluation de l'AERES concernant la demande de création par restructuration de l'unité mixte de recherche intitulée **Mort cellulaire, Infection, Inflammation « MCI2»**, portée par M. Gilles Chioccia, et nous remercions les experts pour la qualité de leur travail.

Nous tenons compte des recommandations de l'AERES et étudierons les conditions de la mise œuvre de ce projet, dans la stratégie scientifique de l'UVSQ pour la période quinquennale 2015-2019 dans le contexte de l'Université Paris Saclay.

Nous vous adressons ci-joint les observations et commentaires du porteur de ce projet formulés au regard de ce rapport d'évaluation.

Je vous prie de croire, Monsieur le Président, à l'expression de mes cordiales salutations.

UNIVERSITÉ DE VERSAILLES ST-QUENTIN-EN-YVELINES

Jean-Luc Vayssière
Professeur des universités

Cell Death, Inflammation and Infection: CDI2

Gilles Chiocchia

Directeur

Saint-Quentin-en-Yvelines

May 10, 2014

Réponses au rapport d'évaluation de l'AERES

We acknowledge the report by the committee AERES following their plant on February 13th and 14th, 2014.

We thank the Evaluation Committee for the positive comments and the constructive critiques.

We would like to emphasize that we are appreciative of the recommendations of the committee which match very well the strategic orientation that we have adopted in the Unit, and proposed to reinforce in the future.

We are also particularly pleased that the strong will of the five teams of the Unit to work together has been appreciated, our complementarity noted as a strength and our potential for becoming a reference in translational research for the studied inflammatory diseases evaluated impressive.

- In general, the experts committee has appreciated the different know-how among the teams and the multidisciplinary approaches.
- The potential for becoming a reference in translational research for some inflammatory disorders is impressive.
- The unit will be clearly visible in the French and international research landscape, as each of the future constituting teams is well known in their respective fields.
- The future unit has very good connections with master and medical students. The unit members are deeply involved in teaching and training actions.
- Some of their projects clearly reflect their strong will to strengthen and expand further their collaboration and develop new projects at the interface of their different domains
- Several of the unit teams leaders have a very good to excellent international visibility and reputation.
- The dynamism of some of the team leaders, including the future unit director, has been remarked.
- The amount of contracts with private companies is impressive.
- The different protagonists of the future unit have been able to raise excellent funding from National agencies, but also from European calls.
- In-house facilities are very good and include classic technical services but also different platforms dedicated to mass spectrometry, cellular imaging, confocal microscopy, animal houses, FACS, P3, etc.

To answer to the recommendations and potential weakness underlined by the Committee, we have made the choice of a point-by-point reply.

Responses:

Committee: *Among the 5 teams, there are only two full time researchers and one will be the director of the future unit. There is, therefore, a strong need for reinforcing the pool of full time researchers. The future unit would benefit from the recruitment of an immunology team.*

1. This lack of full time researchers is due to the actual University status only of four of the teams. Obviously the Inserm status will allow us to welcome much more easily full-time researchers and will give all the teams the right to propose candidates for recruitments at Inserm. In line with this point and our scientific priorities, laboratory spaces have been saved to attract new teams and a call is planned for an immunology team. Again, it is obvious that being an Inserm Unit will be a strong added value to achieve these objectives.

Committee: *There is also need of more engineers/technicians.*

2. We absolutely agree on this point and this was one important point in our SWOT analysis. Because the recruitment of engineers and technicians by Universities and governmental agencies have been drastically reduced, we focused our efforts on positions for core facilities.

Committee: *The unit will have to work in order to be more attractive for young researchers (foreigners and French post-doctoral fellows).*

3. Attractiveness is a regular, continuous and permanent work. This commitment is an integral part of our ongoing work to build a strong Unit and the scientific environment, the top level facilities and a brand new building are clearly very attractive. Being recognized as an Inserm Unit will indubitably increase our attractiveness.

In line with this point and our scientific objectives, laboratory spaces have been saved to attract new teams and a call is planned for an immunology team.

Committee: *It will be necessary to provide actions for maintaining the scientific cohesion. Since this is a unit creation, although collaborative projects have been started already, there is not yet any publication, patent or accepted grant for strenghtening these collaborative works.*

4. As mentioned by the Committee, several collaborative projects are already on-going in the Unit which already led to 6 research grant proposals (4 ANRs) and a PHRC has already been obtained. It has to be noted that 3 PhD students will be hired on inter team collaborative works. Furthermore, as it was proposed in our Unit document, a part of the institutional financing will be targeted as a seed financial support dedicated to intra-Unit collaborative works.

Committee: *The number of high ranked publications, at least in some teams, is quite low. Only team 4 has patents.*

5. During the last 5 years, the 5 different teams of the Unit have published more than 350 articles with 156 with an IF > 5 and 22 with IF > 10. We believe that our scientific production is already quite good and we are deeply convinced that working all together will allow us to improve it even more.

Committee: *The scientists should be ambitious enough to push their own research in the front line by initiating and coordinating national and european networks and competing at the highest level for prestigious grants.*

6. Based on the Committee's comments *"The amount of contracts with private companies is impressive. The different protagonists of the future unit have been able to raise excellent funding from National agencies, but also from European calls"*, we definitely agree with the fact that our union within the same unit allows us to be even more ambitious, competitive and and will position us to be greater successful.

Committee: *An unit council should be formed, composed not only by the team leaders but also by at least one representant of each unit workforce. The financial aspects for the unit management should be clearly and rapidly discussed within the unit council.*

7. We would like to mention that all the teams moved to the new building last year. From then onwards, we created a steering committee managed by GC. The role of this committee is to organize all the efforts in setting up all the laboratories, facilities and scientific life in this new place as well as accreditations and financial aspects. Of course, each team kept its already existing unit council.

We think that we have been quite successful in setting up the new organization : *"The strong point of the research unit lies on the fact that constitutive teams are all in the same building and this physical proximity is evident when discussing with the students of the different teams. Another strong point is the impressive facilities, all also within the same building.*"

We are now in the second phase of organization and we have set a Unit Council, including the team leaders, and one or two elected representative of every category of staff: Researchers (not head of a team), engineers and technicians (one for permanent position and one for non-permanent), Post-Doc, PhD.

Gilles Chiocchia

TEAM 2 : Djillali ANNANE

- The team is grateful to the experts panel for their valuable and fruitful evaluation of our team. We would like to thank the experts panel for highlighting the international role of our group in the field of neuroendocrine response to sepsis.

- We fully agree with their analysis that the team's most important contributions in the field were through the organization and conduct of major clinical trials. Not only these trials had impact on daily practice, but also provided us with the opportunity to set up an unique biobank of blood and tissue samples on which we have started our translational program.

- The team is basically working on two sites. The clinical trials unit is based within the intensve care unit at Raymond Poincaré hospital for obvious reason. The translational activities are located now with the research centre building at Montigny-le-Bretonneux, neighbouring the other teams and with immediate access to the various research platforms. We agree that the team leader activities prevent him for being full time at the Montigny-le-Bretonneux site. Therefore, we will follow the recommendation by the experts panel to have Arnaud Mansart, full time on site, has being responsible for the daily organisation of the work.

- We agree that we need to reinforce the translational activities. We assume that our relocation in the research building will allow deeper relationship with basic scientists from the other teams as well as from the other labs that are on site. We'll also have access to a unique platforms to foster more mechanistic approaches in particular in the field of imaging and molecular biology.

- Finally, up to last year, we non had available space and a unique environment to wellcome postdoc toral students. So far we have declined several applications from students due to inadequate facilities. We are highly confident having new applications and that these students would help fasting our translational activities.

TEAM 3: Maxime BREBAN and Gilles CHIOCCHIA

Conclusion from the AERES evaluation committee

Strengths and opportunities:

The projects proposed by experts internationally recognized in the field are ambitious, well constructed, with financial funding. They are highly feasible based on the scientific background of the team, the biological cohorts already established and the technical skills available. These projects strongly focused in the pathophysiology of spondyloarthritis are major assets of the “Cell Death, Infection and Inflammation unit”.

Weaknesses and threats:

In addition to the biological cohorts available, the team is developing rat model of spondyloarthritis. A mouse model would be very useful to develop preclinical approaches of this disease.

Recommendations:

To conclude, the projects proposed are particularly interesting, very well focused, well conducted and show a strong added value for the better understanding of the pathophysiology of spondyloarthritis and for the future therapeutic developments. It is recommended to give a specific attention to reinforce the links with the other teams of the unit. »

Reply

- **Strengths and opportunities:**

We thank the experts of the AERES committee for their nice appreciation of our research program.

- **Weaknesses and threats:**

These experts considered that a mouse model of spondyloarthritis (SpA) would be useful for the purpose of preclinical research. We fully agree with their opinion. This is why we have been recently pursuing such objective: we have obtained HLA-B27 transgenic (tg) mice, that do not develop any phenotype (to the contrary of the B27-tg rat model that we have been using for many years because they develop the full spectrum of SpA). We have already started to backcross the B27-tg mice to mice with specific background with the aim to develop a new model of SpA. We also keep in mind that the discovery of new SpA-suceptibility genes, as expected by our team, would offer us a unique opportunity to develop a mouse model of SpA. Finally, we would like to outline that recent technological developments in the field of genetic manipulations allowed us to produce rats with inactivated gene, such as ICOS (in collaboration with Ignacio Anegon, ITERT, Nantes). Thus, working with rat model might become more handy in the near future.

- **Recommendations:**

We are indeed planning to reinforce our link with the other teams, such as shown by the collaborative projects that we are already developing including the study of apoptosis, UPR and autophagy in SpA, along with the production of B27-tg fruitfly (see p.186-187 of our project, collaboration between teams 1&3). Other collaborative topics that we plan concern: the role of neuromediators in inflammation (collaboration with teams 2); the role of

microbiome and TLR activation in chronic inflammation (collaboration with team 4); macrophages phenotype in inflammatory disorders (collaboration with team 5).

TEAM 4: Jean-Louis HERRMANN

Reply to AERES Comments

- We acknowledge the AERES Committee recommendations, and will focus on organizing the work and interaction of the thematic group into a unified platform. The previously presented two year plan will be carried through to wrap up ongoing projects and we will simultaneously structure Team 4's know-hows into a common platform dedicated to the study of the infectious triggers of inflammatory disease. What was initially thought of as "pillars" with a vertical approach will be restructured into different cores working transversally with the different model pathogens with which the team is proficient. Extending the cores towards the themes of the other teams of CDI2 will also be a goal as the unit members become more familiar with each other's research. The five years goal of the team will be to develop collaborative projects built on the respective abilities of the current members, broadening the spectrum of projects that can be tackled within the unit.

- Considering the Team as a whole, the shared base of competences will provide the different groups with means to explore the inflammatory responses elicited from the host. Briefly, the following cores will be made available to all participants:

- the molecular biology and expression beacons brought by the virology group , combined with the transfection expertise of the mycobacteria group will allow us to develop in vivo and in vitro real time monitoring of the activation pathways of immune cells

- the mycobacteria group and the bone and joint infection group will provide expertise in the study of in vivo host-pathogen interactions through the use of systemic, aerosol and surgical murine models of infections, including a state of the art aerosol generator device developed by the team based on a Pasteur Institute design

- the mycobacteria group and the bone and joint infection group (BJI) will also make available its know-how in the in vitro study of innate immune cells

- the bone and joint infection group will provide expertise in biofilm/immune cells interaction, and will share its expertise in continuous flow cell culture for long term observation of cell cultures

- the Cymage imaging platform is co-managed by a member of our team. His skills in image acquisition combined with the equipment availability will empower all teams in the documentation of in vivo and in vitro phenomena. Automated acquisition of time course flow cell events, high throughput screening and cell sorting techniques will be made available to all group members. .

- As acknowledged by the AERES Committee, RSV is a major health problem, and the virology group has recently emerged as a leader in the generation of novel toolset allowing the study of the infection and host response in vivo and in vitro. Though this group only

recently joined the team, it has developed collaborations and obtained grants to achieve specific projects (ANR 2014-2016, DIM 2014-2015, Research contract with LFB 2014-2015).

➢ The Committee indicated that the coherence of the group was weak, and that the RSV group had poor interactions with the rest of the team during the previous 5 years plan. However, the RSV group started in 2009 with only one MD-PhD (E. Gault), joined by another MD-PhD (MA Welti) in 2010. RSV laboratory research started in 2011, in collaboration with JF Elouët (Inra, Jouy en Josas). The group benefited of the UFR facilities in beginning 2013 only, when all the EA3647 team moved into the new Sciences de la Santé building. Until then, all three groups were dispersed on two sites, making connection between researchers uneasy to establish. Finally, most of the new members, assistant professors and research assistants joined the team between 2012-2014, in the last two years of the contract.

➢ We were asked to present short-term projects (in the next 2 years) on a basis of well-known and controlled technologies, including very innovative tools. But to fulfill the objective of grouping the 5 teams in a future unit devoted to inflammation, we will develop, for the coming 5 years, a thematic centered on inflammatory disease in the context of host-pathogen interaction.

➢ Presently and regarding ongoing projects and publications, both the mycobacteria and RSV subgroup have, in 2014, funded ANR projects and several recent high graded manuscripts published (PNAS; Antimicrobial Agents and Chemotherapy) or under revision (Nature Communications) respectively. BJI group, with his representative M. Rottman also participated in a joint publication in Nature Medicine. In 2014 also, patents and demand of invention are also proposed for the BJI and RSV teams respectively, and the EA3647 is creating a new company (Antagonis). Based on these assets, we aim at linking the abilities brought by the members who have joined the group in the last two years with the expertise previously mentioned for the EA3647 members.

- Setting up a technical platform where all the expertise and innovative tools presented by each EA3647 member will be shared, including expertise with animal models (mice, rabbit, zebra fish…) and amoeba.
- Lung innate responses (with or without genetic deficiencies):

Sabine Blouquit-Laye, coming from team 5 (P. Devilliers), joined EA3647 (team 4) in September 2013. She is in charge of setting up the model of human pulmonary explant allowing culturing lung epithelial cells, to study host-pathogen interactions after infection by the mycobacteria and the RSV models. Anne-Laure Roux has the expertise of macrophages and dendritic cells inflammatory responses when in contact with mycobacteria. Both will share expertise to analyze the innate response when the pathogens are brought into contact with epithelial cells. Contract might be submitted to the “Vaincre la Mucoviscidose Patient Association” or “Legs Poix”, to allow the financial backup for such studies (Submission in first trimester of 2015 allowing getting preliminary results). In addition, P. Devilliers (Team 5) analyzed the innate response in the lung, mainly the M2 macrophage response. We will share expertise with team 5 in order to decipher the whole response, and evaluate different stimuli in human lung model, allowing a perfect connection between teams 4 and 5 (Team 4 and 5 can be partner in such projects). All the cytometry, microscopy will be performed using the Cymages platform with Vincent Rincheval who joined the team in 2013. Vincent Rincheval came from team 1, with an expertise in apoptosis, allowing again a direct

connection with the duration and the intensity of the response. V LeMoigne, a post-doc in the lab can share his expertise in animal models (see below) to complement the responses obtained with cultured epithelial cells.

- BJI –Mycobacterial Infections: How a bacterial change in surface morphology shaped the innate response, in bone, and in lungs. This is of extreme interest as bacteria are able to silencing the response allowing colonization of already altered lungs, or in presence of a material as in BJI. We also have the notion that PR patients (team 3) have their lungs colonized by potential bacterial pathogens like mycobacteria, as shown by the detection of an antibody response in several patients followed by the team 3. M. Rottman will lead this aspect by using different materials and eukaryotic cells to mimic the responses of such cells like dendritic cells, macrophages or osteoblasts confronted to biofilm forming pathogens. Expertise from A.L. Roux for the cells assays, V. Rincheval for the cytometry and imaging, MA Welti for the molecular biology expertise in order to use fluorescence or chemiluminescence markers, will be used. Project can also be proposed through “Domaine d’Intérêt Majeur Ile de France Maladies Infectieuses et Emergentes” (DIM-MIE) proposal in 2015.

➢ *Animal models:*

a. We benefit from the expertise in mice model, developed at the start of the research team by M. Rottman and JL Gaillard. The RSV group developed an innovative tool to monitor RSV infection in mice with non-invasive imaging, by the use of recombinant viruses expressing luciferase (Nature Communications, in revision). As previously done for mycobacteria, this tool, applied to the infection of knockout mice in several immune genes will provide with new means to study the immune response to RSV infection. Here will interact MA Welti, M Rottman, who developed an aerosol model of infection, and expertise to recover bronchial alveolar lavage. D Sitterlin and V Rincheval will help in defining the cell response in the lung environment and in the blood of the infected mice. Such a project will be presented, to the DIM MIE in 2016.

b. Drosophila helped in discovering the Toll like receptor (TLR). Mycobacteria lipoproteins were the first to be shown to interact with TLR-2. We will share expertise with team 1 (B Mignotte) to develop a drosophila model of infection with *M. abscessus*. This model exists in the literature, developed by a Korean team, confirming its feasibility. V. Le Moigne and F. Misguich will be in charge to establish this new model of infection in order to decipher the inflammatory responses linked to live mycobacteria, or to derived mycobacterial products. Here will be focused the duration of the inflammatory process, the death of the innate cells, with as an end-point read-out, the efficiency of the innate response. Again, V Rincheval, coming from team 1, possesses the expertise in apoptosis and in cell imaging and will help in developing the model and in answering specific question regarding down- or up-regulated response depending on the stimuli.

TEAM 5: Philippe DEVILLIER

Answers to the report of the AERES'committee of experts

We thank the Committee for its favourable global assessment of the team. As indicated in the evaluation report, the team is nationally and internationally very well recognized in the field of pharmacological intervention of human bronchial hyperreactivity and inflammation. Privileged partnerships have been established with French institutions such as Pasteur Institute, the Université de Strasbourg and the Université de Rennes. The will to receive extramural funding from pharmaceutical companies is very well established in the team, and the clinical relevance of the conducted research to successfully achieve this support is evident.

Weaknesses and threats:

 "Currently, the project of team 5 appears to be overambitious and the scientific aims require further adjustment to the main group's expertise. A lot of collaborations will be started with different research laboratories, which needs some focus."

- Answers :

We apologize to the Committee if our report did not make clear enough that several parts of the described works were in the final step. We had decided to focus our research on pharmacological intervention on human bronchus reactivity and on the inflammatory responses of the human lung macrophages that open new research avenues on the bronchial reactivity and the reverse being also true. Therefore, we will focus our efforts on research themes with potential research's interests in the two models which is in full accordance with the present Committee recommendation.

Following, we detailed these points.

1- Research activities on human lung macrophages :
The different steps of the characterization of the ex-vivo polarization states of the macrophages have been performed (the remaining step is the final analysis of the data of the high-throughput genome-wide transcriptome).

Among the six themes of research on human lung macrophages listed as on-going or futures activites, the experiments have been recently completed for two themes (15-lipoxygenases and kynurenines), most of the experiments have already been performed for three themes (nicotinic receptors, adipokines (adiponectin and leptin), and thymic stromal lymphopoietin) and experiments have been already initiated for the bitter taste receptors'theme. Therefore, only one theme will require research activities after the end of 2014.

The next experimental themes on human lung macrophages will be mostly concentrated on the collaboration with team 3 (comparison between lung macrophages and dendritic cells in specific environmental conditions) and team 4 (activation of the macrophages by M. abcessus derived products).

2- In vitro reactivity of human bronchus

The data from standardized cyclic stretchs have been extracted and are currently analyzed from bronchi isolated from more than 60 patients. No more experimental steps appear to be required to define the optimal conditions of stretch. The biological material obtained from a large part of these bronchi have been in part tested to explore different pathways and the remaining analyses will not require more than few months.

3- Epithelial cells and inflammation.

The research will be conducted mainly with team 4 to provide lung tissue or access to cell preparation required for their own research activities. No research's theme specifically devoted to this cell type will be conducted by team 5 itself.

 "The entire team should come on the site."

- Answer :

As clearly stated by the AERES'committee : "The major strength and opportunity of team 5 is its close scientific interaction with the leading human lung transplant center in France, hospital Foch, from where abundant and permanent access to human lung explant tissue has been established. This source of human lung material enables the researchers to focus on human-predictive *in vitro* model systems, which will be exploited for various clinically highly relevant pharmacological approaches, all of which are firmly established.".
The group would like to thank the committee for the recognition that the group is developing highly relevant pharmacological approaches. Of course, and as outlined by the Committee all the experiments on human bronchus will have to remain in the unit at Foch hospital to maintain a close and rapid interaction with the source of human lung tissue. On the other hand and again we fully agree with the Committee, experiments requiring access to the high-quality technological resources at the UFR will be conducted on the St-Quentin site as well as the experiments in collaboration with team 3 and 4 (i.e. all or major parts of the experiments on macrophages and epithelial cells).

 "The project would profit from focusing its aims on the primary scientific and clinical expertise of the group related to pharmacological intervention of bronchial hyper-reactivity. A better scientific focus might help the team to aim at higher impact publications, which in turn may further improve their industrial funding success"

- Answer :

We agree that pharmacological intervention on human bronchus reactivity is the primary and clinical expertise of the group and we will do our best to keep this expertise to the highest scientific level. In addition, the studies on the responses of the human lung macrophages open new research avenues on the bronchial reactivity and the reverse is also true. Therefore, we will focus our efforts on research themes with potential research's interests in the two models.