ICPH - Intéractions cellulaires et physiopathologie hépatique

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on research units and interdisciplinary research units

Interactions Cellulaires et Physiopathologie Hépatique

ICPH

Under the supervision of the following institutionsand research bodies:

Université Paris-Sud

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

December 2013

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,

- Mr. Richard MOREAU, 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 experts committee,the composition of which is specified below.

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

Unit name:	Interactions cellulaires et physiopathologie Hépatique
Unit acronym:	ICPH
Label requested:	UMR S
Present no.:	UMR S_757
Name of Director (2013-2014):	Mr Laurent COMBETTES
Name of Project Leader (2015-2019):	Mr Laurent COMBETTES

Expert committee members

Chair:	Mr Richard MOREAU, Institut National de la Santé Et de la Recherche Médicale and Université Paris Diderot
Experts:	Mr Éric CHEVET, Université Bordeaux Ségalen
	Mr Nicolas DEMAUREX, University of Geneva, Switzerland
	Mr Laurent MARTINEZ, Université de Toulouse
	Ms Valérie MCLIN, University of Geneva, Switzerland
	Ms Catherine POSTIC, Université Paris Descartes
	Ms Véronique TREZEGUET, Université de Bordeaux (representative of CoNRS)

Scientific delegate representing the AERES:

Mr Jean GIRARD

Representatives of the unit's supervising institutions and bodies:

Mr Étienne AUGE, Université Paris Sud

Ms Chantal LASSERRE, Institut National de la Santé Et de la Recherche Médicale

Mr Olivier NÜSSE (Directeur-Adjoint de l'École Doctorale N°419)

1 • Introduction

History and geographical location of the unit

The proposed unit is an extension and a restructuration of the UMR S_757 (that was endorsed by both the Université Paris-Sud and the INSERM). There will be two teams participating in the present project. All Team 1 members will come from UMR S_757. Team 2 will include members from different origins. Two will come from UMR S_757, one will move from UPR2301 (CNRS) and the last one from UMR8619 (CNRS-UPS). Teams will be located at the same place as the UMR S_757, i.e., and will occupy 1200 m^2 in a building (number 443) located in the Campus of the Université Paris-Sud, city of Orsay.

Management team

The proposed Unit will be directed by Mr Laurent COMBETTES; Team 1 will be directed by Mr Laurent COMBETTES and Mr Thierry TORDJMANN and Team 2 by Mr Oliver NÜSSE and Ms Cécile BOUTON.

AERES nomenclature

SVE1_LS4; SVE1_LS3

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	11	13
N2: Permanent researchers from Institutions and similar positions	2	5
N3: Other permanent staff (without research duties)	8	8
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2	4
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**24**	**32**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit*	2	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	12	13

2 • Overall assessment of the interdisciplinary unit

The proposed unit is an extension and a restructuration of the UMR S_757. Overall there will be a significant reinforcement of the UMR S_757 that was already strong. The future unit will be unique as it will concentrate most of the local forces in the field of biology, these forces being appointed by the Université Paris-Sud, INSERM and CNRS. In other words, the "revised" UMR S_757 will be a model of "multi-organisms" integration. The integrative research project of the "revised" UMR S_757 will combine multi-disciplinary expertise including biochemistry, molecular biology cell biology, imaging, animal models, and clinic. This should foster new approaches in basic and translational research. The restructuration into two teams is logical. Team 1 will include "historical" components of UMR S_757 and will pursue research in the field of liver physiology and pathophysiology, which was the major theme of this Unit. Team 2 will include two researchers interested in inflammation (immunopathology) and oxidative stress who were already working at the UMR S_757 and newcomers who are experts in the field of metalloproteases and nitrosative stress. The extension and restructuration of the UMR S_757 should be viewed as a first significant step of a larger reorganization of biology laboratories in the south of Paris under the umbrella of the Institute for Research on Medication and Innovative Therapies (IRMIT). This reorganization develops in the context of the creation in 2014 of the new Campus Paris-Saclay that will involve about 25 institutions of research and higher education (including Grandes Ecoles such Ecole Polytechnique).

Strengths and opportunities related to the context

The project will cover a large spectrum of activities from basic to clinical research creating opportunities for innovation.

The project of Team 1 will continue to explore liver regeneration (a major theme of UMR S_757) but also will develop bridges to inflammation (via its interest in bile acid effects) and hence will benefit from the expertise of Team 2 in this field. Interestingly Team 2 which is mainly involved in basic research on mechanisms of cell stresses and immunopathology will find a field of application by collaborating with Team 1 in studies on mechanisms of liver injury and degerulation of liver reparation.

Unit members, in particular its Leader are very involved in the Campus Paris-Saclay initiative. The Unit should benefit from the multidisciplinarity of the IRMIT. The Unit will have the opportunity to develop further beneficial collaborations with researchers in physics and biophysics working at the Campus Paris-Saclay.

Weaknesses and threats related to the context

The document entitled “Internal Rules” included in the project is not detailed; in particular it does not take into account the division into two teams and does not define the role of the Internal Council of the Unit.

An engineer appointed by the CNRS has been working for a long time with a group which is currently outside the UMR S_757. This group will participate in the future Team 2 and the engineer wishes to move with researchers. There is no information on whether or not this engineer will be able to move.

Four engineers or technicians who are currently at UMR S_757 will retire during the next period.

Recommendations

The Comittee strongly supports the presented project.

Internal Rules should be more clearly described.

3 • Detailed assessments

Assessment of scientific quality and outputs

There are excellent scientific quality and outputs. Members of the future Unit have published 167 peer-reviewed articles during the last period. Among these there are original articles not only in high impact factor specialty Journals (e.g., Hepatology with IF = 12) but also very good "generalist" Journals such as Nature Communications, PNAS, or JBC. Scientific results have been presented as oral presentations or posters in national/international meetings or workshops. The scientific production of each Team will be detailed below.

Assessment of the unit's academic reputation and appeal

Academic reputation and appeal are very good to excellent. There are very efficient translational collaborations with clinicians and physicists and chemists. Important grants were obtained from this collaborative work. Unit members are involved in projects that have been selected in the context of the "Investments for the Future" (Equipex Morphoscope) or in the Clinical Consortium DHU "Hepatinov". The team members are principal investigators or participate in different national basic science networks (9 ANR). A clinician is in charge of the National Reference Center on biliary atresia. Unit members are expert reviewers for a large number of scientific journals and agencies (AERES, ANR, INSERM, etc..). Senior researchers have been regularly invited to give lectures at national or international levels.

In term of appeal for young researchers 9 post-Doc have been trained and 8 established investigators with University, INSERM or CNRS permanent positions joined recently the unit.

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

Interactions with the social, economic and cultural environment are very good. The Unit leader Mr Laurent COMBETTES is significantly involved in the process of reorganization of biology laboratories of the south of Paris as well as that of integration of biology in the new multidisciplinary Université Paris-Orsay. This will allow the Unit to play a crucial role in the emergence of interdisciplinary research projects.

Clinicians participate in French TV or radio programs (France 5, France 2, Le Figaro). One Unit member is among the Scientific Committee of a Center organizing conferences and seminars about the evolution of research and its place in the Society. There is strong involvement in dissemination of knowledge at the undergraduate degree levels.

Assessment of the unit's organisation and life

The Unit project includes 44 persons: 7 established investigators from the INSERM (2) and CNRS (5), 13 established investigators from the University (including Medical School), 1 clinician without university position, 9 technicians and Engineers, 1 technician with a temporary position, 10 students (7 PhD, 3 Master 2) and 3 post-docs. The Unit will be organized into two Teams and such an organization is coherent with the scientific projects and objectives of the Unit. The arrival of several researchers was of great help to the setup of two Teams. All members of Team 1 were previously members of the UMR S_757. Team 2 will be composed of ex-UMR S_757 members and new comers from outside. The fact that Team 2 is a "composite" will favor the integration of new comers.

The Unit will benefit from large surfaces localized in a building at Campus of the Université Paris-Sud (Orsay). The clinical research will be carried out in 2 different Hospitals (Pediatric and Adult Liver Units at Hôpital Kremlin-Bicêtre and Hôpital Paul Brousse, respectively). It could be argued that a dichotomized organization of the Unit into teams and the different geographical locations may represent a limit to the scientific interactions of the teams. However, this risk will be limited by the fact that the team projects have been designed to induce multidisciplinary collaboration between the two teams.

In the context of the new Campus Paris-Orsay and reorganization of biology laboratory (IRMIT, see supra), it is planed that the Unit will occupy a new building along with laboratories from the Faculty of Pharmacy (currently at Châtenay-Malabry) and from the Chemistry department in Orsay. The new building will be located about 2 km from the current location and should be operational at the end of the decade. This reorganization will be a unique opportunity to promote interdisciplinary research on innovative therapies.

The document entitled “Internal Rules” included in the project is not detailed enough; in particular it does not take into account the division into two teams and the fact the 6 engineers or technicians will compose a “pool” shared by the unit Teams. In addition, the document does not define the role of the Internal Council of the Unit in the overall management of the Unit. Nevertheless it is important to note that the functioning of the UMR S_757 is harmonious; during private interviews with the Visit Committee, every member of personel expressed their entire satisfaction with working in this Unit. Since the UMR S_757 is the back bone of the future Unit there is not doubt that the harmony will be preserved and excellent.

Regarding technical support, Team 1 will have four engineers or technicians. The issue regarding the presence of an engineer in Team 2 has been mentioned earlier. Six other engineers or technicians will be dedicated to different tasks (such as administration, biochemistry, imaging, cell culture, flux cytometry) and will be shared by the two Teams. A full-time personel in charge of flux cytometry has been recruited very recently via the University. As mentioned before, four persons involved in the technical support of the Unit will retire during the next period.

Assessment of the unit's involvement in training through research

The Unit’s involvement in training through research is excellent.

The members of the Units teams have trained 15 PhD students and more than 20 Master students since 2008; 12 Master/PhD students are undergoing training.

Past Master students were recruited from: M1 Erasmus University of Wrocław, Poland and Paris-Sud; M1 Biologie-Santé, Université Paris-Sud; M1 Surface, Electro, Radiation, and Photo Chemistry (Serp chem), Université Paris-Sud; M1 Biologie Informatique Université Paris-Diderot; M1 Biologie-Santé. Université Versailles St Quentin; M1 physiologie et physiopathologie, Université Pierre-et-Maire Curie; M2 signalisation et neuroscience, Université Paris-Sud; M2 Produits de Santé issus de la Biotechnologie, Universités Paris-Sud, Paris-Descartes and Paris-Diderot; M2 Dynamique cellulaire, microbiologie et biotechnologies, Université Paris-Sud; M2 Génome, Cellules, Développement, Evolution (GCDE), Université Paris-Sud; M2 Biologie Cellulaire Physiologie et Pathologies (BCPP), Université Paris-Diderot; M2 Sciences-Santé, Université de Picardie.

Several members of the Unit are responsible for and/or involved in teaching programs: Co-direction of the Doctoral school “Biosigne: Signalisations et réseaux integrative en biologie” (ED 419); Organization of Post-graduate courses “Mitochondrion” PRES UniverSud Paris; Teaching in Master Biologie Santé, "Signalisation et Physiologie Cellulaire; Neurosciences" Université Paris-Sud; Teaching at "Omics in pharmacology and toxicology" Master degree, Université Paris-Descartes; Teaching at Master "Longevity and Aging", Université de Versailles-Saint Quentin; Co-organization of the 2nd year of biology (300 students); Responsibility for the "Magistère of Biology and Biotechnology" in Orsay; Responsible of PCSO (Préparation aux Cursus Scientifiques d'Orsay: a one year preparatory course for about 130 high school students who need to improve their science education before entering the regular licence program); Involvement in the new Institute "Georges-Charpak" at Palaiseau; Responsibility of the WIMS initiative in order to develop a distance education at the L1 level; Involvement in MOOC (massive open online courses) project in collaboration with the chemistry and physics of Paris-Sud; Teaching in the science and engineering program at Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI ParisTech); Responsibility for program and course of Cell Biology at ESPCI ParisTech; Program Manager for the "Scientific Projects in interface with biology" and in charge of the relations with biotechnology companies for ESPCI ParisTech; Responsibility for the implementation of programs for the biology License at PSL (Paris Sciences et Lettres); Teaching in the Erasmus Mundus program in SERP chem.; Responsibility for the flow cytometry platform of the institute, which is open for research and teaching from license to PhD level; Teaching and co-organizing the CNRS flow cytometry course in Gif/Orsay.

Unit members participate in several University Councils and Committees related to teaching.

Assessment of the strategy and the five-year plan

The strategy for the next 5 years will use interdisciplinary approaches covering a large spectrum from basic to clinical research to create opportunities for therapeutic innovation. As mentioned earlier the Unit will be composed of two Teams; the project of Team 1 is entitled “Biliary Homeostasis and Liver repair” and the one of Team 2 “Inflammation, Metallo-Proteins and Redox Systems”. Each Team will both develop its own projects based on past history and specific interdisciplinary expertise and collaborate with the other Team through integrative projects. For example:

a) The project regarding the role of purinergic receptors in liver regeneration is common to the two Teams;

b) A completely new project on infantile liver disease due to mutations in the gene called tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase (TRMU, a protein coding gene) has been created by combining clinical expertise from members of Team 1 with biochemical skills from new members of Team 2; and c) The phenotypic polarization of macrophages will be addressed in mouse models of liver disease as well as in vitro studies of redox biology.

Overall, this is an ambitious and exciting project that appears feasible based on the competence and excellence of the two teams. It is important to underline that a part of Unit project has been already evaluated positively and granted through different frameworks.

4 • Team-by-team analysis

Team 1 : Biliary homeostasis and liver repair

Name of team leader: Mr Laurent COMBETTES and Mr Thierry TORDJMANN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	11 (5)	6 (2.5)
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	8 (7.8)	7 (6)
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2 (1.3)	2 (1.3)
N6: Other contractual staff (without research duties)	1 (0.5)	1 (0.5)
TOTAL N1 to N6	**24**	**18**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	12	8

• Detailed assessments

Assessment of scientific quality and outputs

Team 1 has excellent scientific quality and outputs. The success of Team 1 is the result of a long-lasting history of involvement in research in the field of "liver science". Major points include:

1) The development of cell lines expressing polarity of hepatocytes and allowing to address questions raised in liver physiology;

2) The demonstration of the role of calcium signaling in liver regeneration;

3) First demonstration of the role of purinergic signaling (in particular P2X4 and P2X7 receptors) and the beneficial role of the bile acids receptor TGR5 in liver regeneration;

4) The first demonstration of the potential therapeutic interest of a new drug in patients with mutations of BSEP (also known as ABCB11) which cause Progressive Familial Intrahepatic Cholestasis (PFIC2).

Team 1 has an excellent publication track record since it published 120 original articles, including publications produced by the Team itself in Gastroenterology (IF=12.2, n=1); Hepatology (IF=12, n=5); Nature Communication (IF=10, n=1); J Hepatol (IF=9.8, n=5). Moreover Team 1 did 56 oral presentations in national/international meetings or workshops.

Assessment of the unit's academic reputation and appeal

Team 1 has a very good to excellent academic reputation and appeal. It has developed efficient translational collaborations with clinicians and physicists and chemists and important grants were obtained from this collaborative work. It was involved in the co-organization of a workshop on Cellular Biology (130 participants). The two "historical" Team leaders Mr Laurent COMBETTES (calcium signaling) and Mr Thierry TORDJMANN (liver regeneration) are renowned scientists; two scientists who joined the UMR S_757 in 2008 are both renowned pediatricians specialized in liver diseases. The team has been enriched by the arrival in 2012 of an expert in cilia biology.

Mr Laurent COMBETTES and Mr Thierry TORDJMANN are involved in "Morphoscope" (created on December 2011), which aims to establish state-of-the art facilities for optical imaging and image analysis of living systems. It is funded by a major grant (MORPHOSCOPE2, 9 million euros) from the National Agency for Research (ANR) which has been selected for the second round of national "Equipement of Excellence (EQUIPEX)", part of the operation "Investments for the Future" set up by the French Ministry of Research. It will integrate cutting-edge technology in photonic microscopy and computational analysis dedicated to in vivo multiscale investigations in integrative biology, based on the expertise of its core developing partners. This unique platform with emphasis on technology development and innovation will be located at Ecole Polytechnique (one of the funding members of the Campus Paris-Saclay initiative).

Members of Team 1 are already involved the Clinical Consortium DHU "Hepatinov". This DHU has been created in January 2013 under the umbrella of the Assisitance Publique Hôpitaux de Paris. It gathers a large number of clinicians and researchers who are working in partnership with SMEs with the objectives of developing new diagnostic and therapeutic approaches for liver diseases. Members of Team 1 are involved in "Hepatinov" in two ways: first as basic researchers and second as clinicians of the Department of Pediatric Hepatology and Pediatric Liver Transplantation at Bicêtre University Hospital (a tertiary care center for pediatric liver diseases including genetic cholestasis) which is headed by a university hospital professor member of the team.

Teams members are involved in networks awarded by the ANR (Mr Thierry TORDJMANN PI of one completed project and of another one which is ongoing; another scientist is co-investigator of one completed project). The team includes a university hospital professor who is responsible for the French national reference centre for biliary atresia.

Team members are expert reviewers for scientific journals and national agencies (AERES, ANR, INSERM etc..)

In term of appeal of young researchers two post-docs have been trained and two established investigators with University permanent position joined recently the Team.

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

The interaction with the social, economic and cultural environment is very good. Pediatricians are involved in multifaceted relationships (with the Agence of Biomedicine; patients families and Family patients associations) related to their involvement in the management of severe liver disease and liver transplantation. Mr Emmanuel Jacquemin often participates to TV and radio programs (France 5, France 2) and gives press interviews (Le Figaro).

Assessment of the unit's organisation and life

The team's organization and life is excellent.

The team project includes 19 persons: 3 established investigators from the INSERM (2) and CNRS (1), 6 established investigators from the University (including Medical School), 1 clinician without university position, 4 engineers and technicians, 4 students (1 PhD, 3 Master 2) and 1 post-doc. In addition, as mentioned earlier, Team 1 will have technical support from 6 engineers or technicians who compose a "pool" shared by the two Unit Teams.

The team structure is appropriate regarding the underlying scientific strategy. Although there have been successive waves of retirements, this is in part compensated by the recruitment of young MCFs. It should be emphasized that the relationships between researchers and technical personels are excellent due to an "intrinsic" culture of dialog.

Assessment of the unit's involvement in training through research

The involvement in training through research is excellent. All team members are very involved in teaching and tutoring.

Since 2008 20 students were trained in the team. Five PhD theses were completed over the period.

Team members are responsible for or involved in teaching programs: 2nd year of biology (300 students); "Magistère of Biology and Biotechnology" in Orsay; PCSO (Préparation aux Cursus Scientifiques d'Orsay: a one year preparatory course for about 130 high school students who need to improve their science education before entering the regular license program); responsibility of the WIMS initiative in order to develop a distance education at the L1 level in the new Institute "Georges-Charpak" at Palaiseau and Boris MOOC (massive open online courses) project in collaboration with the chemistry and physics of Paris-Sud; teaching in the science and engineering program at Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI ParisTech); responsibility of the program and course of Cell Biology at ESPCI ParisTech; Program Manager for the "Scientific Projects in interface with biology" and in charge of the relations with biotechnology companies for ESPCI ParisTech; responsibility of the implementation of programs for the biology License at PSL (Paris Sciences et Lettres).

One of the scientists is involved in the council of the department of biology; she is also assistant vice-president of teaching; finally she is member of the national commission (CNU section 65, cellular biology) in charge of teaching and research personnel.

Assessment of the strategy and the five-year plan

The strategy and five-year plan are excellent. The scientific objectives of Team 1 are in continuity with past findings and address the following three points.

1) The Role of purinergic and bile acid signaling in liver repair and biliary homeostasis. The general objective is to determine the impact on liver regeneration of the purinergic signaling through P2X4 and P2X7 receptors on the one hand, and bile acid signaling through the TGR5 receptor on the other hand. The project is very original and capitalizes on available mice models to study liver ATP and bile acid signaling. This project will be led by Mr Thierry TORDJMANN and involve two engineers, one post-doc (to be recruited), one PhD student; one Master 2. Interestingly the project will benefit from the expertise of Team 2 members and clinical connections with "in-Team" Pediatricians and hepatologists from the Centre Hépato-Biliaire (experts for liver diseases in adults).

2) Progressive Familial Intrahepatic Cholestasis type 2 (PFIC2): pathophysiology and treatment. This project will be divided into two parts. The first part of the project is entitled "Specific pharmacotherapy for PFIC2". A polarized hepatocellular line isolated in the UMR S_757 (Can-10 cells) will be used to study the consequences of missense mutations identified in patients. This part of the project will also use stable clones expressing different Bsep mutants.

In these models, a library of chemical compounds will be screened in collaboration with UMR 8076 CNRS-Université Paris Sud - BioCIS and the Innovation Thérapeutique LabEx LERMIT. The second part of the project is entitled “Anti-BSEP alloimmunization after liver transplantation for PCFIC2: Screening, natural history and identification of antigenic target”. Overall, this project will benefit from an available prospective and well-annotated patients cohort indispensable for high-quality translational medical research.

3) Ciliary proteins and cholangiocyte differentiation. During development and during regeneration after massive hepatocyte loss or during chronic liver injury, the differentiation of cell precursors in cholangiocytes and the subsequent organization of the ductal plate are conditioned by multiple signaling pathways in particular Notch, Hedgehog or TGFß. Studying the role of cilia in bile duct formation is timely, very original and important for the overall team’s project. An important step of the project is the optimization of culture conditions which will determine the ability to perform studies on the effects of mechanical stress, biochemical environment, hedgehog signaling as well as the influence of inactivation of ciliary proteins on the differentiation and organogenesis of cholangiocytes. The project includes the development of 2D or 3D micropatterns in collaboration with the Institut Curie and the University of Singapore, to identify the optimal conditions to obtain "functional" cholangiocytes.

The overall Team 1 project is feasible and addresses the question of mechanisms of liver regeneration/reparation in the context of societal issues related to liver transplantation which is the only available treatment of very severe acute or chronic liver diseases. However liver transplantation is costly and there is organ shortage which is associated with ethical issues related to justice and equity. Improved knowledge in this field is a prerequisite to the development of novel therapeutic approaches that are alternatives to or allow delaying liver transplantation. Logically Team 1 is a significant component of the DHU “Hepatinov”.

Conclusion

- **Strengths and opportunities:**

The team has been developing a strong expertise for many years in the studied field and contributed to the knowledge in liver physiology and pathophysiology. The proposed project is very original and addresses the crucial question of improving knowledge of mechanisms of liver regeneration and reparation. This should help to address unmet medical needs in the field of therapies for liver diseases.

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

- **Weaknesses and threats:**

Some engineers and technicians who play significant roles in the scientific activity of the team will retire during the next period.

- **Recommendations:**

The Committee welcomes and recognizes the high interest of the team's projects.

Team 2 : Inflammation, Metallo-Proteins and Redox Systems

Name of team leader: Mr Oliver NUSSE and Ms Cécile BOUTON

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	NA	6 (3)
N2: Permanent EPST or EPIC researchers and similar positions	NA	3
N3: Other permanent staff (without research duties)	NA	1
N4: Other professors (PREM, ECC, etc.)	NA	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	NA	1
N6: Other contractual staff (without research duties)	NA	
TOTAL N1 to N6	NA	**12**

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

Detailed assessments

Team 2 will include 4 different groups. Two groups are already located at UMR S_757. One group will move from UPR2301 (CNRS). Another group will move from UMR 8619 (CNRS-Université Paris-Sud).

Assessment of scientific quality and outputs

Team 2 has very good scientific quality and output. The group of Mr Oliver NÜSSE is recognized for having produced significant methodological advances in ROS imaging; it has regular publications in good impact journals (J Leukoc Biol IF=4.6; Free Radic Biol Med IF=5.3). The group of Ms Cécile BOUTON has 27 publications (FEBS J IF=4.2; JBC=4.6) and 2 invited book chapters; a third group has 20 publications (JBC IF=4.6; Nitric Oxide IF=3.2).

Assessment of the unit's academic reputation and appeal

Team 2 has an excellent academic reputation and appeal. Mr Oliver NÜSSE has an excellent international reputation in the field of oxidases. The group of Ms Cécile BOUTON had invitations to 6 international meetings including 2 Gordon Conferences; Mr Jean KANNELOPOULOS gave 2 international lectures and Mr Olivier Guittet gave one; Mr Jean KANNELOPOULOS is member of PULMO-NET (Research training network-Marie Curie Actions). Two post-docs will participate in the team's project.

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

The interaction with the social, economic and cultural environment is very good to excellent. Mr Oliver NÜSSE is member of the Council of the "Centre d'Alembert" at Orsay. Ms Cécile BOUTON has given combined lectures and practical courses for general public and participated in Science Workshops for later years of primary school. Mr Franck Brouillard has participated in the creation of the Villebon-Georges Charpak Institute, a boarding high school, for students motivated by science and technologies. This academic project involves several big companies, including SNCF, Orange, Areva, Microsoft, Société Generale, Solucom. Several team members are involved in the review panels of national agencies/Institutions (e.g., ANR, AERES, INSERM, University) and international agencies (FNRS, Mardsen Fund (NZ), TEAM program evaluation).

Team members have shown their ability to raise funding (ANR, FRM). Mr Pierre BOBE has filled three international patents and one national patent; one international patent has been licensed; all are related to arsenic trioxide treatment.

Assessment of the unit's involvement in training through research

The involvement in training through research is excellent.

All team members are very involved in teaching and tutoring. They are involved in PhD supervision (7 current PhD students), teaching in post-graduate courses, Masters (1 and 2) and undergraduate degrees. Six PhD theses were completed over the period. Several members of the Unit are responsible for and/or involved in teaching programs. Mr Oliver NÜSSE is Co-director of the Doctoral school "Biosigne: Signalisations et réseaux integrative en biologie" (ED 419). Ms Cécile BOUTON is Co-Organizer of Post-graduate courses "Mitochondrion" PRES UniverSud Paris. Other team members teach in Master Biologie Santé, "Signalisation et Physiologie Cellulaire; Neurosciences" Université Paris-Sud; at "Omics in pharmacology and toxicology" Master degree, Université Paris-Descartes; in the new Institute "Georges-Charpak" at Palaiseau; at the Erasmus Mundus program in SERP chem. Mr Oliver NÜSSE is responsible for the flow cytometry platform of the institute, which is open for research and teaching from licence to PhD level. Mr Oliver Nüsse is also co-organizing and teaching the CNRS flow cytometry course in Gif/Orsay.

A team member is member of the science council of the faculty of Sciences in Orsay.

Mr Oliver NÜSSE is a member of the council of the department of biology and is president of the commission (CCSU section 64-69) in charge of the teaching and research personnel in biology (promotion and recruitment) of the biology department.

Assessment of the strategy and the five-year plan

The strategy and five years plan are very good to excellent. Team 2 will combine expertise in cell redox mechanisms, iron metabolism and phagocyte biology as well as in autoimmune and auto-inflammatory diseases. The main goal is to get more insight into the cell redox phenomena and their link with inflammation and pathologies of the immune system, in the frame of hepatic fibrosis, liver regeneration and mitochondrial infantile diseases. The project will address the following points.

1) Production of ROS and RNS.

Studies will be divided into two parts.

The first part is entitled "Regulation of NADPH oxidase and ROS imaging". This very interesting project will investigate NOX2 at the cellular level (new signaling pathways) by exploring the role of phosphoinositide in NOX2 assembly. This implies the development of new tools for ROS and RNS imaging in collaboration with Team 1 and a group from the Laboratory of Physical Chemistry, LCP, Orsay. The model system of host-pathogen relationship is the interaction between phagocytes and Candida glabatra (an opportunistic pathogen) and will be extended to liver inflammation. Team 2 members involved will be Mr Oliver NÜSSE, two other scientists, one post-doc (FRM funding) and 3 PhD students.

The second part is entitled "Regulation of iNOS expression and macrophage phenotype by p73". The role of the antioxidant bZIP transcription factor NRF2 will also be addressed. There will be a collaboration with the Karolinska Institute in Stockholm. Part of the task will involve collaboration with Team 1 (mouse model of chronic inflammation of liver, macrophage polarization). The project involves 2 scientists and one PhD student.

2) Fundamental and pathophysiological studies on Fe-S proteins.

Ms Cécile BOUTON and another scientist will address the very interesting hypothesis that mitoNEET is part of a novel branch of the mitochondrial Fe-S export pathway to repair the [4Fe-4S] cluster of IRP-1, an important regulator of cellular iron homeostasis. Team 2 members involved are Ms Cécile BOUTON, 3 other scientists, one post-doc (to be recruited, ANR funding) and one engineer (if available, see infra) This project will combine expertise in Fe-S biochemistry and cell biology (Ms Cécile BOUTON and colleagues), genetics of human Fe-S deficiency (IGBMC, Illkirch), biochemistry and biophysics on metalloproteins (CEA Grenoble and Saclay, and ICSN Gif) and cell imaging (Team 1).

Ms Cécile BOUTON and colleagues will be also involved in a new project on infantile liver disease due to mutations in the gene called tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase (TRMU, a protein coding gene). This project will be conducted in collaboration with Team 1.

3) New mouse models autoimmune and autoinflammatory diseases.

This project will address the important question of the role of the death receptor Fas and P2X7 purinergic receptor in the development of autoimmune diseases with multiorgan injuries (including the liver) in relation to proliferative and autoreactive T-cell subsets. The project involves 2 scientists and 3 PhD students. This group recently developed a novel mouse strain (called B6/lpr-P2X7R KO) characterized by a deficiency in both Fas apoptotic pathway (lpr mutation) and P2X7 purinergic signaling pathway in normal C57BL/6 (B6) genetic background. These mice develop an autoimmune disease very similar to that observed in MLR/lpr mice (a paradigm for murine autoimmune disease which is due to a complex interaction between lpr mutation and MLR background). The project is very interesting: they will develop different strains of conditional KO mice, in which P2X7R expression is abolished in T lymphocytes, macrophages or dendritic cells only. These conditional KO mice will be then crossed with B6/lpr mice. These novel mouse strains raised on a B6 genetic background has much less complex genetic background than the MRL/lpr mice and will allow to identify more easily variations in gene expression involved in T-cell proliferation and autoreactivity. An ANR France-Taiwan (2014-2016) will support this project.

4) Targets of arsenic in the treatment of autoimmunity and inflammation.

All members of Team 2 will take part in a common project to understand selectivity of arsenic trioxide treatment (in line with their previous studies). They will address gene expression, Fe-S cluster assembly, iron metabolism and NOX2 activity in selected T-cell lines. Each participant will contribute according to his/her technical and scientific skills.

Conclusion

- **Strengths and opportunities:**

The Team has been developing a strong expertise for many years in fields of NOX, ROS imaging, redox systems, metallo-proteins and murine models of auto-inflammatory diseases. Overall the team projects will address paradigmatic and poorly understood mechanisms underlying immunopathology (i.e., collateral tissue damage, including liver injury, caused by the immune system of the host). Team 2 will provide an "added value" to Team one, and vice-versa.

- **Weaknesses and threats:**

The overall 5-year program of Team 2 is broad and ambitious.

One of the incoming groups has worked for a long time with an engineer appointed by the CNRS. There is no information on whether or not this engineer will be able to follow the researchers in the new structure. The fact that some Team members might move to the new structure not accompanied by the engineer would weaken the group.

- **Recommendations:**

The Committee recognizes the high interest of the Team's projects and the strong expertise of Team members to address important questions related to inflammation. The project is ambitious and the Team is encouraged to propose a more focused work plan.

5 • Conduct of the visit

Visit date:

Start:	Friday, December 20, at 09:00 am
End:	Friday, December 20, at 04:30 pm
Visit site:	Faculté des Sciences d'Orsay
Institution:	Université Paris-Sud
Address (no. street town):	Bât. 443, Université Paris Sud 11, 91405 Orsay cedex

Conduct or programme of visit:

09:00	Welcome (closed-door) Visiting Committee with the AERES Scientific Advisor
09:30	Director of the Unit: Presentation of the past activities and project
10:00	Team 1: "Biliary homeostasis and liver repair" Mr Thierry TORDJMANN Mr Emmanuel GONZALES Ms Pascale DUPUIS-WILLIAMS
11:20	Team 2: "Inflammation, Metallo-Proteins and Redox Systems" Mr Oliver NÜSSE Ms Cécile BOUTON Mr Michel LEPOIVRE
12:00	Discussion with the representatives of the managing bodies and Doctoral School
13:00	Lunch
14:00	Parallel meetings with personnel: Discussions with engineers, technicians, administrative Discussions with staff scientists Discussions with students and post-docs
14:30	Private meeting of the Director of the Unit with the Visiting Committee (in presence of the AERES scientific advisor)
14:40	Private meeting of the visiting committee (in presence of the AERES Scientific Advisor)
16:30	End of the visit

6 • Supervising bodies' general comments

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Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 25 février 2014

N/Réf. : 28/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007892

Monsieur le Directeur,

Vous m'avez transmis le 5 février dernier, le rapport d'évaluation de l'unité de recherche - - INTERACTIONS CELLULAIRES ET PHYSIOPATHOLOGIE HEPATIQUE – n° S2PUR150007892 et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.

Les points à améliorer seront discutés avec le directeur d'unité dans un esprit constructif pour l'avenir de la recherche à l'université.

Vous trouverez en annexe les éléments de réponse de Monsieur Laurent COMBETTES, Directeur de l'unité de recherche.

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

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Unité de Recherche U757
Signalisation Calcique et Interactions Cellulaires dans le Foie
Dir Laurent Combettes

Orsay, 17th of February, 2014

Dear Sir,

We thank the AERES committee for its evaluation work and the report which was sent to us. We welcome the very positive feedback on our ongoing and future projects and on the new lab structure. We sincerely thank the committee for its support, and we wish to respond to some points raised by the expert committee.

Concerning the "Internal Rules" which should be more clearly described: the policy of the lab has always been to promote the participation of everyone. Thus, the laboratory council brings together ALL members of the unit. This strengthens group cohesion and everyone's adhesion to the project and until now, this enables to share all laboratory resources both technical and financial. We agree that the new structure of the laboratory will render this policy more difficult. This is why we chose co-directions for both teams, which will promote exchanges among the two teams and between the teams, and will enable our new colleagues being integrated more easily and quickly into the lab.

Concerning the new team 2, we agree that the project is ambitious and that it would merit to be a bit more focused. However, we would like to point out that the project of team 2 is based and evolves from the ongoing projects of the different groups who will join the team. These projects are supported by various grants (ANR, FRM, DIM, CSC…). Based on this background, we have defined 3 priorities: 1) Regulation and consequences of ROS and RNS production in phagocytes 2) Functional characterisation of Fe-S proteins, especially mitoNEET 3) New mouse models of autoimmune and autoinflammatory diseases. All three projects are related to the adaptive cellular response to inflammation and redox imbalance. Once all members of team 2 will be in the same building, the intersection between these priorities will be naturally reinforced by daily interaction, joint team meetings and shared expertise, promoting thus a more focused work.

Regarding the technicians, we are well aware that a majority of them will go soon into retirement. We are confident that our institutions will pay attention to this crucial issue and compensate for these departures. A position has just been assigned to our laboratory by the University Paris-Sud; the person will be recruited this spring and will be in our lab starting from the next academic year. Concerning the engineer appointed by the CNRS, as four new members are CNRS scientists, an accreditation by CNRS will be requested. Endorsement by CNRS will be decisive to allow the CNRS engineer to follow the team with whom she works for a long time.

Yours faithfully

L. Combettes

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