Physiopathogenèse et traitement des maladies du foie

Rapport Hcéres

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

Section des Unités de recherche

AERES report on unit:

Pathophysiology and treatment of liver diseases

HEPAREG

Under the supervision of the following institutions and research bodies:

Université Paris-Sud

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

January 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,

- Mr Fabien ZOULIM, 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:	Pathophysiology and treatment of liver diseases
Unit acronym:	HEPAREG
Label requested:	UMR_S
Present no.:	UMR_S785
Name of Director (2013-2014):	Mr Didier SAMUEL
Name of Project Leader (2015-2019):	Mr Didier SAMUEL

Expert committee members

Chair: Mr Fabien ZOULIM, Université de Lyon

Experts:

Mr Matias AVILA, CIMA-University of Navarra, Pampelune, Espagne

Mr Jean-François DUFOUR, Université de Berne, Suisse

Ms Chantal HOUSSET, Université Paris 6

Mr Jerôme LEMOINE, Université de Lyon

Mr Michel SAMSON, Unviversité Rennes 1 (representative of CSS INSERM)

Ms Christine SILVAIN, Université de Poitiers (representative of CNU)

Scientific delegate representing the AERES:

Mr Daniel OLIVE

Representatives of the unit's supervising institutions and bodies:

Mr Etienne AUGE, Université Paris-Sud

Mr Marc PALLARDY (representative of Doctoral School n°425, Innovation thérapeutique, Université Paris-Sud)

Ms Anne ROCHAT, INSERM

1 • Introduction

History and geographical location of the unit

UMR_S 785 (INSERM & Université Paris-Sud) is part of the Centre Hépatobiliaire (CHB) located at Paul-Brousse Hospital, Villejuif. This unit has emerged from the fusion of the INSERM unit 370 and the EA 3541, in January 2006. This merging was aimed at creating a research unit in a clinical environment of liver diseases. The research unit UMR_S 785 was renewed in 2010 (AERES: A, CSS6 Inserm: 6/31). UMR_S 785 is part of a European Associated Laboratory (EAL) with the Laboratory of Gene Expression (LGE) at University of Rome La Sapienza, Italy.

The research program of UMR-S-785 includes mechanistic studies of hepatobiliary diseases and valorisation/development studies in the prospect of clinical applications, and was initially subdivided into two themes. Theme I "Liver Regeneration and Primary Liver Cancers" aimed at elucidating the molecular mechanisms controlling the fate of hepatic cells during liver regeneration and carcinogenesis, and includes translational researches for the management of patients with acute liver failure and primary liver cancers. Theme II "Molecular Virology and Auto/Alloimmunity in Liver Transplantation" related to viral and immune disorders in the context of liver transplantation. In 2010, a Researcher (DR) joined the unit leading to the emergence of a third theme "Investigating liver diseases by multimodal spectroscopy and imaging".

Over time, the UMR-S 785 has progressively evolved towards the future structuration of the research unit from a "mono-équipe/mono-thématique" to a "pluri-équipe/mono-thématique" organization with several other groups aiming to join the future unit which will be organized in four teams :

- Therapeutic innovations in liver disease and liver transplantation, and translational research (PI: Mr Didier SAMUEL);

- Integrative biology, modeling, and cell therapy of liver diseases (PI: Mr François LE NAOUR);

- Microbiota, inflammation and liver cancer (PI: Ms Jamila FAIVRE);

- Cellular and molecular mechanisms of adaptation to stress and carcinogenesis (PI: Mr Christian POUS).

Management team

The future research unit will be led by Mr Didier SAMUEL. An executive committee composed by the team leaders will assist the director to define strategic and scientific issues. Regular meetings will take place once a month. A laboratory board composed by the executive committee and representative members of the postdoctoral fellows, the ITAs, the Ph.D. students, the hygiene and safety adviser, and the administrator will be hold twice a year. Once a year, the executive committee will organize a meeting of the entire unit for scientific auto-evaluation of the progress regarding the different research programs.

AERES nomenclature

SVE1_LS4 Physiologie, physiopathologie, biologie systémique médicale

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	8	16
N2: Permanent researchers from Institutions and similar positions	5	14
N3: Other permanent staff (without research duties)	18	26
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		2
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	7	9
N6: Other contractual staff (without research duties)	14	18
TOTAL N1 to N6	**52**	**85**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	10	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit*	6	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	15	27

2 • Assessment of the unit

Strengths and opportunities related to the context

The unit is in a unique position to develop a translational program focussed on liver disease pathophysiology. It is integrated in an internationally recognized expert center in Hepatology and Liver Transplantation, and will benefit from the complementary expertise of the different teams as well as the access to high quality technology platforms and to clinical samples. Partnership with academic teams in international/European networks and with pharma industry will also represent an asset. The success of the DHU project “Hepatinov” should also reinforce the translational research programs of the unit.

The clinical (medical and surgical) and laboratory environment represents an excellent attractiveness for basic scientists and fellows, and the unit itself has a fast growing dynamics

The unit also showed its capacity to favor the emergence of new team leaders.

Weaknesses and threats related to the context

The end of the hepatitis C epidemic is not foreseen within the next five years although the major focus of hepatitis C research will shift to other directions, i.e. mainly pathogenesis of HCV induced liver injury and other various etiologies (toxic, viral, autoimmune).

The project proposes a new structuration with several groups joining the former unit, increasing the number of research topics that will be performed on two geographical sites. A careful management strategy will need to be implemented to ensure an efficient collaboration and interaction between the teams.

Recommendations

Since the unit will undergo a new organization with the emergence of three teams and the addition of new research topics, the diversity of the research topics, the management of two sites and new teams will represent a challenge. It is therefore recommended to seek the advice, on a yearly basis, of an external scientific advisory board (SAB), which could share common members with the Hepatinov DHU SAB, acquainted to part of the research projects of the unit.

However, the unit and the DHU should both keep their own specificities in terms of organization and scientific goals.

Based on discussion with the research staff, it is recommended to organize meetings of all PhD students and post-docs on a weekly basis to facilitate integration of the new teams and collaborations between them.

Since the unit will be organized in four teams, it will be necessary to pre-define rules of budget distribution among the teams, depending on the resources (INSERM/University core grant versus research contracts obtained by PIs for specific projects) .

The strategy of the unit needs to fully integrate its contribution to the platforms of the SFR which will be critical for the development of the unit.

3 • Detailed assessments

Assessment of scientific quality and outputs

The scientific production was found excellent.

Overall the unit had a quite strong scientific output with several important discoveries in the field of liver diseases pathogenesis:

1) demonstration of the role of EMT and TGF-ß in HCV induced carcinogenesis (J Hepatol 2013) and the role of the cell polarity in HCV replication pathway (Mol Biol Cell 2013);

2) preclinical studies demonstrating the potential of patented drugs such as a human recombinant protein HIP/PAP for the stimulation of liver regeneration, and a recombinant viral vector AdHIP-NIS for the radiotherapy of HCC. They established the preclinical proof of concept for the therapeutic use of the human HIP/PAP protein (Hepatology 2011) against acute liver failure (ALF) and then conducted, in partnership with the Biotech Company ALFACT Innovation, a Phase I clinical trial and a multicentre randomized European Phase 2 trial on 60 patients with ALF;

3) description of new biological properties of the iodure sodium symporter NIS in non-thyroid carcinogenesis (2012 Cancer Res; 2013 Cell Death & Disease) with subsequent application to NIS-mediated radiotherapy in primary liver cancers (Plos ONE 2012);

4) use of multimodal spectroscopy (Anal Chem 2010; Anal Chem 2012) and quantitative proteomic analyses to investigate membrane proteome (PLoS ONE 2013) with applications in the field of HCV entry (collaboration with the team of T Baumert (Cell Host & Microbe 2013) or in autoimmune hepatitis (Hepatology 2013). With high quality technological platform, the unit performed chemical analysis and imaging of liver steatosis (PLoS ONE, 2009) and its application in liver graft analysis;

5) in the field of liver transplantation, the unit described for the first time the role of the new Direct Acting Anti-viral agents in the treatment of HCV recurrence after transplantation (J Hepatol 2014 in press) and the main worldwide experience of HIV HCV coinfection after transplantation (Hepatology 2008, AJT 2011). They also participated in a multicentre study demonstrating for the first time the place of liver transplantation in life-threatening alcoholic hepatitis (NEJM 2011).

Assessment of the unit's academic reputation and appeal

The international reputation of the unit is excellent.

During the last 5 years, the unit attracted a DR INSERM and a DR CNRS emeritus in 2010, a CR1 INSERM (recruited in 2011), a MCU (recruited in 2012), two PU-PH senior surgeons in 2012 and 2013. It gave rise to three Interface Contracts with INSERM. In addition, three engineers/technicians (ITA) were recruited: an engineer assistant from INSERM in 2010, a Technician from University in 2010, a Technician from INSERM in 2013. Twenty-two Masters, 18 Ph.D. students and 9 Postdoctoral fellows came to reinforce and enlarge the research unit testifying of its attractiveness. This development was made possible by several European and National fundings, representing 4 880 000 € in total, since 2008.

The unit was also able to attract at least two other research groups to form a multi-team unit.

The unit is involved in several national consortia (PLI-K, IMODI, HECAM) and ANRS studies (CUPIC, HEPATHER, CUPILT, etc.), and european consortia (MODHEP granted by EC, and the EASL-CLIF consortium).

The unit was central to the DHU project called « Hepatinov », which federates the unit and the Centre Hepatobiliaire with several other clinical units and research laboratories involved in Hepatology research.

The unit director is the editor in chief of Journal of Hepatology (IF 9.9) and is the president of the International Liver transplantation Society.

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

The unit is strongly involved in the transfer of the knowledge to the social and economic environment; this activity was judged excellent.

The laboratory has a strong interaction with the economic sector with several research contracts in collaboration with pharma industry and the clinical units performs international clinical trials for the treatment of viral hepatitis. The interaction with the social environment is also strong with respect to patients' care and interaction with patients' advocacy groups.

The unit also developed 5 patents in the field of HIP/HAP therapy and the analysis of liver graft function (Teams 2 and 3).

Assessment of the unit's organisation and life

Excellent organization of the unit.

The unit organization is very clear with an undisputed leadership of Mr Didier SAMUEL. The unit has evolved towards a multi-team organization with the emergence of two leaders for teams 2 and 3 and the arrival of team 4 leader. The unit strategy is to integrate basic and clinical research, as well as Medical Doctors and Surgeons in the overall research program. The PIs and team leaders meet frequently to openly discuss results and scientific strategies. All staff members are enthusiastic about the translational program unifying the four teams around a common aim on liver disease pathogenesis and liver transplantation.

Assessment of the unit's involvement in training through research

This was judged excellent. The unit members are involved in teaching in different Master courses and University diploma. The unit has trained 9 PhD, 2 ParmD and 1 MD who defended their thesis during the last 5 years. 32 students preparing a Master degree were trained in the unit. Team 4 leader is strongly involved in the Doctoral School "Therapeutic innovation from basic science to application" and will become the director of this Doctoral School. Furthermore, the unit is involved in the DHU Hepatinov which also has specific training objectives for MDs and nurses on the topic of clinical research in hepatology.

Assessment of the strategy and the five-year plan

This was judged excellent. The research unit will be organized into four complementary teams to address key medical questions on acute and chronic liver diseases including inflammatory, metabolic and cancerous diseases. Studies will be performed to understand the involved underlying mechanisms, to model some liver diseases, to accelerate translational researches and finally to discover potential diagnostic/prognostic biomarkers and therapeutic products. The molecular and cellular signaling networks, which are profoundly deregulated in viral hepatitis infection, dysmetabolic and cancer diseases will be investigated by several global interdisciplinary approaches and integrative biology. A variety of competences ranging from biophysic to medicine will be an asset to implement such interdisciplinary projects. Mechanisms of the cellular responses to stress including viral infection will be investigated along different lines: cell polarity and morphogenesis, microtubule dynamics, organelle alterations, cellular trafficking, cell signaling and extracellular remodeling. The crosstalk between the gut microbiota and the liver will emerge as a major topic. This will include the study of the gut/liver functional interactions, the role of innate immunity in liver cell homeostasis and finally the contribution of commensal microbiota in the initiation/amplification of inflammatory/oxidative signals. Finally, stem cell biology and cell reprogramming will allow modeling liver diseases and will pave the way to bioengineered organ.

This is a very ambitious program which will benefit from the full integration of the research unit within the Centre Hépatobiliaire. If successful, the unit should become one of the major players in the field of translational research in Hepatology with a strong emphasis on treatment innovation and clinical applications.

4 • Team-by-team analysis

Team 1: Therapeutic innovations in liver disease and liver transplantation, and translational research

Name of team leader: Mr Didier SAMUEL

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4	4
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	14	13
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	9	9
TOTAL N1 to N6	**28**	**27**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
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	7

• Detailed assessments

Assessment of scientific quality and outputs

The scientific quality and outputs are excellent. The team made significant scientific contributions in the last 5 years. It consistently published original results dealing with liver transplantation in the best Journals. It participates to paradigm-shifting clinical trials like for example liver transplantation for alcoholic hepatitis. In hepato-biliary surgery it performed pioneer operations like laparoscopic liver living donation.

Assessment of the unit's academic reputation and appeal

The team academic reputation is outstanding. It establishes itself over the years as one of the best centres for hepato-biliary surgery and liver failure. It has a worldwide visibility. Its charismatic leader is an internationally recognized expert. He is regularly invited to speak at international meetings. He is currently Editor-in-Chief of the Journal of Hepatology and President of the International Liver Transplantation Society. This positive visibility attracts foreign visitors interested in an academic career in hepato-biliary surgery and liver reanimation.

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

Excellent. The team organized in the last years several courses and engaged in disseminating its knowledge. The center had 'open door' day, which is particularly important for a centre so heavily involved in organ transplantation. Economically, the team developed artificial liver device and an ingenious tool to control the flow in the portal vein and as a consequence the portal pressure, post-liver resection. The assessment of the team's interaction with the socio-economic environment is excellent as it is involved in the most important international clinical trials in the field. Cultural environment is not applicable.

Assessment of the unit's organisation and life

Excellent. The team seems to have a congenial, internal organisation rather flexible and not too pyramidal. This leaves the necessary freedom to the members of the team to develop their potential. Several of them have already a national and for some of them international visibility. Post-docs and Ph.D. students participate to the life of the team, about 50 % of them are foreigners creating strong bonds among them. Their supervision seems to be of very good quality with access to the PI, although lab meetings are not occurring always on a regular basis.

Assessment of the unit's involvement in training through research

Very good. The assessment of the unit's involvement in teaching is very good. The team 1 contributes to courses in 2 Master programs (Sciences Biologiques et Médicales, Interactions hôtes microorganismes). In the last 5 years this team supervised 9 PhD thesis and 32 Master students from 14 different programs. The team organises weekly seminar with invited seminars and the students have the possibility to attend countless presentations on the campus.

Assessment of the strategy and the five-year plan

Excellent. The team is ideally positioned to continue successfully in the next five years. It developed thematics where it has a leading place such as treatment of patients after transplantation with the new anti-hepatitis C drugs. It already positions itself in important future topics such as gut microbiota and is putting in place important collaborations in this perspective. The Team 1 is articulating its research in the next 5 years around 6 axes. All the topics are interesting, but prioritisation will be important to focus the attention of the team on the best projects. These axes will also provide the basis for the translational programs developed by the other teams. Based on the track record of the team feasibility is judged excellent.

Conclusion

- **Strengths and opportunities:**

This team has several strengths: its international visibility, the quality of its leaders, the unique expertise which has been acquired over the years, its absolutely unique integration of the hepato-biliary surgery in a larger hepatology team. This created opportunities, which form the basis for the next 5-years strategic plan.

- **Weaknesses and threats:**

The weaknesses are in the topic selected with the end of the importance of hepatitis C in the liver transplant field. The team is already taking some positions in topics which will be of relevance thereafter. Another weakness is that in several of the large clinical trials the team is participating with a limited role as promoter of the project.

The threats are in the technological advances and the team should keep up and invest on this basic aspect if it wants to secure its long term success.

- **Recommendations:**

The governance of this group should be well structured and consequent. This team cumulates several ambitious projects involving several individuals. Focusing and prioritisation of topics will be essential. The experts committee recommends to stick to weekly data sessions to monitor closely progressess and difficulties in the performance of research projects by the team leader and senior researchers.

Team 2: Integrative biology, modeling, and cell therapy of liver diseases

Name of team leader: Mr François LE NAOUR

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	3
N2: Permanent EPST or EPIC researchers and similar positions	2	3
N3: Other permanent staff (without research duties)	2	3
N4: Other professors (PREM, ECC, etc.)		1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	5
N6: Other contractual staff (without research duties)	1	3
TOTAL N1 to N6	**10**	**18**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	2	
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	3	7

• Detailed assessments

Assessment of scientific quality and outputs

This was judged excellent. Within a few years, the team has developed quite ambitious interdisciplinary projects based on proteomics and multimodal spectroscopy for deeper molecular characterization of liver components. These projects are closely connected with liver diseases such as cirrhosis, steatosis, HCV infection and autoimmune disorders. They mainly aim at the identification of tissue biomarkers, membrane autoantigens and autoantibodies. These topics are therefore of high clinical relevance. The outcomes are excellent and include:

I) the proof of concept of liver tissues imaging by spectroscopy, some using new multimodal synchrotron lines,

II) identification of new organic and inorganic components related to cirrhosis and steatosis,

III) development and validation of proteomic tools for membrane proteins and identification of autoantigens in autoimmune hepatits. Important techological advances have been made as evidenced by publications in Anal Chem, PlosOne, J Immunol, J Proteomics, Hepatology 2008 & 2013 etc, and collaborative work has provided significant insights into key mechanisms in liver diseases such as hepatitis C virus entry (published in Cell Host Microbes, etc.). The team leader has published 17 articles over the period of reference.

Members of UMR_S 972 who join this team also bring in an expertise in the field of liver stem cell therapy (published in Hepatology 2009, Hum Gen Ther, BMC Biol, etc.) or iPSCs (J Clin Invest 2011, etc.) with the development of partial portal embolization improving hepatocyte engraftment (Hepatology 2009, etc.).

Assessment of the unit's academic reputation and appeal

This was judged excellent. The team leader himself is a highly recognized expert in the proteomics community for his multidisciplinary research covering translational medicine, applied spectroscopy and selection of candidate biomarkers. Numerous local and national fundings (14 projects granted by FRM, ANR, ANRS, etc. for a total of 1,130 k€ since 2008) and invitation as a speaker (18) prove this strong expertise.

Team members are reference experts in the field of Wilson's disease (more than 30 invited lectures in 5 years) and from UMR_S 972, in liver cell therapy (coordination of 2 EU FP7 programs).

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

Excellent interaction with the social and economic environment. The team has patented a method for measuring steatosis of frozen tissue section by IR microspectroscopy in the context of quality control for liver transplantation. The method has been transferred to hospital. A method for hepatic differentiation of progenitor cells has also been patented.

Assessment of the unit's involvement in training through research

Excellent attractiveness towards foreign young scientists (currently 1 PhD student from China, 2 Post-Docs from Lebanon and Spain).

Altogether, the team leader and new members from UMR_S 972 have hosted 9 Post-Doc, 15 Master 2 students in the past period, while 8 PhD thesis have been defended.

Coordination by team members of a Master program in surgery, training programs of Ateliers Inserm.

Assessment of the strategy and the five-year plan

This was judged very good. Team 2 is built by gathering highly complementary groups, two from UMR_S 785 and one from UMR_S 972. A relevant and strategic research program is proposed that will:

a) strengthen the translation of spectroscopy-based detection into clinical applications by addressing new issues I) stratification of cirrhotic nodules vs malignancy, II) risk of cancer recurrence, III) diagnosis of Wilson disease;

b) focus on innovative therapeutic strategies by I) antibody-based tumor targeting, II) identifying new therapeutic targets and deciphering deregulated cellular pathways III) bioengineering from pluripotent stem cells. The project leaders will rely on existing or new collaborations (ENS Cachan, CEA, Villejuif).

Conclusion

- **Strengths and opportunities:**

The proposed team is truly interdisciplinary using highly sophisticated technologies and integrative biology to address relevant clinical questions

Strenghts also include the expertise and recognition acquired by the team and access to human biologic resources

- **Weaknesses and threats:**

The multiplicity of questions addressed (i.e. HCV entry & signaling, NAFLD, liver cancer (hepatocellular carcinoma and cholangiocarcinoma) diagnosis and therapeutic targeting, antigenic signatures, autoimmunity, Wilson and cell therapy) in addition to ongoing technological developments is a threat for competitiveness.

The workforce is limited questioning feasibility of certain topics like NAFLD relying on multiple liver cell and animal (including transgenic) models.

- **Recommendations:**

Wilson's disease is an emerging common theme between the different team members from diagnosis to cell therapy that deserves to be boosted.

The team should implement a clear strategy plan with the identification of research priorities and of the PIs in charge of the main research themes and with a re-evaluation of each one on a yearly basis.

Team 3: Microbiota, inflammation and liver cancer

Name of team leader: Ms Jamila FAIVRE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	3
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4
N6: Other contractual staff (without research duties)	4	4
TOTAL N1 to N6	**13**	**15**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	5	
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	4	6

• Detailed assessments

Assessment of scientific quality and outputs

This was judged excellent. The projects developed by this team focus on key issues of liver pathophysiology: liver regeneration/hepatoprotection and molecular mechanisms of hepatocarcinogenesis. These themes are of high clinical relevance. Original outcomes include the development of new strategies to treat acute liver failure (the HIP/PAP protein), and to diagnose and treat cholangiocarcinoma (the sodium iodide transporter, NIS). Important advances have been made in these two fields as evidenced by the number and quality of the publications (Cell, Hepatology, J. Hepatology, Mol. Cell. Proteomics, Cancer Res., etc).

Assessment of the unit's academic reputation and appeal

This was judged excellent. The team has an excellent reputation. The team has established fruitful international collaborations (paper in Cell), and participates in international projects (FP7 MODHEP project). It has received substantial external funding (12 projects awarded in the past 5 years). The PI of the team regularly participates in international conferences as invited speaker (six times in the past 5 years). A widely recognized expert in hepatocarcinogenesis, has recently joined the team as Emeritus DR, attesting the attractiveness of this research team and its projects.

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

This was judged excellent. The team has carried out two contracts with industrial partners during the evaluated period. They list three patents, one under consideration. One of these patents pertains to the product ALF-5755, which has been developed in collaboration with an industrial partner (Alfact Innovation), and is currently undergoing Phase II clinical trials.

Assessment of the unit's involvement in training through research

This was judged excellent. Eleven master's degree students, together with seven PhD students, have been supervised by the team's PI during the evaluated period. There are three PhD students currently in the team, together with three postdoc.

Assessment of the strategy and the five-year plan

This was judged excellent. The proposed research plan is based on previous published and unpublished preliminary observations of the team, and therefore its viability is guaranteed to a great extent. The successful international collaboration with MMRI, Brisbane, United Kingdom on the study of inflammation and hepatocarcinogenesis will continue. The project incorporates novel approaches to the study of the complex interactions between gut microbiota and the liver in the development of hepatic cancers, including both experimental models and clinical samples. The team's PI has successfully established external collaborations with groups of complementary expertises: gut microbiota experts at INRA; structral and functional analyses of HIP/PAP, and UMR 8000, Orsay. Translational studies are also contemplated, with the development of novel oral formulations of HIP/PAP, aimed at the modulation of gut microbiota and the protection of the colonic mucosa. The studies dealing with inflammation and liver carcinogenesis include extensive interactions with Team 1.

Conclusion

- **Strengths and opportunities:**

The team is in an excellent position to undertake the proposed research program. This is supported by the previous and preliminary results presented during the site visit, and the scientific capacities of the team's leader plus the established scientists within the group. The close collaboration with external partners, and also within the unit, will provide the scientific and technological complementary skills needed to undertake the ambitious research plan. The translational orientation of the team, bridging basic research and clinical developments is remarkable.

- **Weaknesses and threats:**

The topic of the research, particularly the crosstalk between the gut microbiota and the liver in hepatocarcinogenesis, is a highly competitive field. There are several international leading groups pursuing this research, and this may represent a threat in the competition for priority publications.

- **Recommendations:**

The team must focus on the proposed objectives, keep up with the external collaborations, and try to recruit talented, highly skilled and committed post-docs. This will benefit the development of such an ambitious program in very competitive and wide topics.

Team 4: Cellular and molecular mechanisms of adaptation to stress and carcinogenesis

Name of team leader: Mr Christian POUS

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	6
N2: Permanent EPST or EPIC researchers and similar positions		8
N3: Other permanent staff (without research duties)		8
N4: Other professors (PREM, ECC, etc.)		1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		2
TOTAL N1 to N6	**1**	**25**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	11	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	8	8

• Detailed assessments

Assessment of scientific quality and outputs

The scientific production is excellent.

This team is entirely new gathering people with excellent track records:

- the team leader himself (current leader of EA 4530 at Châtenay-Malabry), who provided seminal insights into the mechanisms of microtubule rescue and who identified septins as key proteins that bind to microtubules and confer resistance to paclitaxel (published in Science 2008, J Biol Chem, Proteomics, etc.)

- members of UMR_S 1004, who showed that autophagy was induced during hepatic steatosis or ischemia/reperfusion and regulate cell survival in these settings (published in J Hepatol, Cell Death Dis, Autophagy,

Hepatology, etc.) and contributed to the discovery of EGF gene polymorphic variations in hepatocellular carcinoma (JAMA 2008)

Assessment of the unit's academic reputation and appeal

Very good academic repution attested by the publication of several reviews by the team leader in Nat Cell Biol, J Cell Sci, Autophagy, Cell Signal, etc; Reviewing in Traffic, Mol Cancer Ther, BBA, Biol Cell, Blood, Exp Cell Res, etc; expertise for Hong-Kong university and ANR; invited conferences at national meetings; co-direction of a cell imaging platform.

Assessment of the unit's involvement in training through research

The team leader has an excellent activity in training, including the chair of a Master 2 program and of a PhD School dedicated to “Therapeutic innovation, from basic to applied science”.

Completion of 11 PhD in the leader’s team (6), or under the direction of members from UMR_S 1004 (4) or UMR_S 785 (1).

Assessment of the strategy and the five-year plan

Very good strategy developed to combine the expertise from researchers who currently belong to three different units into a translational program on the adaptative response to stress. The program includes fundamental aspects of microtubule dynamics and pathophysiological aspects related to stress response and autophagy in viral hepatitis and liver cancer. It also relies on rare clinical resources in the national reference centers of viral hepatitis A and E and of congenital disorders of glycosylation. Multiple questions are addressed such as the relations of microtubules dynamics with JNK pathway, O-glycosylation, mitochondria dynamics and lipid droplets formation, autophagy in viral hepatitis A and cancer resistance to tubulin-binding agents. Collaborations have been undertaken between the team leader and UMR_S 1004 members and common meetings are ongoing.

Conclusion

- **Strengths and opportunities:**

Novel input of high-level expertise on microtubule dynamics into liver pathophysiology.

Potential new therapeutic targets such as tubulin acetylation and new mechanisms of chemoresistance in tumors.

Strong involvement in PhD training.

- **Weaknesses and threats:**

Lack of preliminary results on the autophagic status of infected cells in viral hepatitis.

Multiple objectives contrasting with the absence of full-time researchers.

- **Recommendations:**

Because of the diversity of the research axes, it is recommended:

1) to clarify the research priorities;

2) to actively recruit Post-Doc(s) and increase the PhD students/HDR ratio to increase the team workforce consistently with the research priorities;

3) to perform a yearly auto-evaluation of the different research objectives for Go-No Go decision.

The potential interactions with the other teams should also be reviewed on a regular, yearly basis.

5 • Conduct of the visit

Visit date:

Start:	Tuesday, January the 7th at 9.00 am
End:	Tuesday, January the 7th at 6.30 pm

Visit site:

Institution:	INSERM UMR_S 785 at Centre Hépatobiliaire (CHB) located in Paul-Brousse Hospital
Address:	12 avenue Paul-Vaillant Couturier, 94800 Villejuif

Conduct or programme of visit:

09.00 am	Welcome (closed-door) experts committee with the AERES Scientific Delegate (DS) (the role and procedures of AERES). Distribution of tasks among the expert committee members.
09.30 am	Director of the unit (presentation, discussion) Presentation of the past activities and project
10.10 am	*Team 1: Therapeutic Innovations in Liver Disease and Liver Transplantation and Translational Research* (Mr Didier SAMUEL)
10.50 am	*Team 2: Integrative biology, modeling and cell therapy of liver diseases* (PI: Mr François LE NAOUR)
11.30 am	Coffee break
11.40 am	*Team 3: Microbiota, Inflammation and Liver Cancer* (PI: Ms Jamila FAIVRE)
12.20 am	*Team 4: Cellular and molecular mechanisms of adaptation to stress and cancerogenesis* (PI: Mr Christian POUS)
01.00 pm	Lunch with poster presentation by PhD students and post-doc fellows
02.30 pm	Parallel meetings with personnel Discussions with engineers, technicians, administrative Discussions with students and post-docs
03.15 pm	Discussion with the representatives of the managing bodies (INSERM, université, école doctorale)
04.00 pm	Coffee break
04.15 pm	Discussion with the head of the unit (if necessary)
05.00 pm	Private meeting of the experts committee (in presence of the DS)
06.30 pm	End of the visit

The leader of the unit made a presentation of the strategy of the unit for the next 5 years. This was followed by discussions with the experts committee.

Then, each team leader presented the scientific report and 5 year research plan. At lunch break, a visit of poster presentations by PhD students / post-docs was organized.

Then parallel meetings with the staff were organized in three groups:

1) discussions with engineers, technicians, administrative;

2) discussions with staff scientists;

3) discussions with students and post-docs.

A meeting with the representatives of the managing bodies (INSERM, université, école doctorale) was organized and followed by a private discussion with the head of the unit.

Finally, a closed door meeting of the scientific evaluation committee took place.

Specific points to be mentioned:

Dr Jérôme LEMOINE could not be present at the site visit but contributed to the evaluation of the written application and provided his comments to the experts committee.

6 • Supervising bodies general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

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 18 mars 2014

N/Réf. : 56/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150008294

Monsieur le Directeur,

Vous m'avez transmis le 24 février dernier, le rapport d'évaluation de l'unité de recherche - Physiopathogenèse et traitement des maladies du foie - N° S2PUR150008294, 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.

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

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

Jacques BITTOUN
Président

UNIVERSITÉ PARIS SUD
PRÉSIDENCE
Bâtiment 300
91405 ORSAY cedex

Siège :
Université Paris-Sud
15 rue Georges Clemenceau
91405 Orsay cedex
www.u-psud.fr

Tél : 01 69 15 74 06 – Fax : 01 69 15 61 03 - e-mail : president@u-psud.fr

Answer to the AERES report on Unit Pathophysiology and Treatment of Liver Diseases

First we wish to thanks the committee for the in depth and very precise analyses on the strengths and weaknesses of the Unit. We are particularly grateful to the committee for their judicious recommendations, which will certainly help to further improve the scientific and academic forces of our Unit.

We will answer point-by-point

Weaknesses and threats

"*The end of the hepatitis C epidemic".*

It is true that the advent of very potent direct antiviral agents against hepatitis C and the increase in the number of patients with sustained virologic response will modify in depth the clinical impact of HCV epidemic and as a consequence, the future of research. In the next 2-3 years, a major focus will be made on these new treatments and in particular in the difficulty to treat patients, i.e. cirrhotic and post-transplant patients, which is one of our main axes of research. However, the success of these treatments will not affect the consequences of previous HCV infections, many patients being at more than 20-30 years after the onset of their infection and reaching the stage of liver cirrhosis or liver cancer. Liver cancer secondary to HCV will continue to increase in the next 5 years. Therefore our main focus will indeed progressively shift to HCV carcinogenesis and HCV induced pathogenesis, but also to other causes of severe liver diseases, i.e. alcohol, and non-alcohol induced cirrhosis and HCC.

"*The new structuration with several groups, increasing the number of research topics on 2 geographical sites."*

We are well aware of the scientific, and organisational challenge of this new structuration with both an important growth of the unit, and a location on 2 sites at least during the first years.

From the organisational point of view, the unit will have monthly meetings of an executive committee that comprises the director of the unit and the team leaders. We will have a meeting with all seniors searchers every 3 months. In these meetings, organisational, budget, and scientific issues will be discussed.

From the scientific point of view, regular seminars will be organised on a weekly basis with PhDs, post-doc and master students, in order to share scientific progress, discuss scientific technical issues and interact with invited external experts. Two seniors researchers (who will change every year) will coordinate these seminars. The fact that the teams are on 2 different sites can be seen both as a weakness and a strength; the problem of the distance will be overcome by regular meetings and also by setting up videoconferences. The strength is the ability to benefit from 2 technical platforms on the site Paul Brousse and on the site Châtenay-Malabry. In addition, the unit will benefit from the access of the doctoral school "Therapeutic innovations" directed by C Poüs. The executive committee will encourage transversal research projects between research teams of the unit, some being already in place.

Recommendations:

"*Need for a scientific advisory board".* We agree with the committee that a yearly external SAB meeting will be helpful to evaluate the progression of the unit and of the teams towards their scientific objectives. We agree that, to avoid duplication, part of the SAB members can be solicited in the DHU hepatinov. However, our suggestion is to appoint additional members to this SAB since the DHU only partly overlaps. This SAB will be constituted within the next weeks.

" Position of the DHU and the Unit" We agree that the unit and the DHU share some common objectives, but are distinct entities with their own scientific goals.

"Organisation of seminars" As said above and in answer to the committee, we will organise regular seminars on a weekly basis with all PhDs and students, these meetings will be organised by 2 senior researchers.

"*Budget rules"* The executive committee will organize the repartition of the budget between the teams. It will establish a common budget, mixing the financial resources from Inserm and from the university; it will also organize the repartition between human resources and equipment.

"*Contribution to the platform of the SFR André Lwoff".* The existing 785 unit is already part of the SFR, already uses the facilities of these platforms and participates in shared equipment demands. This policy will be pursued, and developed with the future UMS, which will be led by team leader 2 François le Naour, reinforcing the links between the platforms and the future unit.

Team 1 answer

We thank the committee for their supportive comments. Regarding the points that were raised:

"The end of the hepatitis C epidemic". Please see answer to this question above. As most patients with hepatitis C are already at the stage of cirrhosis and HCC, this theme of research will be present for the next five years. However the team is already considering an evolution of the research towards HCC, alcohol and non-alcohol induced liver diseases. This will be in partnership with the other teams from the unit

"*Position of the team in collaborative projects*". Members of the team are primary investigators of 3 PHRC, 4 ANRS collaborative studies and some industrial trials. We cannot be the promoters of all collaborative projects, but we aim at continuing the development of new projects as PI in the next years.

"*The team should keep up and invest on basic aspects*". The research objectives of the team is focused on translational projects, and we agree with the committee on the importance to maintain a strong link with basic research, this will be done through the strong collaborations with other teams of the unit.

"Governance and prioritisation" In addition to the governance of the unit, this team will have his own governance with regular meetings to evaluate the advances of research projects and to decide prioritisation of means and projects on a monthly basis with a yearly auto evaluation of the results. The team leader will encourage senior scientists to develop their projects with regular evaluation. We will evaluate both the results of our team and our capacity to enhance collaboration with the other teams of the unit, and our ability to develop new projects.

Team 2 answer

We thank the members of the AERES committee for their positive comments and we are grateful for their helpful recommendations. We will take into account these recommendations.

The committee has suggested that the team should implement a clear strategy plan with the identification of research priorities and of the PIs in charge of the main research themes and with a re-evaluation of each one on a yearly basis.

We will plan research along three main topics that will be headed by PIs as follows:

HCV-induced carcinogenesis – PI: François Le Naour
The topic is focused on HCV entry mechanisms and the signaling pathways deregulated in liver carcinogenesis.

- We have already identified the components of the machinery involved in HCV entry and performed functional tests on infection. The molecular mechanisms involved in HCV entry are not restricted to HCV but are also shared by other viruses such as influenza virus.
- The identification of signaling pathways deregulated by HCV core has been already performed using phosphoproteomics. The studies will be further focused on the targets identified and the role of these signaling pathways in liver carcinogenesis. Despite the occurrence of new treatments of HCV infection, patients with HCV-induced cirrhosis will develop cancer. This project is of major interest for identifying deregulated signaling pathways and further blocking liver carcinogenesis.
The topic is developed by two postdoctoral fellows, Nazha Sidahmed-Adrar (HCV entry) and Cosette Abdallah (deregulated signaling pathways) supported by ANRS.

NAFLD – PI: Franck Chiappini

This topic corresponds to a major health issue worldwide. We are focused on two important aspects mainly diagnosis of NASH and molecular mechanisms of lipotoxicity.
- New diagnosis are developed using spectroscopy based-approaches focused on the detection of early stages of NASH. This part has already been valorized by several publications, a patent and some grants. It is currently developed by a PhD student -Chengyuan Peng- under supervision of Dr. Slavka Kascakova (MCU, biophysicist).
- The mechanisms of lipotoxicity have been addressed first by performing the lipidomic analysis of patients with steatosis and NASH followed by unsupervised statistical analysis using appropriated and sophisticated approaches. This piece of work is already done leading to the identification of differentially abundant lipid species between steatosis and NASH in human. These results identifying lipid markers of NASH will be published as soon as possible. The studies will be further focused on the role of lipids in inflammation in particular on activation of Kupffer cells using animal models and clinical resources (Pathology Department headed by Pr. Catherine Guettier).

We are aware that this topic is highly competitive. However, a comprehensive lipidomic analysis followed by sophisticated statistical analysis has never been performed. The functional role of lipids has also never been addressed. We believe that our angle is currently still original to fight the high competition. To reinforce the topic, we have mobilized several members of the team. A Master student -Romain Fournier- and a PhD student -Audrey Coilly (MD)- are working along with Dr. Franck Chiappini (postdoc, CDD FRM) who is responsible of the whole topic. The high priority of the team will be to allow Franck Chiappini to be recruited on a permanent position.

Stem cells and cell therapy – PI: Anne Dubart-Kupperschmitt

As mentioned by the AERES committee, *"the project on Wilson's disease (WD) is an emerging common theme between the different team members from diagnosis to cell therapy that deserves to be boosted"*.

- Diagnosis of WD by using fluorescence X, developed by Dr. Slavka Kascakova (MCU, biophysicist), is going to be submitted soon. Two manuscripts are in preparation respectively focused on diagnosis of WD on tissue sections or on paraffin embedded biopsies. These publications and the method will constitute a robust basis for developing the project. Patenting is also on going.

- In order to boost that topic on cell therapy, we have recently engaged a PhD student – Jérôme Caron- for derivating iPSCs from patients with WD.
- A recent meeting has been organized in order to set up a consortium including national reference centers of WD (Pr. Emmanuel Jacquemin and Pr. Jean-Charles Duclos-Vallée), Pathology Department (Pr. Catherine Guettier) and industrials (e.g. Phenocell). This will lead to writing up proposals applying to ANR or European Union for funding our research on modeling, drug screening, molecular mechanisms and cell therapy.

Team 3 answer

Team 3 greatly thanks the committee members for their encouraging and constructive remarks in this review as well as during the visit of the laboratory. We are pleased that the experts appreciated the efforts Team 3 has collectively made over these last years. We naturally agree that research on gut/liver axis and hepatocarcinogenesis is a highly competitive field. However, as it is new (it has as yet hardly been explored), there is room for invention and for building on our specificities (including our network of external collaborations). With regard to the recruitment of post-docs, we agree that their commitment and creativity are crucial factors for success in an innovative project.

Team 4 answer

The members of the team 4 would like to thank the committee for its fair evaluation and for its recommendations regarding the prioritization and the progress of the project. To give deeper insights into the strategies that will be undertaken to support these recommendations:

We plan to start internal meetings of the team on a regular monthly basis as soon as of spring 2014. This will help to clarify some priorities and to focus appropriate task forces on the objectives that deserve concept proofs or rapid exploration.

This organization will parallel the anticipation of the research in some axes considered more "risky" like the status of autophagy in cells infected by HAV and HEV. We are confident in the opportunity to identify such mechanisms as hepatocytes are already known to respond by autophagy mechanisms to other viral hepatitis and as autophagy is widely involved in the cell response to RNA viruses. In this respect, the team has already applied for a grant from the region Ile-de-france to welcome a post-doc on this topic. In the case our efforts would now allow to initiate this axis of research, we will refocus on other mechanisms of cell adaptation involving oxidative stress, cell response to hypoxia, and general stress response signalling pathways. Such mechanisms have been already identified in the context of viral hepatitis A or E but much information is still missing, especially that connected with the control of microtubule modifications and dynamics.

Regarding the policy that aims at installing a more stable basis of permanent researchers and to increase the research potential of the team, we plan to take advantage of our future status to help us in recruiting at least one full-time researcher. Also, as soon as they will meet the necessary requirements to do so, one of the primary goals will be to encourage some teaching researchers of the team to obtain their HDR. These actions will allow a broader recruitment of PhD students. A significant effort will also be made to attract talented post-doctoral students.