Pathogénèse et traitement de l'hépatite fulminante et du cancer du foie

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research Unit :

Physiopathogenesis and treatment of fulminant hepatitis and liver cancer

University Paris 11

December 2008

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et de l'enseignement supérieur

Section des Unités de recherche

Evaluation report

Research unit

Physiopathogenesis and treatment of fulminant hepatitis and liver cancer

University Paris 11

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

December 2008

Evaluation report

The research unit :

Name of the research unit : "Physiopathogenesis and treatment of fulminant hepatitis and liver cancer"

Requested label : UMR_S

N° in case of renewal : U785

Head of the research unit : M. Didier SAMUEL

University or school :

University Paris 11

Other institutions and research organization:

INSERM

Date of the visit :

November 13th of 2008

Members of the visiting committee

Chairman of the commitee :

M. Francesco NEGRO,Geneva

Other committee members :

Ms. Marina BERENGUER, Valencia, Spain

M. Steven DOOLEY, Heidelberg, Germany

M. Markus HEIM, Basel, Switzerland

M. Philippe MERLE, Lyon, France

M. Frederik NEVENS, Leuven, Belgium

CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD... representatives :

M. Fabien ZOULIM, CNU representative

M. Louis BUSCAIL, CSS INSERM representative

Observers

AERES scientific representative :

M. Pierre BEDOSSA

University or school representative :

M. Laurent BECQUEMIN, University

Research organization representative :

Mme Marie-Josephe LEROY, INSERM

Evaluation report

1 • Short presentation of the research unit

- Numbers of lab members :
  - Researchers with teaching duties : 11
  - Full time researchers : 3
  - PhD students : 9
  - Engineers, technicians and administrative assistant : 12
- Numbers of HDR : 8
- Numbers of PhD students who have obtained their PhD : 2 in 2 years (the unit was created in 2006)
- Average length of a PhD during the past 2 years : 2.5 years
- Numbers of PhD students currently present in the research unit : 9 including 8 with a fellowship
- Numbers of lab members who have been granted a PEDR : 0
- Numbers of "publishing" lab members : 14 out of 14 among researchers with teaching duties and full time researchers.

2 • Preparation and execution of the visit

During the visit, the committee had the opportunity to discuss with the Director, the Co-Director, the researchers, the students as well as the administrative and technical personnel, and review the scientific activity of the Unit spanning the period January 2006 to present. The Director, the Co-Director and some selected investigators presented their academic achievements with the help of slides, while the remaining personnel held more informal talks with the experts. Some administrative and budgetary information was also provided, although the fine details of the complete financial structure and support of the Unit remained vague and could not be appreciated in full.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The Unit 785 was formed at the end of 2005 by joining two former research groups, one more clinical research-oriented, the other essentially dedicated to basic studies, but both strongly committed to the study of various aspects of liver diseases, from the pathogenesis to the clinical management. The two leaders of the former groups had a long-standing experience in the research on various aspects of fulminant liver failure, viral hepatitis, and hepatocellular carcinoma, as shown by their extensive publications track record, and were appointed respectively Director and Co-Director. The major goal of this joint venture was to foster translational research exploiting the respective competences of the two research groups, while maintaining at the same time their specificities. Thus, the goals of this evaluation were to assess the scientific productivity during the last two years together with the degree of integration and synergism between the two former teams.

The research objectives of the Unit are focusing on (i) the treatment of acute liver failure, hepatocellular carcinoma and cholangiocarcinoma, (ii) the pathobiology of hepatitis virus infection in the setting of liver transplantation, with particular emphasis on the mechanisms of viral persistence, viral compartmentalization, the factors of liver disease progression including the mechanisms of virus-induced fibrogenesis, and (iii) the auto- and alloimmunity in the setting of liver transplantation.

From the clinical standpoint, the patients' recruitment rate of the Centre Hépatobiliaire, where the Unit is located, is impressive: in 2007, as many as 138 liver transplantations have been performed (approximately 15% are due to fulminant liver failure) and 300 new cases of primary hepatocellular carcinoma cases were seen. Clinical data and material are available for retrospective analyses, and the prospective enrolment of patients in clinical trials is assured.

The dual specificity of the Unit has attracted interactions with other institutions, both national (INSERM and CNRS research groups operating in the André-Lwoff Federative Research Institute at Paul-Brousse Hospital) and international (University La Sapienza, Rome, and the Universities of Dundee, Zurich and Aachen).

4 • Appreciation of resources and of the life of the research unit

The academic personnel consists of 6 university professors, 5 *maîtres de conférence* and 3 senior scientists (*chargés de recherche*): the latter ones have been recruited since 2006, i.e. after the unit was created. There are 8 additional investigators and 12 employees involved in the administration and technical support. Currently, there are 9 PhD students (two are MDs) and three Master students, recently recruited. Three PhD theses have been completed since 2006, and more are underway.

The investigators of the Unit have raised funding from several institutions and agencies (ANR, PNRHGE, INCA, ARECA, ANRS and the European Commission) for a total of 451K euros in 2006, 619K euros in 2007, and 734K euros in 2008. These figures include the annual support from INSERM and from the University Paris-XI. These funds have been obtained, sometimes repeatedly, by no more than 6 academic members of the unit.

The Unit has published several original papers in peer-reviewed journals: 5 in the second half of 2006, 10 in 2007 and 8 so far in 2008. These figures include both clinical and basic papers, and do not take into account editorials and review articles even when published in peer-reviewed journals. Half of the papers are collaborations: thus, the investigators of the Unit have signed, as last authors, 11/22 papers over the 3 years, contributing to 86.115 points of impact factor (almost 60% of the total). Five academic members of the unit have signed an original article as last (*senior*) author.

The investigators of the Unit have filed two patents: one for the *HIP/PAP polypeptide composition for use in liver regeneration and for the prevention of liver failure* (deposited in 2004, i.e. before the Unit was created, and published in 2006), and the other for the *Nucleic acids for expressing a polynucleotide of interest in mammalian cancer cells* (deposited in 2007).

5 • Recommendations and advice

— Strong points :

o Both team leaders have an outstanding track record in clinical and basic research respectively.

The patients' recruitment rate is a major asset, as this is one of the pillars of all translational research programs.

o The scientific level and background of most permanent researchers are rather strong, and in a few cases impressive and convincing; some topics are novel (like the proteomics mapping of cholangiocellular carcinoma, the radioiodine liver mass imaging, or the mechanisms of fibrogenesis via EMT) and some cutting-edge (like the study of liver cell polarization).

The fact that the amount of competitive funds is increasing over the years is a very positive aspect of the vitality of the Unit (at least of some of its members, see below, among the weak points).

The fact of having patents is another very important asset and a strong premise to attract industrial partners: as a matter of fact, the Unit is working in close interaction with a start-up (ALFACT Innovation) for preclinical and clinical development of molecules potentially active in the treatment of fulminant liver failure (HIP-PAP protein, ALF-5755) and hepatocellular carcinoma (Adenovirus-HIP-NIS).

The melting process involving basic and clinical projects is certainly a difficult one and probably slower than initially planned, also owed to the complexity and multiplicity of the research topics that are pursued; the interview with the Director and the permanent researchers gave however the impression that the process is ongoing, and that there is a sense of direction in the overall research activity; in addition, this process benefits of the active support of a whole network of surgeons, virologists and pathologists.

The ongoing applied research projects are likely to proceed towards the clinical experimentation: in one case (involving the use of HIP/PAP, for which the GMP process is completed) a multicenter, Phase I trial in healthy volunteers should start at around mid-2009, and the protocol is currently being finalised; in the other case (involving the use of gene therapy with Adenovirus-HIP-NIS, a somehow higher-risk project than the previous one), contacts are underway for additional toxicology studies in the animal model (with a company based in San Francisco, CA), and therefore, if everything goes as planned, the Phase I study may start in 2010.

The Unit has been able to actively recruit scientists and fellows from outside institutions, including international ones, suggesting a certain level of attractiveness; this is not only true for senior scientists but also for PhD students; it was quite instructive through the discussion with the latter ones, since it underscored the level of enthusiasm of these young fellows and their competitiveness (all students in their third year or higher had at least one paper published or in press); on the other hand, the meeting with the administrative and technical personnel underlined another aspect of the working environment, i.e. that of a deep respect of the professional expectations of all human resources (this detail was particularly appreciated by the committee).

— Weak points and recommendations :

- Although the clinical research studies are important and have impacted on the clinical management of patients with fulminant liver failure, hepatocellular carcinoma and viral hepatitis in the setting of liver transplantation, they are all retrospective, as there is an evident lack of prospective validation studies; given the patients' recruitment rate, it is a bit surprising that this kind of approach has not been pursued further; thus, we recommend to focus more on prospective validation studies in the clinical setting;
- There is some concern that, in some cases, junior scientists may not receive sufficient encouragement to build their own group. In addition, some of the academic members do not seem to apply for their own research grants or conduct their own independent research. The team leaders should do every effort to stimulate all researchers to apply for their own grants and improve their own national and international visibility, given the potential of the institution. One has to consider that, among the 22 "publishing" members of the Unit, at least 11 (6 professors and 5 "maîtres de conférence") may have the status of group leader, only 5 have published an original article as last (*senior*) author during the past three years.
- Although the Unit has been started in 2006, and its scientific output cannot be appreciated in full, the number of publications in high-ranking scientific journals seems insufficient, given the potential of the Unit; thus, the number of publications in high-rank journals can and must be increased, involving the members of the unit who have not sufficiently contributed so far;
- Some experts raised the concern that in a few cases the experimental design of the scientific projects may not be sufficiently systematic and mechanism-oriented: to consolidate the current achievements, lab meetings and progress reports, with outside experts, should be implemented with higher frequency;
- There was almost a consensus that some research topics seem less attractive and may not lead to major breakthroughs, such as that on the autoimmunity in the setting of liver transplantation.

The committee wondered whether some degree of reorganization may even benefit the other, more attractive sectors of research.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A+	A	A

UNIVERSITÉ
PARIS-SUD 11

Le Président de l'Université Paris-Sud 11

à

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

Orsay, le 20 mars 2009.

N/Réf. : 72/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012396

Monsieur le Directeur,

Vous m'avez transmis le vingt trois février dernier, le rapport d'évaluation de l'unité de recherche «Pathogénèse et traitement de l'hépatite fulminante et du cancer du foie» - UMR S 785 , et je vous en remercie.

L'université prend bonne note de l'appréciation et des suggestions faites par le Comité.

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 Didier SAMUEL, Directeur de l'unité de recherche.

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

Guy COURRAZE
Président

UNIVERSITE PARIS-SUD 11 - Président - 91405 ORSAY CEDEX

P.S. : Les représentants de l'université Paris-Sud 11 étaient Mme Anita BERSELLINI – Présidente et Mr Laurent BECQUEMONT – Médecin Enseignant Chercheur.

P.J. : Commentaires de Mr SAMUEL

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Unité de recherche U785
Pathogenèse et traitement des Hépatites Fulminantes et du Cancer du Foie

Institut national de la santé et de la recherche médicale

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Villejuif, 9 March 2009

Answer to the report from the AERES visiting committee of Research Unit UMR 785 : Physiopathogenesis and treatment of fulminant hepatitis and liver cancer, Inserm-University Paris 11

We thank the visiting committee for this report. We thank the committee for the strong points of the Unit underlined in the report.

Regarding the weak points and the recommendations, we have the following answers.

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a) We acknowledge the importance of developing prospective studies and we will develop much stronger active collaboration between clinical and research teams.

b) We are of course willing to encourage young junior scientists from the team to develop their own group and apply for their own research grants.

c) Regarding the publications, we acknowledge the fact that we are still lacking major publications in top rank general scientific journals, however we were able to produce seven papers in the highest ranking journals of the specialty with IF > 10 (Gastroenterology, Hepatology) within the last 3 years. Since the visit of the committee, we have 3 additional papers in favorable revision: 2 on HIV and Liver Transplantation in the Journal of Hepatology (IF 6.6) and AIDS (IF 5.8), 1 on autoimmune hepatitis post-transplantation in the American Journal of Transplantation (IF 6.4); 1 paper on the relation between EMT TGF beta and HCV core is now accepted for publication in Plos one (Battaglia S et al. Liver cancer-derived hepatitis C

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virus core proteins shift TGF-Beta responses from tumor suppression to epithelial-mesenchymal transition Plos One 2009 ; 4(2).

d) Lab meetings are already frequent (every week), in addition a monthly meeting of the "Virus group" joins together clinical and research teams. However, as suggested by the committee, we will encourage the development of Mechanisms-oriented lab meeting and Progress reports.

e) Regarding the last point about auto and allo immunity in liver transplantation. This research group is currently growing, and has published several papers within the past 3 years including one in Hepatology (IF 10.6) and one in Proteomics ; an additional one is currently under revision in the American Journal of Transplantation (IF 6.4). Considering the correlation between emergence of autoimmune hepatitis and transplantation, this project is fully integrated in the thematic of the Unit. This group is an example of the relationship between clinical interest and fundamental mechanistic insights that we wish to develop.

Yours sincerely

Prof Didier SAMUEL
Director Inserm-Paris XI Unit U785